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Ulster Med J 2015;**84(3):**149-150

Editorial

Counting on better health?

Summer 1981 - first year medicine, QUB. Professor Ian Roddie was due to give a physiology lecture on "Diet and Exercise". The Prof was obviously important - his name was on the front of our physiology text-book (along with Professor William Wallace), so there was quite a sense of anticipation in the room. Without a word, the Prof walked up to the blackboard, wrote "Eat less" at the top of the board then "Exercise more" at the bottom and joined the two together with curved arrows. He turned to look at the class for a few seconds, then walked off in silence. Total duration of lecture - 45 seconds.

The point was powerfully made but converting ideas to action is much more difficult. In our professional roles, we all advise smoking cessation, more exercise and eating less along with alcohol and salt moderation but it seems as though we are losing the battle. According to 2014 figures, 60% of adults in Northern Ireland are overweight or obese and 28% of adults take less than 30 minutes of exercise per week[1]. A 2012 study suggested that the annual cost of obesity to the Northern Ireland economy was £370 million[2].

Can technology help? The Internet has become an all-pervasive force in modern life and has gone through a number of iterations. The latest is "the Internet of me" - collecting data about all aspects of oneself. One manifestation of this is the "selfie" photograph, but the tools and gadgets exist for the individual to collect extensive physiological data such as heart rate, steps taken, distance travelled on GPS, weight and percentage body fat along with calories consumed and burnt.

The term "Quantified Self" was coined by Kevin Kelly and Gary Wolf, editors of technology magazine Wired in 2007 to describe this trend , alternate terms are "life-logging" or "body-hacking"[3].

The trend hit the mainstream in 2014 with the marketing of "wearables" - sensor devices that usually interact with a smartphone to display data which is stored on remote servers. According to the Wall Street Journal, many millions of dollars of venture capital has been invested in tracker firms making devices such as Fitbit[4] and sports clothing manufacturer Under Armour recently purchased a market leading smartphone app that records dietary calories and nutrients, MyFitnessPal, for $475 million[5]. The richest technology company on the planet, Apple, has joined in with the Watch.

The Quantified Self has also extended into the realm of genetics. Not so long ago, gene testing was astronomically expensive. The budget for the Human Genome Project, a complete mapping of human DNA was $2.7 billion back in 2003[6]. American company, 23 and Me, now offers this service in the UK for £125 based on the collection of a little saliva.

Results are divided into:

Genetic risk factors including alpha-1-anti-trypsin deficiency, APO-E variants for Alzheimer's disease and BRCA-1 and BRCA-2 variations for breast and ovarian cancer.

Inherited conditions including cystic fibrosis, beta-thalassaemia and G6PD deficiency.

Traits including carrier for red hair, lactose intolerance and tendency to male pattern baldness.

Drug responses including clopidogrel efficacy and risk of simvastatin-induced myopathy.

Broad brushstroke ancestry data are included along with an indication of percentage Neanderthal ancestry.

Over and above the headline results, your complete genome is listed and can be browsed for specific variations or downloaded and stored in the family data archive!

There are of course, many ethical and data security issues to consider. Should you disclose any significant results to a life insurance company? Should you tell your family about findings that may affect their future health? How will your GP respond if you want to take a positive result further?

The question also arises about who has access to the data. It is interesting to note that Google, well known for data harvesting, has invested heavily into 23 and Me. It has been said that if something you use on the Internet is free then you are paying with your data and privacy - perhaps the same is true of our physiological and genetic data.

Some commentators in the UK have expressed a hope that a nation of self-motivated, life-logging individuals could impact on the huge financial burden of treating obesity, poor diet and sedentary behaviour. Set against this, I have seen asymptomatic individuals at clinic worried about a high resting heart rate or an excessive heart rate during exercise measured by their trackers. Interestingly, these particular individuals weren't taking very much exercise - somehow the expectation was that the tracker itself would improve things.

Diet and exercise in 2015? Eat less. Exercise more. Collect data.

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John Purvis Hon. Editor (2.8% Neanderthal).

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Medicine outside the comfort zone

A Journey to Kitovu

Sandra McNeill

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Provenance: invited article

IN AT THE DEEP END

I arrived in Kitovu Hospital, Masaka, Uganda late on Sunday evening as the sun was setting over Lake Victoria. I was just unpacking when the door was thumped repeatedly - 'Sandra, Sandra, come quickly! They have a lady bleeding in theatre'. Outside my door stood an elderly white lady. *Where is theatre and how do I get there?* I am thinking. 'Quickly! Follow me!' she says and dashes away.

Off I go into the pitch black darkness of an African sky along a little bumpy path following a septuagenarian Irish nun with a torch. 'Quickly, quickly!' she says. *Um well, I'm trying not to break my neck keeping up with you!*

She says 'I'm so glad you are here as we can't find Mr. Wanziza (*Who is he?*), the surgeon is on holiday and there is no-one else'. *Good start!*

She unlocks a door and I'm in an office. She sizes me up quickly and thrusts a pair of theatre scrubs in my hands, stands there and says 'Well, hurry up and get changed'. 'Here?' – 'Well yes, where else!' By now I reckon she's thinking, oh my lord, what have they sent me?

She bustles me out of the office and bursts into theatre saying 'It's okay, Dr. Sandra is an obstetrician from Ireland – things will be okay now'. Whatever gave her that impression is beyond me!

I look around trying to get a measure of what is happening. There is a lady on the table with her legs in stirrups and blood pretty much everywhere but it's very quiet, not really like an obstetric emergency at home.

'Who's in charge?' I ask. Eyes from behind masks all look at one another – no-one speaks. 'Okay' I say. 'Well, I'm Dr. McNeill and I am an obstetrician from Ireland, just as Sr. Maura said. So who are all of you?' Well, there's 'Paul' and 'Ingonge' and 'Nelson' and 'Asaph' and 'Sr. Josephine' who appears to be an anaesthetist.

'Okay' I say. 'Sorry, but not just your names. Are you doctors and if so what level are you at?' – another pale face emerges from behind and says 'I'm Geert, a Belgian surgeon and I think we have a surgical & gynae intern and an obstetric medical officer'.

Well, at least I know the team now, so after 'well. What's the craic here' (Derry colloquialism for 'Dear chap, please give me the full clinical history') failed to be understood - it emerged that a 24 year old prim had arrived in established labour at possibly 29 weeks with a breech presentation and delivered a fresh still birth, very rapidly followed by a massive PPH, about an hour earlier.

Fig 1. - Theatre

'So, what's happening now?' I ask. 'We are trying bimanual compression' – 'Okay, but for how long' – 'About 45 minutes' – 'So what's the plan after that' – silence. 'What about packing? What about some drugs?' I ask – *but what do they have?* I do not know, so I ask, trying not to sound surprised

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or shocked 'Has she had syntocinon or Ergometrine?' Eyes look again at each other from the masked faces. 'Would you like us to get them' – 'Yes please'. So the anaesthetist and two of them start to leave – 'No, No don't all go, can't one of the nurses get them?' - 'Well, they are in getting the next lady ready for section' – *What next lady?* – a nurse arrives and says 'We have no packs left, so is it okay if I tie some wipes together?' – *what's a wipe?* – But sure, whatever – so swabs the size of a Kleenex get tied together and I get scrubbed.

Does she have an atonic uterus? – does she have vaginal or cervical trauma? – no one knows – just 'bleeding' – so I sit on the stool to inspect. 'Can I have the theatre light redirected?' There is one satellite light circa 1950 with 4 of its 8 bulbs working – not really much use. Asaph says 'let's use my mobile' and turns on a much better light source. I think its atonia and ask Sr. Josephine if the patient is stable enough to have a hysterectomy – no answer. I stand up from between the legs and realize that there is myself, Geert and one of the gang of 3 left – 'Where is everyone?' – 'Oh Dr. Sandra they are doing the section next door' – 'Has she had the synto' – silence. 'Do we have Misoprostol or Haemabate?' 'Well, they are cash drugs' – *what does that mean?* So I say to Geert the Belgian surgeon – 'I think the only way to attempt to save this lady is with a hysterectomy" – *who makes that call? – can I after only arriving an hour ago? – Where is the obstetrician (Mr Wanziza)? – do I need to run it past him?'*

Geert says 'I reckon you are in charge, so your call' – I can think of no other solution as its now 8pm, she arrived at around 5.30pm and we have no idea of how much blood she has already lost. So Geert, the nurse and I get on with it. It is not a difficult procedure as she is a young slim lady with no previous surgery. A laparotomy reveals a ruptured uterus. She barely bleeds – basically because I think she has exsanguinated most of her blood volume. Whole blood is transfused in – no pumps or filters or blood warming machinery in sight. As we finish, she gets wheeled out in the corridor to recover or not!

Fig 2. - ICU sign

The next morning I find her in ICU – basically just a side room with an "Intensive Care" sign on the door (Figure 2 - ICU sign) – she is agitated but not bleeding. Her BP is stable and she is producing urine. Naively, I ask for her blood results. The team of Drs Paul, Asaph and Nelson shift from one foot to another and look at the ground – *did I say something wrong?* 'Well,' Paul says 'blood tests cost money so we have just given her more blood as she looked pale.'

Fig 3. – Ward round

She remains in 'ICU'- looked after by her mother and sister – no-one checks her vital signs unless we are doing a ward round and I ask for them – the observation chart is an A4 page stuck with cellotape to the back of the door – mostly empty.

Fig 4. – ICU bed

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I am at a loss what else to do – Mr. Wanziza never appears – Sisters Maura and Bernadette thank me – *what for?* – the woman is dying – but they are happy that an effort was made. 3 days later she passes away, never having regained consciousness. No-one calls me or tells me – I am walking around the hospital on the way to the shops to buy a Coke when I come across women wailing and my daughter (who came out as part of her gap year) asks what's happening and I say 'Someone must've died'.

We check the ward and sure enough the lady has died and her body has already been taken home – *Will there be a PM? – Will there be an SAI investigation? –Do we present it at an M&M meeting? - Do we have a team debrief?* They look at me blankly and say 'Thank you Dr Sandra'.

RCOG FELLOWSHIP

In early 2014 I read a short article in the RCOG news about the ongoing problem of Obstetric fistula mainly in Sub-Saharan Africa. A fistula unit already existed in Kitovu Hospital, Masaka, Southern Uganda, but was reliant on foreign doctors staffing camps that ran 4 times a year. The RCOG were keen to support local doctors being trained in order to try and move the service to a year round provision. Sr Florence Nalubega had stepped up to go to the Hamlin Hospital in Addis Ababa, Ethiopia, to undertake training and through a generous donation by Mr Marcus Filshie, a fellowship had been set up by the RCOG, to send a UK doctor out to backfill for Sr Florence when she was away.

I had long held thoughts of going out to work in a less developed country but the usual distractions of work and family had kept me occupied. However, I was now a consultant of 10 years and my children were virtual adults, so I thought -'I could do that'. I applied, was interviewed, appointed and in October 2014 set off for Uganda accompanied by one of the same virtual adults for the experience of a lifetime.

My first day as outlined above was by far the most dramatic day of my tenure.

The lady was unfortunately not the only maternal death during my time there and the perinatal mortality rate would make most of my paediatric colleague's cry with despair.

As expected equipment is basic, there were no X-ray or ultrasound facilities on site – patients could go into town and pay a private radiology clinic for investigations if they chose.

There was a laboratory and a lab school, but each investigation cost money, so they were carried out very sparsely. The hospital did charge for treatment but ran on a not for profit charitable basis. Costs to us in the UK were minimal – but could run to many months' salary for a Ugandan. Most drugs were just added to the bill, a 'cash' drug had to be paid for by the patients' family up front before it was issued from pharmacy, and emergency obstetric drugs such as Misoprostol and Haemabate fell into this category. All drugs for the treatment of HIV and malaria were provided free, some paid for by the Ugandan government but usually by overseas NGOs or charities.

Personally, it was a lesson in going back to basic clinical skills which thankfully were still lodged deeply in the back of my brain.

The staff were all lovely and made me very welcome. Medical staff are well trained and worked hard, nursing is a very different profession to the UK and their practices certainly made me appreciate how lucky we are to have such fantastic nursing and midwifery colleagues here at home.

It's very difficult to come from a well-resourced society and go into somewhere else without thinking about changing some of the practices you see – 2 months is too short to have any lasting impression on a hospital system but not on me as an individual.

Dr. Enid Michael, a newly retired consultant obstetrician from England will soon take over as the next Marcus Filshie fellow, to return to Kitovu and assist Sr Florence.

I have been appointed as the RCOG Global Heath Engagement officer – to try and encourage UK trainees to volunteer and to assist them if they do.

The RCOG have set up a new Excellence Course with THET funding to go back to Kitovu and teach local medical, midwifery and nursing staff to become facilitators for fistula prevention. The first course is in September 2015 – I will go back in November as a trainer on the second course.

I hope my affiliation with Uganda will continue long into the future…

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Clinical Paper

HbA_{1c} for Diabetes Screening in Acute Coronary Syndrome: time for a reappraisal of the guidelines?

McCune C[1], Maynard S[1], McClements B[1], Lindsay JR[2]

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Provenance: externally peer-reviewed.

ABSTRACT

Objective: Diabetes is highly prevalent in individuals with acute coronary syndrome (ACS). Current NICE guidelines recommend diabetes screening of hyperglycaemic patients using a fasting plasma glucose after 4 days from admission. In 2012 the World Health Organisation (WHO) approved the use of HbA_{1c} in the diagnosis and targeted screening for type 2 diabetes. We introduced a service improvement project using HbA_{1c} for diabetes screening in patients with no previous diagnosis of diabetes admitted with ACS regardless of glycaemic state.

Method: An initial retrospective audit utilised 21 months of data from the MINAP database to identify patients meeting current NICE criteria for diabetes screening. A prospective service improvement project was undertaken over a 4 month period using HbA_{1c} as a universal screening test to categorise ACS patients based on WHO criteria.

Results: The retrospective audit identified 93 of 420 (22%) patients with pre-existing diabetes and 8 of the remaining 327 (2.4%) were hyperglycaemic, thus meeting NICE criteria for diabetes screening. In the service improvement project 2/49 patients (4%) met NICE criteria for diabetes screening. Twenty six of these 49 patients had a HbA_{1c} test on admission and 17/26 (65.4%) were classified as probable diabetes or high risk.

Conclusion: A significant proportion of ACS patients have diabetes, which may be undetected by current NICE criteria. Universal HbA_{1c} testing offers utility as a simple and effective screening test for diabetes in the ACS population.

Keywords: Diabetes Screening, HbA_{1c}, Acute Coronary Syndrome

INTRODUCTION

Diabetes mellitus is a significant public health challenge associated with cardiovascular morbidity and mortality.[1] The prevalence of diabetes in Northern Ireland is currently around 5.3%, with new diagnoses increasing by around 33% in the past 5 years.[2] It is estimated that up to 12,000 individuals within the region with diabetes remain undiagnosed.[2] A targeted programme of diabetes screening, particularly for those with established cardiovascular disease is recommended to identify and treat individuals at high risk.

Coronary heart disease is a leading cause of morbidity and mortality in diabetes, and around 22-27% of patients admitted with acute coronary syndrome (ACS), have established diabetes.[3,4,5,6] As in the general population, unrecognised diabetes is an unmet need for up to 22-31% of others presenting with ACS.[3,4,5,6] NICE (National Institute for Health and Care Excellence) guidelines for diabetes screening recommend that all patients with admission blood glucose concentrations above 11.0 mmol/l should have a fasting plasma glucose no earlier than day 4 after ACS onset or have an HbA_{1c} test before discharge.[1]

The WHO have recommended HbA_{1c} as the preferred screening test for the diagnosis of type 2 diabetes mellitus.[6] Others have highlighted the potential role for HbA_{1c} as a universal screening test in the ACS setting.[7] More recently the ESC/EASD (European Society of Cardiology/European Association for the Study of Diabetes) have recommended all ACS patients be screened for diabetes.[8]

We undertook a retrospective audit of NICE diabetes screening guidelines followed by a service improvement project assessing the utility of universal HbA_{1c} screening in the ACS population.

METHODS

Audit

The Myocardial Ischaemia National Audit Project (MINAP) is a clinical database, for collection of clinical data on all patients admitted with ACS. 420 patients who presented to the Mater Hospital were identified using the MINAP database

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over a 21 month period. 93 had previously diagnosed diabetes and 8 met NICE criteria to be screened for diabetes.

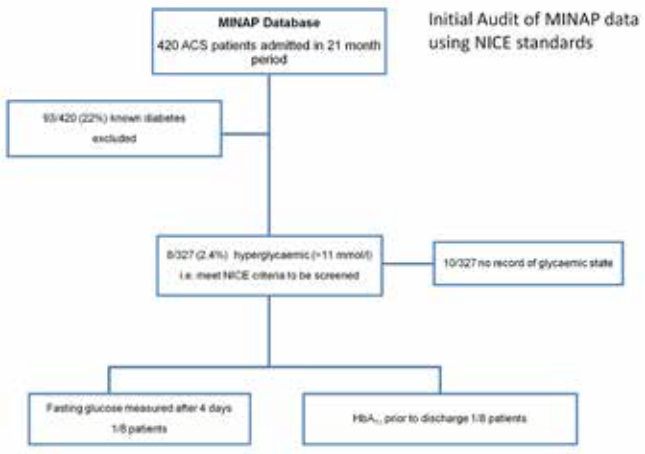

Fig 1. Initial Audit of NICE Guidelines

Service Improvement Project

HbA_{1c} testing was recommended for screening in ACS regardless of glycaemic status during a service improvement project.

No patients tested were known to have medical conditions that could influence HbA_{1c} measurement. This included factors that affect erythropoiesis such as iron or B12 deficiency or supplementation, haemoglobinopathies and conditions that affect erythocyte life span such as splenectomy or splenomegaly.[6] Patients were not screened for chronic aspirin use which may cause a falsely low HbA_{1c} in certain assays.[6]

We categorised patients according to WHO criteria as "probable diabetes" (HbA_{1c}≥48 mmol/mol), "high risk" (HbA_{1c} 42-47 mmol/mol) and "not diabetes" (HbA_{1c}<42 mmol/mol).[6,7]

RESULTS

Over the previous 21 month period 93 of 420 (22%) ACS patients were identified with established diabetes. Of the remaining 327 patients, only 8 (2.4%) met NICE criteria for diabetes screening and only one patient was tested (Figure 1).

During the service improvement phase, 17 of 66 ACS patients had established diabetes. Of the remaining 49 patients only 2 met criteria for screening and neither had fasting glucose tested. 26 of 49 patients (52%) were tested with a mean HbA_{1c} level of 45.1 mmol/mol (range 31.1-65.0 mmol/mol).

7/26 (26.9%) of these were categorised as "probable diabetes", 10/26 (38.4%) were at high risk of developing diabetes and 9/26 (34.6%) had diabetes excluded (Figure 2).

DISCUSSION

Diabetes mellitus is increasingly prevalent and is a significant public health challenge.[2,6] Diabetes is associated with increased cardiovascular risk, and in patients presenting with acute coronary syndrome; it is an independent predictor of mortality and is associated complications including heart failure and bleeding.[8] For these reasons, the European Society of Cardiology (ESC) recommend that all patients admitted with ACS are screened for diabetes and have recently recommended the adoption of HbA_{1c} as a screening tool in line with the World Health Organisation.[8]

Targeted diabetes screening as advocated by NICE using hyperglycaemia as an inclusion criterion appeared to lack sensitivity and was not readily implemented in clinical practice during our recent audit. Use of universal HbA_{1c} screening on admission appeared to be more practical and effective with improved detection rates in this setting. In our service improvement project we identified a higher prevalence of probable diabetes and pre-diabetes cases (65.4%) compared with earlier published series.[3,4,5,6] We detected a prevalence rate of established diabetes of around 22%, which is similar to earlier published reports.[3,4,5]

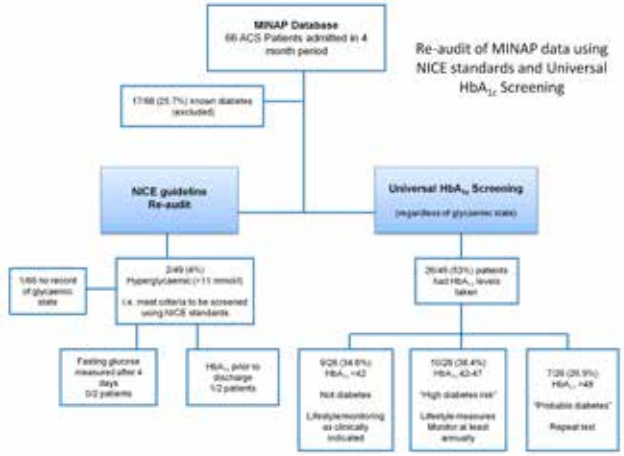

Fig 2. Re-audit of MINAP using NICE standards and Universal HbA_{1C} Screening Project

Poor utilisation of current NICE screening may reflect the guidelines complexity, limited awareness and the small numbers of qualifying patients. In addition, patients may not be screened with day four fasting glucose measurement due to increasingly shorter length of stays.

There are a number of potential benefits in using HbA_{1c} as a screening tool for diabetes. Firstly, it is less likely to be impacted by short term fluctuations in glycaemic control, including stress hyperglycaemia. While HbA_{1c} testing is more expensive (£6.81) than fasting plasma glucose (£2.05) it compares favourably to the cost of an oral glucose tolerance test at £7.48.[9] HbA_{1c} testing is not recommended for screening in type 1 diabetes, secondary diabetes or pregnancy. In these scenarios, established fasting plasma glucose and/or glucose tolerance testing criteria remain valid and are recommended for use. Other confounders include alcoholism, chronic renal failure and conditions affecting erythropoesis.[6]

This study has a number of limitations. As this was an audit and service improvement project it was not designed to determine sensitivity and specificity against a gold standard test. Despite staff education a significant proportion of

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patients (47%) were not tested using HbA_{1c}. Had we achieved screening of consecutive ACS patients, we would have anticipated a higher proportion of patients testing positive for diabetes. Nevertheless, introduction of HbA_{1c} as a screening test for diabetes during this service improvement project was considered to be of clinical value as a practical, widely accessible, and reproducible method for the purpose for ACS patients who have been hospitalised. Indeed, this approach has utility, including for patients attending other cardiac services such as rapid access chest pain clinics.[10]

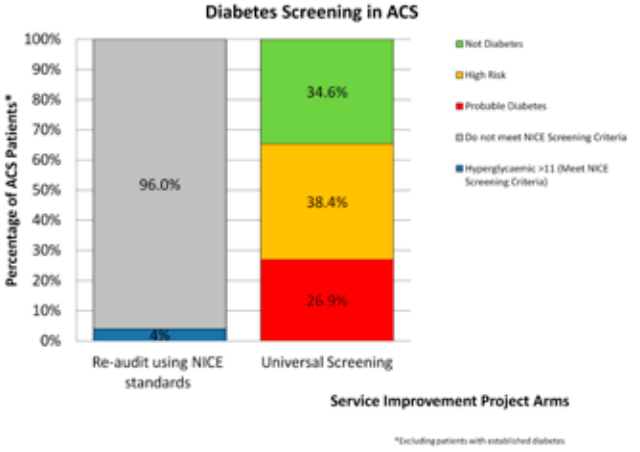

Fig 3. Comparison of NICE Guidelines to Universal Screening strategy

This service improvement project revealed a missed population of patients with "probable diabetes" (26.9%) and at "high risk" (38.4%) of diabetes who were largely previously unscreened when NICE guidance was followed (Figure 3). We believe that introduction of HbA_{1c} as part of an ACS admission profile offers a simplified and accessible screening test for the early diagnosis and management of patients with diabetes. Perhaps it is time for a reappraisal of UK guidelines?

The Authors have no conflict of interest.

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Clinical Paper

The male to female ratio at birth in the Republic of Ireland and Northern Ireland: influence of societal stress.

Victor Grech

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Provenance: externally peer reviewed.

ABSTRACT

Introduction: Male live births occur slightly in excess of female births. The ratio of male divided by total births is referred to as M/F. Many factors reduce M/F including toxins, stress, and privation, with excess male foetal loss. "The Troubles" (1969-1998) of Northern Ireland (NI) and the economic downturn of Republic of Ireland (ROI) from 2007 posed stresses with corresponding controls. This study analysed M/F in NI and ROI.

Methods: Annual male and female live births in NI and the ROI were compared using chi tests.

Results: M/F was significantly higher in NI than in ROI. M/F in NI dropped after 1974. M/F rose in ROI up to 1994, then fell.

Discussion: Violence-related stress may have been the cause for the M/F drop in NI. Economic improvement followed by recession may have caused parallel M/F changes in ROI. These findings agree with the stress hypothesis of M/F.

INTRODUCTION

The ratio of male to female live births is expressed as the ratio of male live births divided by total live births. It almost invariably exceeds 0.5 and is conventionally referred to M/F.[1]

In man, there is a slight excess of male live births (circa 3%). However, this ratio varies secularly,[2] and by region. For example, gendercide, the selective abortion of female infants in Asian societies that highly prize male offspring has resulted in a highly skewed ratio in China, Korea and India, with the ensuing loss of tens of millions of women.[3]

A huge number of additional factors have been implicated as affecting M/F.[1,4] Most factors tend to reduce the ratio by inducing spontaneous abortions which affect male foetuses more than female foetuses. These influences include exposure to toxins,[1,4] stress,[5] and privation.[6]

Stress has been shown to be particularly important in reducing M/F. For example, after the September 11 2001 terrorist attacks on New York, M/F fell sharply just a few months later and recovered equally quickly.[5] This effect was also noted on the other side of the continent in California which was not directly affected by the violence unleashed in the attack.[7] A transient drop was also noted in the entire country with a corresponding male foetal loss.[8]

Similarly, the 10-day war in Slovenia in 1991 sufficed to transiently but significantly depress M/F,[9] as did the economic turmoil and uncertainty in East Germany in 1991 following the reunification of Germany in 1990.[10]

Ireland provides an interesting location for the analysis of M/F since the country is divided into two: Republic of Ireland and Northern Ireland. Rising standards of living in Northern Ireland (NI) along with the flourishing of industry and manufacturing resulted in better economic conditions in NI than in The Republic of Ireland (ROI).[11] The situation was reversed with the onset of sectarian violence in NI and a booming economy in ROI.

NI has had a turbulent history, with a minority Catholic population at odds with the Protestant community.[11] In the early 20th century, the Protestant and Catholic communities became divided over the issue of home rule. Most Irish Catholics (republicans/separatists) desired complete independence from Britain as it was perceived that this would lead to more equal treatment and less discrimination in everyday life on the basis of religious belief, but Irish Protestants (loyalists/unionists) resisted.[11]

Violence erupted in the late 1960s as the incumbent Protestant administration's attempts to resolve discrimination against the Catholic minority were perceived to be inadequate by the Catholic community and excessive by the Protestant majority.[12] "The Troubles" colloquially refers to these dark years of Irish history and are considered to have commenced in 1969 and ended in 1998.[12]

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Table 1:

M/F for the two Irelands, in 5-year intervals

	1950-54		1955-59		1960-64		1965-69		1970-74		1975-79		1980-84	
	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI
M	74244	162524	77252	155258	84761	158723	85954	159865	77741	173377	67824	178020	70433	179294
F	69574	153642	72420	148044	79467	150937	80180	151098	72464	163819	64521	168606	66690	168648
T	143818	316166	149672	303302	164228	309660	166134	310963	150205	337196	132345	346626	137123	347942
UCI	0.5188	0.5158	0.5187	0.5137	0.5185	0.5143	0.5198	0.5159	0.5201	0.5159	0.5152	0.5152	0.5163	0.5170
M/F	0.5162	0.5140	0.5161	0.5119	0.5161	0.5126	0.5174	0.5141	0.5176	0.5142	0.5125	0.5136	0.5136	0.5153
LCI	0.5136	0.5123	0.5136	0.5101	0.5137	0.5108	0.5150	0.5123	0.5150	0.5125	0.5098	0.5119	0.5110	0.5136
ch		1.9		7.2		5.4		4.7		4.8		0.5		1.1
p		0.168		0.007		0.020		0.031		0.029		0.496		0.300
	1985-89		1990-94		1995-99		2000-04		2005-09		2010-		Total	
	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI	NI	ROI
M	70211	148592	64664	131325	61001	134229	56003	152144	61870	177303	25742	148775	877700	2059429
F	66189	140272	61789	123057	57786	125881	52822	144215	58722	169215	24846	141587	827470	1949021
T	136400	288864	126453	254382	118787	260110	108825	296359	120592	346518	50588	290362	1705170	4008450
UCI	0.5174	0.5162	0.5141	0.5182	0.5164	0.5180	0.5176	0.5152	0.5159	0.5133	0.5132	0.5142	0.5155	0.5143
M/F	0.5147	0.5144	0.5114	0.5163	0.5135	0.5160	0.5146	0.5134	0.5131	0.5117	0.5089	0.5124	0.5147	0.5138
LCI	0.5121	0.5126	0.5086	0.5143	0.5107	0.5141	0.5116	0.5116	0.5102	0.5100	0.5045	0.5106	0.5140	0.5133
ch		0.0		8.1		2.1		0.5		0.7		2.1		4.4
p		0.835		0.005		0.151		0.485		0.408		0.144		0.036

In economics, a recession is defined as a business cycle contraction with a slowdown in economic activity that produces negative gross domestic product values for at least two consecutive quarters. A depression is a sustained and severe recession accompanied by an increase in unemployment and bankruptcies and a decrease in the availability of credit and of all economic activities in general. Ireland was hard hit, commencing in 2007.[13]

The two parts of Ireland constitute parts of a relatively small island with very similar ethnic and racial mixes, and may be considered as controls for each other with regard to M/F. This study was carried out in order to compare M/F in the two parts during the Troubles and after the onset of the Irish economic recession.

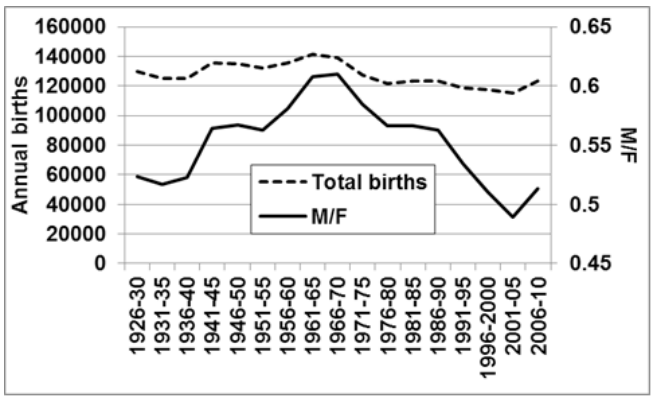

Fig 1. M/F in Northern Island, 1926-2010 and total births.

METHODS

For ROI, annual male and female live births were obtained from a World Health Organisation Database (HFA (Health for All) Database) for the period 1950-2013.

For NI, the equivalent data was available from the Northern Ireland Statistics and Research Agency (NISRA) website, as well as data going back to 1926.

Data available relates to registered dates and not birth dates but this makes no practical difference for the purposes of this study.

Excel was used for data entry, overall analysis and charting. The quadratic equations of Fleiss were used for exact calculation of 95% confidence intervals for ratios.(14) Chi tests and chi tests for trends for annual male and female births were used throughout using the Bio-Med-Stat Excel add-in for contingency tables.[15] SPSS was used to perform Spearman correlation. A p value < 0.05 was taken to represent a statistically significant result.

RESULTS

Five year M/F and total M/F are depicted in table 1. For the period studied wherein overlap occurred (1950-2011), M/F was overall significantly higher in NI than in ROI.

NI

There was a rising trend in M/F ratios up to the early 1970s (figure 1). M/F dropped suddenly after 1974 (1970-74 vs. 1975-79; chi=7.2, p=0.007 – figure 1) and this drop continued until the end of the study (chi for trend=5.5, p=0.02). M/F fluctuations were closely paralleled by total births (figure 1) and correlated well (rho=0.69, p=0.002).

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ROI

M/F in ROI rose steadily between 1955 and 1994 (chi for trend=8.4, p=0.004 – figure 2), remained constant for the next five years then fell to the end of the study period (1995-2013; chi=8.9, p=0.003). Annual births increased until the early 1980s and then dropped markedly down to the year 2000, rising again to early 1980s levels.

Comparison

For 1955-1974, M/F in NI was significantly higher than in ROI (table 1). M/F in NI then dropped to levels below ROI up to 1994, but only to statistically significant levels for 1990-94. M/F continued to be higher (non-significantly) in ROI till 1999, dropped (non-significantly) to below ROI levels till 2009, then showed slight recovery.

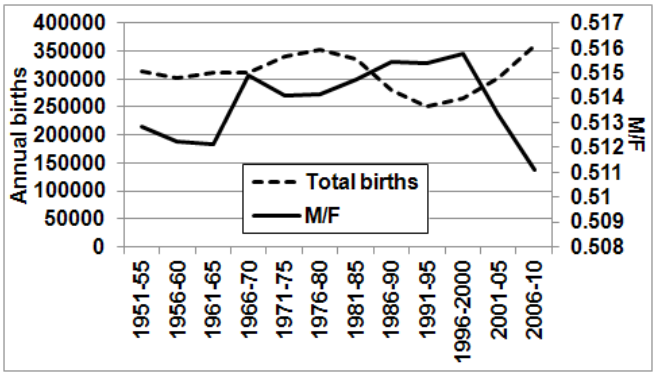

Fig 2. M/F in the Republic of Ireland, 1951-2010 and total births.

DISCUSSION

The overall higher M/F in NI when compared to the ROI agrees with the economic stress theory in that the less affluent south had a lower M/F than the more affluent north. The rise in M/F in ROI would suggest that if the economic stress hypothesis alone impinged on M/F, then the economy in NI was not very badly affected when compared with the ROI. However, the rise in M/F may also have been influenced by other factors that were not available for analysis.

The drop in M/F in NI commenced in the early 1970s some years after the onset of the Troubles in1968/9. The Troubles brought years of bloody civil conflict. By 1997, 3600 deaths, 34000 shootings and 14000 bombings had been recorded and the majority of deaths were civilian.[16,17] The population stress engendered in this period is evidenced by the residual psychological trauma. Indeed, Northern Ireland has the world's highest reported rates of post-traumatic stress disorder rates which per capita exceed that of war-torn regions such as Israel and Lebanon.[18] It is estimated that the annual combined direct and indirect costs of treatment is around £175 million based on the year 2008 as a sample year.[16] Progressively increasing levels of stress as The Troubles escalated may have therefore surpassed the level wherein M/F becomes negatively affected, resulting in a lowering of M/F several years into the this period.

The oral contraceptive pill was introduced in the early 1960s and this may have been associated with the decline in births.[19] However, this is probably not related to the decline in M/F in this period since effective contraception leads to higher maternal age which is in turn associated with an increase in M/F.[1] This is thought to be due to normal higher circulating levels of gonadotrophins in older women which is in turn associated with higher levels of M/F.[1]

In contrast, the annual number of births in ROI continued to increase until the early 1980s and this may be related to the slower introduction of the oral contraceptive pill in this Catholic community. The increase in births from the early 1990s may be related to the influx of immigrants and asylum seekers that occurred around this time.[19]

The situation for the ROI was different and although The Troubles did not directly impinge on the Republic, the effects of the global economic depression was devastating.

The international financial crisis was precipitated on the 9th August 2007 when one of the world's largest banks (BNP Paribas) acknowledged a looming debt crisis by closing two funds. It was at this point that the world's financial services acknowledged that tens of trillions of dollars of financial derivatives were of doubtful security, leading to a convulsion in the global banking system.[20]

Prior to 2007, the ROI economy was touted as one of the most successful models worldwide. Economic growth had commenced in the mid-1990s to the early 2000s due to catch-up expansion to reach levels attained by Europe's other economies. Growth was encouraged by favourable demographics which produced an increase in the total number of available workers who also had a high level of education. This precipitated a second and more treacherous growth period fuelled by credit expansion and an increase in individual personal indebtedness. This in turn caused property prices to soar to unsustainable levels, masked by unwise bank lending.[21,22] It is perhaps for this reason that M/F rose continually up to the 1990s.

Irish banks were not immune to the problem and were highly vulnerable and exposed. Property prices fell and banks took huge losses.[21,22] The economic recession may potentially have been responsible for the fall in M/F during this period.

Whatever the nature of stress, it appears capable of lowering M/F. It has been suggested that the process is via a an excess of prenatal foetal losses which are skewed such that males are lost at a higher rate than females.[5,8]

This is in agreement with the Trivers-Willard hypothesis (1973) which proposes that natural selection has favoured parents who bias offspring gender in favour of the sex with the best reproductive prospects in accordance with then extant peri-conceptual and gestational conditions.[23] Briefly, poor conditions may preclude successfully carrying a male baby to term since a male requires greater maternal gestational resources.[24,25] Should such pregnancies go to term, a frail male may ensue who will compete unfavourably for mating

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privileges with other stronger males. However, even under adverse circumstances, a female foetus may be successfully carried to term, survive, and eventually produce offspring of her own.

Conversely, under favourable conditions, carrying a male to term will result in a good quality male with far more reproductive opportunities than a good quality female who is hindered by a nine month gestational period and subsequent nursing. Thus, since resource abundance or scarcity affects reproductive success, the Trivers–Willard hypothesis predicts that natural selection will favour parents who tend to produce females under poor conditions and males in good circumstances.[23]

Natural disasters have also been shown to lower M/F and these have included earthquakes,[26] floods and the Great Smog of London in 1952.[27] In conclusion, M/F was higher to be highest in NI and ROI stress-free times of affluence, and lower in economically depressed times and during periods of stress. Birth rates may also have played a role but this only appears to have influenced NI.

The overall findings of this study appear to be agreement with the Trivers-Willard hypothesis. M/F may provide a sensitive indicator of a population's stress, whether caused by economic hardship or internal violence.

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The author has no conflict of interests:

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Clinical Paper

Intravesical chondroitin sulphate for interstitial cystitis/painful bladder syndrome

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ABSTRACT

Introduction: Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic inflammatory condition of the bladder. Bladder instillation is one avenue of treatment but evidence for its effectiveness is limited. Chondroitin sulphate solution 2.0% (Urocyst) is a glycosaminoglycan (GAG) replenishment therapy instilled for patients with IC/PBS. We assessed its effectiveness for treating IC/PBS in Northern Ireland.

Methods: Patients with IC/PBS were assessed with the O'Leary-Sant interstitial cystitis index score and global response assessment questionnaire prior to commencing treatment. Assessment with these questionnaires was performed after 6 treatments (10 weeks) and again after 10 treatments (24 weeks). Assessment end points were pain, urgency, symptom score and problem score.

Results: Data was collected on 10 patients, 9 female and 1 male. 6 patients had failed RIMSO-50 dimethyl sulphoxide (DMSO) 50% treatment prior. At baseline the mean pain score was 6.6, urgency score 7.00, symptom score 13.5 and problem score 12.5. After 24 weeks the mean pain score fell to 2.0, urgency score to 1.80, symptom score to 6.89 and problem score to 5.67. At 10 weeks the global response to treatment was 100%. Nocturia was the first symptom to improve with urgency and pain following. No side effects were noted during instillation and all patients tolerated the treatments.

Conclusion: IC/PBS is a difficult disease to treat. It requires a multimodal approach. We found that intravesical chondroitin sulphate reduced pain, urgency and O'Leary-Sant symptom and problem scores in patients with IC/PBS. All patients tolerated the treatment and no side effects were reported.

INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS), is a painful and debilitating chronic inflammatory disorder of the bladder. The disorder can have a significant impact on many aspects of a patient's life and some have suggested that the quality of life of IC/PBS patients is equivalent to those with end stage renal failure.

The disorder is characterized by suprapubic pain, often associated with urination, urinary frequency, urgency, and pressure in the bladder or pelvis. Patients may also experience nocturia and pelvic floor dysfunction making urination difficult and sexual intercourse painful. Symptoms can fluctuate from patient to patient, and from time to time for a given patient, making it a difficult condition to diagnose and manage.

Various different treatment modalities have been used to treat IC/PBS. Oral medications include pentosan polysulfate (Elmiron) and amitriptyline. Pain control is a major issue and some patients may need non-steroidal anti-inflammatory (NSAIDS) and/or narcotics. Second line treatments are bladder instillations or bladder coating therapies. Bladder coating treatments have shown positive results in the management of IC/PBS and are believed to replace the deficient glycosaminoglycan (GAG) layer on the bladder wall however the evidence for its effectiveness is limited. In this study we prospectively sought to determine the effectiveness of Chondroitin sulphate solution 2.0% (Urocyst) for the treatment of IC/PBS.

METHODS

A prospective interventional single centre study of 10 patients with IC/PBS was conducted. Eligible patients were male or female patients, 18 years or older with a diagnosis of IC/PBS confirmed by cystoscopy, hydrodistension and bladder biopsy. Exclusion criteria included recurrent urinary tract infection (UTI), overactive bladder, bladder cancer or cystitis of another aetiology. Patients who had failed a previous intravesical therapy were included in the study.

This study was conducted in compliance with Good Clinical Practice guidelines. Chondroitin sulphate solution is given directly into the bladder by urinary catheter by a urology nurse

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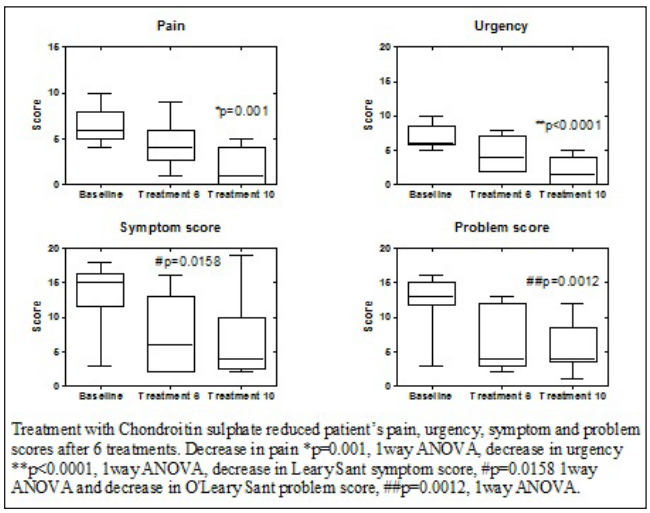
specialist. Patients were then commenced on instillations of chondroitin sulphate solution 2.0% intravesical therapy for 24 weeks. Six treatments were administered in the first 10 weeks and 4 treatments were administered over the next 14 weeks. At each treatment 20ml of the solution was instilled with patients were instructed to hold it in the bladder for at least 30 minutes.

The co–primary efficacy end points were change from baseline in the number of pain and urgency episodes as assessed by interstitial cystitis symptom index responders at week 10 and week 24. Secondary outcome measure is global response assessment (GRA) responders at week 10 and at week 24. Baseline assessment of symptoms severity was performed by assessment with O'Leary-Sant interstitial cystitis index score. This is a questionnaire filled out by the patient encompassing symptoms of urgency, frequency, nocturia and pain/burning. It has been shown to be a valid and reliable method of measuring change in IC symptoms. Response to treatment was assessed with the global response assessment questionnaire. The GRA measures overall improvement with therapy. It is now used as the primary end point in clinical trials of therapies for IC/PBS. Responders to treatment is indicated by a "marked" or "moderate" improvement as assessed on the 7 point scale. Unless otherwise stated, data is represented as mean (interquartile range: IQR). Differences in distribution of clinical data and the development of a SSI were evaluated using 1way ANOVA. P value less than 0.05 was assumed to be significant. All calculations were done using Prism version 5.0 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Patient demographics and baseline IC/PBS related variables

There were 10 patients included in the study; 9 (90%) female and 1 (10%) male. Mean age was 52 (27 – 81) years. Baseline assessments showed 7 patients (70%) had moderate IC/PBS and 3 patients (30%) had severe IC/PBS. There were no patients with mild IC/PBS. Mean urinary frequency prior to treatment was 12.6 IRQ (8.4-15.5) voids per day and all patients had remained symptomatic on oral medical therapies (5 patients (50%) were taking the tricyclic anti-depressant amitriptyline). 5 patients (50%) were taking hormone replacement therapy (HRT). No patient was taking antihistamines, antibiotics, anticholinergics or Pentosan polysulphate (Elimiron). 6 (60%) patients had failed previous intravesical RIMSO-50 dimethyl sulphoxide (DMSO) 50% w/w treatment prior to instillation of chondroitin sulphate. No patients had been treated with Hyaluronate (Cystistat), Chondroitin sulphate 0.2% or Heparin (Table 1). Baseline mean pain score was 6.6 IRQ (5-8), urgency score 7.00 IRQ (5.75-8.5), O'Leary-Sant symptom score 13.5(11.5-16.3) and O'Leary-Sant problem score 12.5(11.75-16) (Table 2).



Treatment with Chondroitin sulphate reduced patient's pain, urgency, symptom and problem scores after 6 treatments. Decrease in pain *p=0.001, 1way ANOVA, decrease in urgency **p<0.0001, 1way ANOVA, decrease in Leary Sant symptom score, #p=0.0158 1way ANOVA and decrease in O'Leary Sant problem score, ##p=0.0012, 1way ANOVA.

Fig 1. Treatment response

10 week assessment

After 6 intravesical chondroitin sulphate treatments the mean pain score fell to 4.3 (2.75-6), urgency score to 4.4 (2-7), O'Leary-Sant symptom score 7.5 (2-13) and O'Leary-Sant problem score to 6.5 (3-12). The global response to treatment was 80% (i.e. patients had a marked" or "moderate" improvement) (Table 2). Patients reported that nocturia was the first symptom improved followed by urgency and pain.

TABLE 1.

Demographics and IC related variables at baseline

Variable	Total (N) %
Age of patient (mean, IRQ)	52 (27 – 81)
Sex of patient	
Male	9 (90%)
Female	1 (10%)
Severity of IC	
Mild	0 (0%)
Moderate	7 (70%)
Severe	3 (30%
Urinary frequency, (mean, IRQ)	12.6 (8.4-15.5)
Oral therapy:	
Antidepressants	5 (50)
Antihistamines	0 (0%)
Hormonal agonists or antagonist*	5 (50%)
Pentosan polysulphate (Elimiron)	0 (0%)
Antimicrobials	0 (0%)
Anticholinergics	0 (0%)
Prior intravesical therapy:	
Hyaluronaic acid (Cystistat)	0 (0%)
Heparin 10,000 IU	0 (0%)
RIMSO-50 dimethyl sulphoxide (DMSO)	6 (60%)

N indicates number of patients; IQR, interquartile range; IU, International units. *Hormone replacement therapy

24 week assessment

After 10 intravesical chondroitin sulphate 2.0% treatments the mean pain score fell to 2.0 (0-4), urgency score to 1.8 (0-4), O'Leary-Sant symptom score 6.89 (2.5-10) and the O'Leary-Sant problem score 5.67 (3.5-8.5) (Table 1). The fall in score was significant compared to the baseline assessment; decrease in pain score p=0.001, urgency, p<0.001, O'Leary-Sant symptom score p=0.0158 and O'Leary-Sant problem score p=0.0012 (1way ANOVA). The global response to treatment was 70% (Table 2). No side effects were reported during instillation and all patients tolerated the drug for the required length of time.

DISCUSSION

IC/PBS is a chronic condition defined by the International Society of Bladder Pain Syndrome (ESSIC) as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency in the absence of proven urinary infection or other

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TABLE 2.

Treatment response symptom scores

End points	Baseline	Treatment 6	Treatment 10	*P Value
Pain, mean (IRQ)	6.60 (5-8)	4.30 (2.75-6)	2.00 (0-4)	0.0001
Urgency, mean (IRQ)	7.00 (5.75-8.5)	4.40 (2-7)	1.80 0-4)	< 0.0001
Symptom score, mean (IRQ)	13.50 (11.5-16.2)	7.50 (2-13)	6.89 (2.5-10)	0.0158
Problem score, mean (IRQ)	12.50 (11.75-15)	6.50(3-12)	5.67(3.5-8.5)	0.0012
GRA	0%	80%	70%	

Treatment response to chondroitin sulphate, baseline symptoms and symptoms after 6 treatments and 10 treatments. IQR, interquartile range; GRA, global assessment response. *All assessed with the 1way ANOVA.

obvious pathology". Patients with cystoscopic features such as glomerulations and Hunner's ulcer are classified as IC and those without as having painful bladder syndrome (PBS); both conditions are encompassed by the term bladder pain syndrome (BPS)[1]. ESSIC have proposed a classification system based on cystoscopy, hydrodistension and biopsy results.[4] IC/PBS has been reported to affect up to 6.53% of the population and is associated with other diseases including IBS, fibromyalgia, depression, vulvodynia, migraine and SLE. [2, 3]

There is currently no definitive pathogenesis for IC/PBS however it is generally thought that an initial insult to the bladder triggers endocrine, inflammatory and neurological changes which may result in defects in the urothelial GAG layer of the bladder wall; exposing submucosal nerve fibres to the toxic constituents of urine. Additionally a ten-fold increase in the number of mast cells in the bladder tissue has been noted in a subset of IC/PBS patients. Neurogenic inflammation can result in bladder wall pain with an increased density of peripheral nerves and neuromediator release confirmed in several studies.[3]

Management of IC/PBS is multidisciplinary and multi-faceted. In addition to lifestyle modification pain control is the first line of treatment with various studies showing amitriptyline, cimetidine and oral pentosan polysulphate to improve pain control.[5] Second line treatments include a wide range of intravesical therapies that have been developed with the aim of replacing the deficient GAG layer of the bladder wall. These include sodium hyaluronate (Cystostat), pentosan polysulphate (Elmiron) and chondroitin sulphate 2.0% (Uracyst). Surgical intervention is often deferred until all other available therapies have failed to control symptoms or improve quality of life.

We assessed chondroitin sulphate as an intravesical treatment for IC/PBS. The goal of treatment is to replace the deficient GAG layer in the bladder and improve symptom control. Using the O'Leary-Sant symptom and problem score as well as mean pain and urgency score we showed an improvement of the scores with intravesical chondroitin sulphate 2.0% treatment in 10 patients with moderate/severe IC/PBS. A response to treatment was noted in patients who had failed a different intravesical bladder therapy (DMSO). Reduction in symptoms was noted after 6 treatments (10 weeks) and continued treatment course reduced symptoms further. All symptom reduction scores were statistically significant, however the reduction in pain and urgency scores was considerably more than O'Leary-Sant scores. The global response to treatment was 80% at 10 weeks and 70% at 24 weeks indicating that that the majority of patients noted a marked or moderate response to the administration of chondroitin sulphate. No patient reported any significant side effects or symptom deterioration due to the treatment. All patients tolerated the catherisation.

These findings are in agreement with the current literature. A study by Steinhoff et al with a group of 18 patients treated with chondroitin sulphate showed a response to treatment in 12 of 13 patients.[6] Another trial by Sorenson et al showed an average improvement in symptoms in 73.1% of patients with refractory IC/PBS with a more concentrated solution needed in 8 patients.[7]

Chondroitin sulphate is priced at £87.50 per instillation which is cheaper than Cystistat (sodium hyaluronate £98 per instillation) and Rimso-50 (DMSO - £101+VAT per instillation). Our findings suggest that chondroitin sulphate 2.0% is a valuable treatment for the short term management of symptoms due to IC/PBS, particularly for patients troubled with pain and urgency.

CONCLUSION

Management of IC/PBS is difficult due to the multifactorial aetiology and diagnostic uncertainty as well as multiple treatment options. A multimodal approach is often necessary; intravesical treatments aimed at replenishing the GAG layer of the bladder are one option for treatment. Although our study has small numbers we demonstrated that intravesical chondroitin sulphate 2.0% is an effective treatment which is well tolerated by patients with no side effects reported.

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Clinical Paper

Assessing the need for low secure care in Northern Ireland

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Aims and method To assess the need for the provision of low secure care in Northern Ireland. A survey of the providers of healthcare in Northern Ireland was conducted using a study tool based on Royal College of Psychiatrists Low Secure Network Standards admission criteria.

Results A total of 105 patients were assessed as needing low secure care including 93 patients currently admitted to hospital in the region and 12 patients admitted to hospital outside of the region.

Clinical Implications The results of this study are similar to previous estimates of need for the provision of low secure care in the UK. The results provide information likely to be of assistance in the commissioning of low secure services.

Declaration of Interest None

It is self evident that what is needed in one part of a service will depend on the provision in other parts of the service. Mental Health Services in Northern Ireland have undergone substantial change in the past ten years through the implementation of the Bamford Review and Transforming Your Care.[1 2 3] A significant consequence has been a change in the provision of inpatient care. A reduction in average available mental health beds by 35% over the past 5 years combined with high occupancy rates (90%) and a 19% reduced length of stay reflect a reduction in inpatient bed availability.[4]

A regional network of forensic mental health services has been developing including the opening of the first medium secure unit, Shannon Clinic, in 2005, the development of community forensic mental health teams, and mental health services in prison.

There are plans for the closure of long stay wards over the next few years.[4] The Bamford Adult Implementation Group is chaired by commissioners and is tasked with planning the provision of low secure care. Low secure units provide rehabilitation for patients who need to be detained to hospital under mental health legislation. The criteria for detention to hospital are that the person suffers from a mental illness and failure to detain them would create a substantial risk of serious physical harm to self or others.

The secure component of care consists of *physical* security, such as locked doors and fences, *procedural* security, such as control of various items coming into the ward, and *relational* security, which involves fostering therapeutic relationships through an in depth knowledge of the patient's illness and behaviour. Low secure rehabilitation aims to reintegrate the patient back into society through multidisciplinary treatment of their illness and a reduction in the risk of harm that led to their detention.

This survey aimed to assess the current need for the provision low secure services in the region. Unlike other parts of the UK, there is no private sector provision of secure mental healthcare in Northern Ireland.

METHOD

A study tool was designed based on Royal College of Psychiatrists Low Secure Network Standards admission criteria.[5] The Associate Medical Director or equivalent and Director of Mental Health (or their nominee) for each Health and Social Care Trust were surveyed and sent the study tool in order to ascertain the number of patients in the Trust area who needed low secure care. The Public Health Agency was also surveyed to assess the low secure need of those patients currently being cared for in other parts of the UK.

STUDY TOOL

Inclusion criteria

1. *May be detained under mental health order (not necessarily presently detained)*
2. *Clinical risk or legal requirement for secure care*
3. *M&F > 18 years old*
4. *May benefit from rehabilitation*
5. *Offending with low levels of violence*
6. *Patient does not require medium or high secure care*

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Exclusion criteria

1. *<18 years old*
2. *Primary substance misuse without mental illness*
3. *Complex needs that can be managed in PICU or open ward.*

Patient Location	**Number of patients**
Low secure/locked rehabilitation ward	
Open rehabilitation ward	
Acute inpatient ward	
PICU	
Other	
Total	

RESULTS

All of the five HSC Trusts and the Public Health Agency responded to the survey and provided the following data

	Patients needing Low Secure Care
Northern HSC Trust	17
South Eastern HSC Trust	13
Southern HSC Trust	18
Western HSC Trust	17
Belfast HSC Trust	28
Public Health Agency	12
Total	105

Of the 105 patients, 43 were in low secure or locked rehabilitation wards, 3 were in PICU, 18 were in acute inpatient wards, 8 were in a medium secure unit and 4 in a neurorehabiliation unit. 17 patients were in distributed across acute inpatient units, PICU and locked rehabilitation. Provision of low secure or locked rehabilitation wards in a Trust area appeared to be associated with fewer patients in acute inpatient wards identified as needing low secure care.

DISCUSSION

Northern Ireland has some significant differences in the provision of secure hospital care in comparison with the rest of the UK and Ireland, most notably that there is no provision of private sector secure hospital care or provision of high secure care. The result of this study that 105 patients require low secure care in a population of 1.8 million fits comfortably with the low secure prevalence of 4.6 per 100,000 in England.[6]

The results of this study provide guidance for the commissioning of low secure services in Northern Ireland which will be conducted in line with the Bamford Review plan for secure rehabilitation for those patients who require treatment under the auspices of mental health legislation.

The strengths of the study were the 100% response rate from the providers and commissioners of care, and the use of a study tool based on Royal College of Psychiatrists Quality Network Standards. In addition, rather than using a point sample or past trends, the methodology measured the current need for low secure services.

A limitation of the study was the service level rather than individual assessment of need. The methodology also includes only those patients known to local psychiatric services. Patients not known to local psychiatric services may also require low secure care but we expect that most needing low secure would be known to services.

A decision was taken not to include prisoners in the methodology of this study due to pending changes in mental health legislation. High levels of psychiatric morbidity exist in prisons, with 90% of prisoners suffering from at least one of: neurosis, psychosis, personality disorder, alcohol abuse or drug dependence.[7] Comorbidity of multiple diagnoses of mental disorders is also common and has been estimated at 40-90%.[8] It would be reasonable to expect that some prisoners may need treatment in a low secure unit, either through a court diversion scheme or by transfer from prison to hospital.

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Paper

Tenckhoff Peritoneal Dialysis Catheter Insertion in a Northern Ireland District General Hospital.

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ABSTRACT

Introduction: Chronic kidney disease (CKD) affects approximately 5% of the population. Based on 2014 data, peritoneal dialysis (PD) is underutilised in Northern Ireland with a prevalence of only 11% in patients requiring renal replacement therapy (RRT). Recent National Institute of Clinical Excellence (NICE) guidelines aim to increase the rate of PD utilisation to 39% amongst patients requiring RRT. In order to implement these guidelines, nephrologists must have access to a reliable, effective PD catheter insertion service. The aim of this study was to assess the outcomes of PD catheter insertions and incident rates of PD use in a single centre in anticipation of a potential increased uptake.

Methods: A retrospective analysis was conducted of all patients who underwent PD catheter insertion between April 2003 and October 2011. Case notes were reviewed for demographic information, complications, need for re-intervention, and primary catheter patency at 12 months. The UK Renal Registry annual reports were also reviewed for data on annual uptake of PD in our institution.

Results: Fifty-four patients underwent PD catheter insertion between 2005 and 2011; 61% were male with a median age of 58 (range 21-82) years. Early complications (≤30 days) included bowel perforation (n=1) and wound infection (n=2). During this study period 17 (31%) patients required manipulation or reinsertion for catheter obstruction/migration. The primary catheter patency at 12 months was 76%. The average uptake of PD as the first treatment modality (incident use) was 21.3% compared to a Northern Ireland (NI) average of 12.4%.

Conclusion: Complication rates were comparable to the International Society of Peritoneal Dialysis (ISPD) guidelines in this case series and PD uptake was higher than the NI average. Therefore, local provision of an expert surgical PD catheter insertion service may potentially facilitate an increased uptake of this modality amongst RRT patients but further research is warranted.

INTRODUCTION

Chronic kidney disease is a major burden in the United Kingdom (UK) affecting approximately 5% of the population.[1] Annually, 2% of the NHS budget is spent on renal replacement therapy (RRT) alone.[1] In June 2014, there were more than 720 people on chronic dialysis in Northern Ireland (NI). Currently 620 of these patients require hospital based haemodialysis (HD), 35 have independent home haemodialysis and 80 utilise peritoneal dialysis (PD). [1] Peritoneal dialysis is underutilised in NI with only 11% of patients on RRT receiving PD compared to a 15% average in the rest of the UK in 2014.[1,2]

Patients who receive HD attend hospital approximately three times a week for 4-6 hours at a time.[3] In HD, waste products are removed from the blood by extracorporeal means via a dialysis machine.[3] In continuous ambulatory peritoneal dialysis (CAPD), the metabolic products are removed via a fixed catheter in the abdominal cavity where dialysis fluid is exchanged using the peritoneum as a dialysis membrane.[3]

Peritoneal dialysis has many advantages over HD, including improving patient independence, social life, well-being and quality of life.[4,5] The CHOICE study, which compared patient satisfaction between HD and PD, demonstrated that patients receiving PD were 1.5 times more likely to rate their care as excellent.[5] A major factor in this is removing the requirement to attend for HD three times a week, especially in cases involving lengthy commutes.

Recent National Institute of Clinical Excellence (NICE) guidelines recommend PD to be considered as the first treatment modality for adults requiring RRT with the aim of increasing the percentage of those on RRT receiving PD to 39%.[2] NICE have calculated annual savings of £20 million

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if the prevalent number of patients on peritoneal dialysis in England increases from the current 15% to the optimal 39%.[2]

In order to successfully implement the NICE guidelines, nephrologists must have good access to a reliable, effective PD catheter insertion service. The aim of this study was therefore to assess the outcomes of a Tenckhoff peritoneal dialysis catheter insertion service along with incident rates of PD use in a single centre in NI in anticipation of the potential increased uptake of this modality of renal replacement.

METHODS

All patients who underwent peritoneal dialysis catheter insertion between April 2003 and October 2011 in our district general hospital were identified from records within the Department of Nephrology. A team of nurse specialists facilitate delivery of the PD service and maintain specific records for individual patients undergoing PD.

A single surgeon performed all insertions using a standardised open paramedian dissection technique.[6] Briefly, an incision is made 3cm lateral to the midline, at the level of the umbilicus, that extends inferiorly. Dissection of the abdominal wall is then performed in layers under direct vision to expose the anterior rectus sheath. The anterior sheath is sharply divided and the rectus fibres are then bluntly dissected down to the posterior sheath before an incision is made in the peritoneum to create a small opening. The intraperitoneal part of the Tenckhoff catheter is positioned in the pelvic cavity using a malleable introducer. The inner cuff is then sutured to the peritoneum and then the rectus sheath is closed with continuous sutures. Before tunneling the catheter in the subcutaneous layer, peritoneal dialysis fluid is introduced to test flow. The skin is then closed with subcuticular sutures.

The medical and nursing records were reviewed for demographic information, medication history, past medical history, date of PD catheter insertion, occurrence of post-operative complications, and dialysis history. Peri-operative complications included bowel perforation. Post-operative complications included exit site infection, wound infection, peritonitis and catheter migration / obstruction. Re-manipulations of PD catheters were performed laparoscopically. All patients were followed up for at least 12 months and the primary outcome was the presence of a patent functioning catheter at 12 months that did not require manipulation / repositioning, removal or replacement. Patients were excluded from this specific analysis if they (i) underwent renal transplant within 12 months of catheter insertion and the catheter was functioning up to the point of transplant or (ii) had a functioning catheter but died within 12 months of insertion and the cause of death was not catheter related.

The UK Renal Registry annual reports provided information on the annual incidence of PD uptake and prevalence of PD use within the population of adults requiring RRT in our institution. This data was available from 2005.

RESULTS

Fifty-four patients (male n=33), with a median age of 58 (range 21 – 82) years were included in the study cohort. The most common cause of renal failure was diabetes (n=12), followed by polycystic kidney disease (n=10), IgA nephropathy (n=9), and hypertensive nephropathy (n=6). Other causes (n=17) included pyelonephritis, Wegener's and glomerulonephritis. The time interval between catheter insertion and use ranged from 3 days to 11 months, with a median of one month.

Review of the UK Renal Registry's annual reports between 2005 and 2011 demonstrates that the average uptake of PD in our institution was of 21.3% and reached 39% in 2013.[7-15] This compares with an average uptake of PD across NI of 12.4% between 2005 and 2011.[9-15] Table 1 demonstrates the average PD uptake across the other sites within NI during the study period and the longitudinal changes in uptake up to 2013. The prevalence by the end of 2011 of PD in the dialysis population in our institution was 9.8% (n= 12 of 123). The corresponding average figure for all centres in Northern Ireland was 9.7% (n= 78 of 803).[16]

Proportion of patients requiring RRT who received PD as first modality of treatment (%)

	*SHSCT**	*NHSCT*	*BHSCT*	*SEHSCT*	*WHSCT*
Average (2005-2011)	21.3	11.4	12.3	9.1	8.1
Year					
2013**	39%	10%	16%	7%	27%
2012**	33%	19%	10%	10%	14%
2011	21%	17%	12%	6%	18%
2010	10%	5%	8%	5%	0%
2009	10%	5%	8%	0%	16%
2008	15%	10%	12%	23%	20%
2007	27%	3%	12%	0%	0%
2006	36%	13%	16%	13%	3%
2005	30%	27%	18%	17%	0%

Table 1. The proportion of patients requiring renal replacement therapy (RRT) receiving peritoneal dialysis (PD) as the first modality of treatment (incident use) in each Trust per year and the average proportions during the study period 2005-2011. (SHSCT – Southern Health and Social Care Trust (*study institution); NHSCT – Northern Health and Social Care Trust; BHSCT – Belfast Health and Social Care Trust; SEHSCT – South Eastern Health and Social Care Trust; WHSCT – Western Health and Social Care Trust; ** Years not part of initial study period).

Peri- and post-operative complications

One patient had a bowel perforation due to the catheter-tip breaching a colonic diverticulum during placement. The presentation was delayed for three days before the patient underwent a Hartmann's procedure and made an otherwise uneventful recovery. This patient was subsequently managed with HD and survived for a further six years. Two diabetic patients developed wound infections, in the first 30 days of operation, which were successfully treated with intravenous antibiotics. There were no episodes of exit-site infection or peritonitis within 30 days.

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Catheter-specific outcomes

The median duration of catheter survival was 17 months, ranging from 3 days to 5 years and 8 months. At 12 months, 38 patients had a primary functioning catheter corresponding to a rate of 76% for our primary outcome. Four patients progressed to renal transplant or died within 12 months of catheter insertion with a primary functioning catheter in-situ.

During the study period, seventeen (31%) patients required manipulation or reinsertion of their PD catheter due to catheter obstruction or migration. Of these patients, 12 (71%) had fully functioning working catheters after surgical manipulation or re-insertion up until the point of death, renal transplantation or the last recorded entry prior to the study endpoint. The remaining five patients (29%) were transferred to HD after a median time of 10 months (range from 2 weeks to 3 years.) Only two patients required re-insertion within 30 days of catheter insertion.

DISCUSSION

This study presents the results of a single centre, single surgeon experience in PD catheter insertion between 2003 and 2011. Overall there was one bowel perforation and two wound infections but no exit site infections or peritonitis in the first 30 days post-operatively. At 12 months the primary catheter patency rate was 76%. Our institution's outcomes therefore compare favourably with reference to the International Society for Peritoneal Dialysis (ISPD) guidelines on clinical practice for peritoneal access (table 2). [17]

Outcome	ISPD recommendation	Current study
Catheter patency at 12 months	>80%	76%
Bowel perforation	<1%	1.9%
Significant haemorrhage	<1%	0%
Exit-site infection within 2 weeks of insertion	<5%	0%
Peritonitis within 2 weeks of insertion	<5%	0%

Table 2. A comparison of our institution's outcomes with the International Society of Peritoneal Dialysis (ISPD) recommendations.[17]

During the study period there were no recorded episodes of peritonitis or exit site infections within four weeks, which is below ISPD's recommendation of 5%. This could be attributed to the routine administration of prophylactic intravenous vancomycin prior to the insertion of PD catheters. The Renal Association guidelines recommend the administration of prophylactic antibiotics prior to PD catheter insertion, with the choice of antibiotic based upon local guidelines.[18] Gadallah *et al* (2000) conducted a three arm randomised controlled trial where vancomycin was superior in the prevention of post-operative peritonitis over cephalosporins and no preoperative prophylactic antibiotics.[19] In our institution all patients were regularly followed up by the specialist PD nurse at five day intervals post-operatively for the first three weeks as a standard. Patients whose catheter was not yet in use were followed up every four weeks to review their exit site and flush the catheter. Therefore, as any PD catheter problems would be communicated by the patients directly to the specialist nurses and subsequently documented we feel the observed level of zero for significant exit site infections is robust.

Our outcomes are comparable to those in other published series as highlighted in table 3. A large retrospective review over 4 years by Liu *et al* (2009) looked at complications after 384 PD catheter insertions.[6] In this study all catheters were inserted using a similar open paramedian approach however they report a significantly higher rate of early catheter migration. Interestingly, a heterogenous group of 22 urologists and general surgeons inserted the catheters in this cohort therefore the inclusion of non-specialists may have contributed to the relatively poor results observed in this regard. In comparison, the strength of our study is the continuity provided by one consultant general surgeon who performed all PD catheter insertions. Another retrospective review of complications after PD catheter insertion by Tiong *et al* (2006) demonstrated that our institution had significantly lower complication rates.[20] In this Singaporean study, PD catheters were inserted via an open paramedian approach by various grades of operator including consultants, registrars and fellows. There was a high rate of infections in this study, however there was no difference in the complication rates between those of varying levels of experience. It could

Study	Year	Patients (n)	Complications recorded	Complication subtype (%)			
				Migration/obstruction	Exit site infection	Wound infection	Peritonitis
Current study	*2011*	*54*	*Within 4 weeks*	*3.7*	*0*	*3.8*	*0*
Wright *et al* [24]	1999	24	Within 6 weeks	0	16.7	-	4.1
Gadallah *et al* [27]	1999	72	Within 2 weeks	8.3	37	-	6
Daschner *et al* [25]	2002	23	Within 4 weeks	8.7	-	-	-
Ogunc *et al* [26]	2003	21	Within 4 weeks	23.8	38	-	38
Jwo *et al* [22]	2006	40	Within 4 weeks	15	0	-	0
Tiong *et al* [20]	2008	139	Within 4 weeks	24	22	38	6
Liu *et al* [6]	2009	319	Within 4 weeks	13.3	6.3	3.6	2.9

Table 3. Observed complication rates in comparative studies using an open technique

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therefore be suggested that a higher quality service can be delivered by a dedicated multidisciplinary team with a smaller number of expert surgeons.

In addition to our comparable outcomes with respect to ISPD guidelines and other published series, our institution also had a higher rate of PD uptake in contrast to the other units in Northern Ireland during the study period (table 1).[7-15] Reviewing the local longitudinal trends in PD uptake there was a relative dip between 2009 and 2010, which interestingly was also evident regionally throughout all centres in NI. However, rates of PD uptake have increased continuously since 2011 in the majority of units in NI, which may be representative of the release of specific NICE guidance at that time.[2] In 2013 39% of patients requiring RRT were treated with PD in our unit in 2013 and while the definitive reasons for a higher uptake compared with other units is beyond the remit of this study, it is interesting to speculate on the direct impact of local access to appropriate surgical expertise. However further studies are required to answer this question as both the number of patients involved and the observation period are relatively small.

Finally, despite the relatively high incident rates over the period 2005-2011, the prevalent rate of PD use amongst dialysis patients in our institution was equivalent to that of other institutions in Northern Ireland. Peritoneal dialysis attrition occurs as a result of transition to haemodialysis, transplantation, or death and we have demonstrated a median PD period of 17 months in this study. Given the observed poor incident rates of primary PD use in 2009 and 2010 across all centres it is not unsurprising therefore that our prevalent rates were similarly poor. The overall results of this study remain encouraging however and the publication of most up to date prevalence rates are keenly anticipated to determine the local impact of recent incident improvements as we strive to accomplish NICE's 39% prevalence goal.

We acknowledge there are weaknesses in our retrospective observational study. Firstly, the variation in time between the insertion of a PD catheter and its use is variable. This can be explained by the fact that PD catheters are often inserted when the patient is stable anticipating its use soon, but sometimes the deterioration does not progress as expected, as was the case in very early use of one catheter. This study was also retrospective and the sample size is small but the nurse specialist records were complete and detailed. The strengths of this study are that all patients underwent a standardised open paramedian approach by a single general surgeon removing variability within our cohort. Our patient sample also reflects the common causes of renal disease and median age for PD insertion in the UK.[21] We also recognise there are other techniques for PD catheter insertion including laparoscopic and percutaneous options. A prospective randomized study by Jwo *et al* (2010) demonstrated that laparoscopic assisted PD catheter insertion was not superior to an open approach and that it was also a less cost effective option.[22] A recent study by Park *et al* (2014) also demonstrated increased mechanical complications with the percutaneous technique compared to the open technique therefore the latter remains the favoured option in our institution.[23]

CONCLUSION

In conclusion, the complication rates observed in this cohort are comparable to other published series and closely reflect the standards set by ISPD. The uptake of PD in our institution was higher than the NI average however the exact reasons for this are unknown. It is interesting to speculate that direct access to a local service with appropriate surgical expertise may be a contributing factor but further studies are required.

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Case Report

Salmonella Osteomyelitis

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ABSTRACT

Salmonella infection can cause four predominant clinical syndromes: enteric fever, acute gastroenteritis, bacteraemia with or without metastatic infection, and the asymptomatic carrier state. Salmonella as an aetiological agent in osteomyelitis is essentially rare and salmonella osteomyelitis in itself is predominantly seen in patients with haemoglobinopathies such as sickle cell disease or thalassemia. There are very few cases reported in the literature in which salmonella osteomyelitis is seen in otherwise healthy individuals. We describe here a case of salmonella osteomyelitis in a young gentleman with no significant co-morbidities who presented with fever and severe back pain, having returned from recent foreign travel. It is therefore important to consider uncommon pathogens in the differential diagnosis of travellers with prolonged fever and insidious symptoms.

INTRODUCTION

Salmonella infection can cause four predominant clinical syndromes: enteric fever, acute gastroenteritis, bacteraemia with or without metastatic infection and the asymptomatic carrier state.

Salmonella as an aetiological agent in osteomyelitis is essentially rare. It is the causative organism in 0.45% of osteomyelitis and salmonella osteomyelitis itself accounts for as few as 0.8% of all Salmonella infections.[1]

Salmonella osteomyelitis is predominantly seen in patients with haemoglobinopathies such as sickle cell disease or thalassemia and it remains a significant cause of morbidity and mortality in this population.[2] Salmonella osteomyelitis, in particular when due to Salmonella typhi, has a predilection for patients with diabetes mellitus, systemic lupus erythematous, lymphoma, liver and cardiovascular diseases, previous surgery or trauma and patient on steroids.[3] There are very few cases reported in the literature in which salmonella osteomyelitis is seen in otherwise healthy individuals and in the majority of cases there is commonly a pre-existing history of intestinal infection.

CASE REPORT

A 37 year old gentleman presented with severe back pain, pyrexia and a four week history of diarrhoea alternating with constipation, following recent travel to Dubai and the Maldives. Right upper abdominal pain, weight loss, anorexia and left leg swelling were also present. There was no history of trauma and no significant past medical history of note.

Examination revealed marked paravertebral spasm and diminution of lumbar and thoracic spine movement but no focal neurological deficit was localised. Hepatomegaly was noted and the left leg was found to be swollen, tender and erythematous.

At presentation, haemoglobin was 123 g/L, white blood cell count 13.7 $x10^9$/l, neutrophils 71.2%, lymphocytes 16.4%, ESR 21 mm/hr and C reactive protein 215mg/L. Liver function tests were noted to be deranged (GGT 552 U/L, ALT 78 U/L, Alk Phos 235 U/L) and D-dimer 5.38 mg/L.

CT Abdomen demonstrated hepatomegaly and splenomegaly but no focal abnormality. The colon was dilated to the level of the splenic flexure with calibre change at this level. Flexible sigmoidosopy demonstrated a left inflamed colon and histopathology confirmed mild inflammation.

USS Doppler demonstrated a deep vein thrombosis in the left popliteal vein which was treated with a six month course of Warfarin.

All blood cultures for the patient were negative. The antibody for human immunodeficiency virus was negative. Cytomegalovirus, Hepatitis B and C, and Q Fever serology were all negative. Stool culture was positive for Salmonella typhi. A urinalysis was normal.

Radiographs showed reduction in intervertebral disc space at T12-L1. MRI demonstrated osteomyelitis of the T12 and L1 vertebral bodies with relative sparing of the intervertebral disc. There was decreased intervertebral disc space at T12-L1, with increased signal intensity on T2 and decreased signal intensity on T1 weighted images (Figure 1). Salmonella infection characteristically traverses the posterior longitudinal ligament and is associated with inflammatory masses extending along several segments, which was in keeping with this patient's MRI findings.

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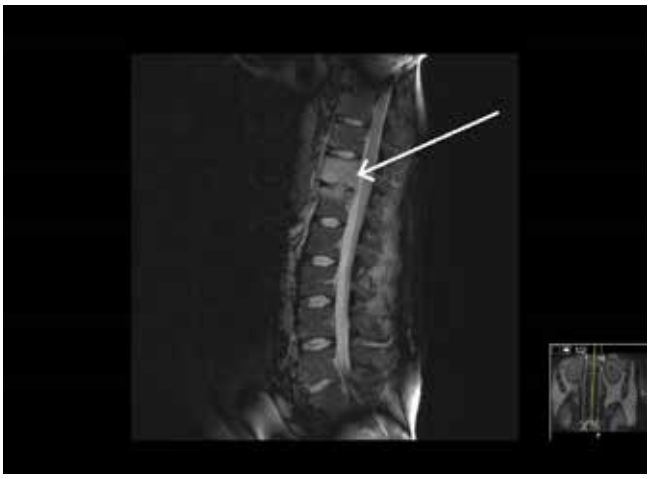

Fig 1. Magnetic resonance imaging demonstrating osteomyelitis of T12 and L1 vertebral bodies (white arrow).

The patient received a six week course of intravenous ciprofloxacin and meropenem and subsequently a six week oral course of ciprofloxacin. At the latest follow-up, the patient had no back pain, was apyrexial with significant clinical improvement in range of spine movements. In addition, radiographs confirmed the healing bone lesion.

DISCUSSION

While Salmonella osteomyelitis is rare, it is typically an infection of the diaphysis of long bones, predominantly the femur and humerus. Other bones commonly involved are the lumbar vertebrae, tibia, radius and ulna. [3,4,5] Salmonella enterica serovar Typhi and Paratyphi and diverse non-typhoidal salmonella are recognised as causes of vertebral osteomyelitis.[6] Santos and Sapicro concluded that fever and back pain were the main symptoms on presentation in 44 cases of vertebral osteomyelitis that they reviewed.[6] Thus one should suspect vertebral osteomyelitis in a patient with fever and back pain, and in particular salmonella infection should be considered where there has been a recent gastro-intestinal disturbance preceding the episode.

The treatment of salmonella is difficult and there are no randomised or case control studies in the currently available literature. Essentially there are no standardised antibacterial therapy regimes or surgical procedures. The most commonly used antimicrobials are chloramphenicol, third generation cephalosporins and fluoroquinolones.[7] In particular Ciprofloxacin has the ability to penetrate macrophages which is imperative in killing intracellular salmonellae and oral ciprofloxacin demonstrates good efficacy in treating bone infections.[8,9] Santos and Sapicro have recommended a duration of 2 months antimicrobial therapy in uncomplicated osteomyelitis, the duration used in this case. [6] However long term antibiotic therapy and radical surgical debridement should be performed in cases unresponsive to antimicrobial therapy.

Although this condition is relatively rare in Western countries, it remains an important entity due to increased international travel and its ability to cause significant morbidity and mortality in immunocompromised patients. Salmonella osteomyelitis should always be considered as a differential diagnosis in a patient with diaphyseal or vertebral osteomyelitis who gives a prior history of prolonged continuous fever or diarrhoea.

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Medical Education

Intersecting Virtual Patients and Microbiology: Fostering a culture of learning

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ABSTRACT

Background: The use and integration of Technology Enhanced Learning (TEL) resources in medical education has attracted considerable commentary and support. "Virtual Patients" are one such resource. Whilst evidence exists supporting the benefits of these resources, there has not been specific consideration of their implications for teaching microbiology; nor attention paid to both the internal and external factors that influence learner engagement with virtual patients. The principle aims of this study are to identify factors that explicitly and implicitly influence the student's interaction with a microbiology virtual patient resource and how these interactions reflect upon the use of the resource.

Methods: A mixed method quantitative (online questionnaire; n=161) and qualitative (student focus groups; N=11) study was undertaken amongst third year medical students enrolled at Queen's University Belfast in the academic year 2012 – 2013.

Results: The results supported prior evidence that virtual patients are a useful learning tool (mean score of 5.09 out of 7) that helped them to integrate microbiology principles with clinical experiences. How students used the virtual patients and the depth of the subsequent benefits was dependent upon their perception of the importance of the resource. This was influenced by a number of factors including how the resources were presented and positioned within the curriculum, whether they were formally examined or timetabled and the importance attributed by peers who had already completed the examinations.

Conclusion: Integration of virtual patients into the microbiology curriculum is widely endorsed and may even be considered superior to other methods of teaching. How students use these resources is dependent upon a positive perception of their importance. Educators should be aware of the factors that shape this perception when integrating TEL resources into curricula.

KEY WORDS: Virtual Patients, Technology Enhanced Learning, e-learning, education, microbiology

INTRODUCTION

Virtual patients (VPs) are one of many Technology Enhanced Learning (TEL) resources that educators may utilise in their teaching. They have been defined as "[a] computer program that simulates real-life clinical scenarios; learners emulate the roles of health care providers to obtain a history, conduct a physical exam, and make diagnostic decisions and therapeutic choices"[1]. In practice, VPs endeavour to replicate a clinical experience in which the student can assume a doctoring role whilst being guided by expert interpretation of the presentation, diagnosis and treatment of key medical conditions. Cook and Triola[2] provide a coherent review of the literature relating to the use and incorporation of VPs into the curricula.

Whilst a positive correlation has been observed between the integration of VPs into other medical curricula and students application of clinical skills[2,3], electronic resources are considered to be context specific and therefore evidence of utility in one discipline should not be directly inferred for other subjects[4]. Further, it has increasingly been recognised that the VP resources themselves cannot be appreciated on a technical level alone but additionally in the social context in which they are framed to students[5].

Student dissatisfaction in the teaching of microbiology using a traditional lecture format has been found to leave them feeling overwhelmed by abstract principles and microbial nomenclature.[6] This has been posited as a reason for superficial, assessment-driven learning[7]. It has been suggested that medical students prefer using TEL resources in microbiology[8] and that VPs can induce benefits such as the development of clinical reasoning[2]. However, there remains a need for research to question *how* VPs teach, *who* learns from them and how VPs can be applied most effectively within microbiology curricula.

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The current study attempts to identify explicit and implicit factors that influence student interaction with a microbiology VP resource to identify how VPs may be better integrated into the microbiology curriculum.

METHODS

Study setting

The study was conducted within the School of Medicine, Dentistry and Biomedical Sciences at Queen's University Belfast (QUB). The medical degree programme at QUB follows an integrated spiralling curriculum with a focus on clinical studies in years 3-5. Data were collected from Third Year Medical Students, the first cohort to be granted access to the microbiology VP resources. Ethical approval was obtained in advance of the study.

Virtual Patients

VPs were introduced into the 2012 – 2013 third year curriculum as part of the "Scientific Basis of Clinical Practice" module. They explored the presentation, diagnosis and treatment of seven scenarios: urinary tract infections, gastroenteritis, pyrexia of unknown origin, meningitis, respiratory tract infections, childhood exanthems and blood-borne viruses. The VPs blended images, audio and video to provide a more stimulating learning experience (Figure 1).

Fig 1. Screenshot of Fictitious Patient from Microbiology VP

A mixed method study was undertaken. In phase 1 an online questionnaire was used to derive initial themes relating to utility of VPs and ability of the resource to facilitate knowledge transfer. These results were subsequently used to guide the approach taken in the phase 2 student focus groups.

Phase 1

All third year medical students (n=278) were invited by email to complete an online questionnaire at the end of the academic year. The online questionnaire was intended to guide preliminary evaluation of student perceptions of the Microbiology VP resource.

A pilot questionnaire was developed by the research team and reviewed by an educational theorist and a sample of year 4 students not involved in the study. Alterations to layout and readability were made before the final 32-item online questionnaire was distributed. The questionnaire was designed to provide demographic information and to investigate the key themes of resource utility and the facilitation of knowledge transfer. Answers were recorded using a 7 point Likert Scale for responses (1= Strongly Disagree, 7 = Strongly agree) or through free text responses (incorporated to provide opportunities for students to illuminate themes that had not been considered by the authors). Simple descriptive statistics were used to analyse data and identify trends to guide focus group discussions in Phase 2 of the study.

Phase 2

Focus groups were used to gain a deeper understanding of student experiences in using the online resource. An email inviting participation was sent to all year three medical students (n=278). Written consent was obtained from volunteers. Participant numbers were limited to a convenience sample but a sampling grid was used to purposely select students on the basis of gender, age, graduate status and VP usage to ensure a representative spread of demographic characteristics. Each group was designed to include at least one participant that had not used the VP resource.

The focus groups were moderated to encourage guided discussion. The principle investigator was excluded from acting as a moderator to reduce potential bias. To aid moderation, key themes derived from analysis of Phase 1 data were used to create a focus group guide. After two focus groups had been completed, iterative thematic coding was undertaken to inform and develop a further focus group guide for the third and final group.

Focus group discussions were audio-recorded and transcribed verbatim. Transcription was checked against audio recordings to ensure accuracy. One author (DMC) identified preliminary codes from transcripts before all authors convened to review and compare the codes and to derive overarching themes. Preliminary coding was then recoded using a final agreed scheme with any discrepancies resolved by consensus. The themes were then reviewed and agreed upon by all members of the research team.

RESULTS

Phase 1

Of a third year medical student population of 278, 197 responded to the online questionnaire of which 161 (57.9%) consented to their responses being used for this research (Table 1). 59.0% of these respondents were female, 17.5% were graduates prior to entry to the course and 22.4% were originally born outside of the United Kingdom. The demographic details of consented participants were broadly representative of the third year student population as a whole. Of the total respondents who consented, 58.4% had used the VPs at some stage during the course.

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TABLE 1:

Demographic details and use of VP resources amongst the third year student population and online questionnaire participants

		Characteristics of third year group (n = 278)	Characteristics of online questionnaire participants (n = 161)
Characteristic	Response	N (%)	N (%)
Gender	Male	134 (48.2)	66 (41.0)
	Female	144 (51.8)	95 (59.0)
Age range	22 or below	212 (76.3)	124 (77.0)
	23-30	63 (22.7)	36 (22.4)
	31 or above	3 (1.0)	1 (0.6)
Previous Education	Non-graduate	238 (85.6)	132 (82.5)
	Graduate	40 (14.4)	28 (17.5)
Nationality	U.K.	231 (83.1)	125 (77.6)
	Other E.U.	17 (6.1)	23 (14.3)
	International	30 (10.8)	13 (8.1)
Used VPs	Yes	-	94 (58.4)
	No	-	67 (41.6)

TABLE 2:

Descriptive coding of respondent feedback from online questionnaire relating to utilising VPs

Descriptive code (coding instances, n)	**Exemplar comments**
Prioritisation of other learning activities due to perceived lack of time (6)	• No time - I have other work to be doing that is important for clinical attachments
Need for better integration into clinical teaching and assessment (5)	• I think there needs to be better integration with the whole curriculum . . . I find it hard to devote so much time to something that is likely to only form a small part of my assessment.
Implied that VP was "non-essential" resource as compared to e-lectures (5)	• No specific time allocated; any time spent on the online resources was using the lectures only. I haven't got as far as using VPs
Students see VPs as a revision tool (9)	• I have chosen to save the virtual ward patients as a revision tool closer to the exams and believe this will be more valuable once I have properly learnt the material

Questionnaire responses

For those who used the VP resource there was overall support for the use of VPs as a useful learning tool (mean score of 5.09 out of 7) with 34.8% returning to complete the same case more than once. Respondents supported the assertion that using VPs had helped them to appreciate the clinical relevance of microbiology (mean of 5.06 out of 7). When comparing student satisfaction with VPs against other methods of teaching such as textbooks, e-lectures and student attachment, VPs were considered a more enjoyable resource (mean score of 4.53 out of 7). When asked what design feature of the VPs was most useful, students reacted favourably to the integration of Multiple Choice Questions (52.3%), Case Histories (20.5%), Images (10.2%) and Open Questions (10.2%). When asked about their least useful features, the integration of Audio files (29.6%) and Guidelines predominated (21%).

Respondents' answers to the open questions provided greater insight into the VP learning experience (Table 2). The major themes proposed by the students related to time management, prioritisation of learning activities, integration of materials and how these impact upon perception and use of the resource. These themes were explored further in Phase 2.

TABLE 3:

Descriptive coding of respondent feedback from online questionnaire relating to facilitating student learning

Descriptive code (coding instances, n)	**Exemplar comments**
VPs provide a structured link from lectures to the clinical context (5)	• Put what you have learnt in the lecture into clinical context • The Virtual Ward resource allowed a logical work through presenting symptoms, investigations, diagnosis and treatment of clinical scenarios
Improving clinical relevance of microbiology (4)	• It was good to see theory used in an appropriate clinical context, as it made it much easier to understand and see the relevance
Provide a memorable and interactive learning experience that could be applied in future assessment (3)	• Made the topics we are learning more interactive and easy to remember • They are helpful scenarios to aid preparation for the exams.

Analysis of the student response to how the VP resource facilitated learning highlighted a number of perceived benefits (Table 3) that were considered further in Phase 2.

Phase 2

Fourteen students volunteered to take part in the focus groups of which twelve were chosen to participate. One participant failed to attend their session. The participants were largely representative of the medical student population as a whole.

In transcription analysis we identified 78 distinct descriptive codes. These codes were used to derive overarching themes. The overarching themes must have been discussed in two separate focus groups before it could be included in final

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Table 4:

Qualitative themes drawn from focus group participants' responses

Theme (coding instances, n)	Descriptive Code	Exemplar Interview Excerpt
Theme 1- Perception of importance of VP: Formal curriculum (6)	The extent to which VPs were integrated into other microbiology resources and other aspects of the curriculum.	S1: The big word comes back again to integration; making sure that we bring it alongside that information so that instead of having to roam
Theme 2- Perception of importance of VP: Null curriculum (18)	How the relative importance of a subject or a resource can be *implied* by students. Factors include the ordering in which the learning materials are to be studied, incorporating timetabled teaching sessions and exam weighting.	S5: If you see something that's more important, it is brought into the curriculum in a more obvious way, instead it was just left on the website. S1: It was almost the way it was laid out . . . you had lectures at the top then you had the Virtual Patient cases at the bottom then it was almost laid out in that the Virtual Patient was almost be used as a formative assessment mechanism.
Theme 3- Perception of importance of VP: 'Hidden curriculum' (12)	The centrality of peer influence in creating a culture of use and promoting integration of the VPs into the student learning experience.	S7: Definitely if the year above kind of approves of something you definitely think you need it. S4: Everyone I've told I've said to use them. Like people I'm working with now have said use them cause . . . they take questions from it.
Theme 4- Prioritisation of course demands (7)	The perception that VPs were considered to be a non-essential learning resource within a time pressured course.	S4: I know friends of mine who said "we are not going to cover microbiology." That's going to be like a sacrifice, you know a collateral damage.
Theme 5 – Confusion as to whether to approach VPs as a tool for primary learning or revision (7)	How VPs were used influenced student perception of VPs. The majority viewed VPs as a revision aid.	S1: It goes back to the purpose of the Virtual Patients. I was using it as a revision tool I would want to spend half an hour on it at the end of my revision session, whereas if it was designed as a primary learning tool, then I might have spent more time on it.
Theme 6 – Application of knowledge (5)	Students applied knowledge gained from VPs in both examinations and on clinical attachments.	S8: I can remember being on the ward and there were several patients we would see and it was, I think it was UTIs. I remembered from Virtual Patients that I applied what I had learned from that to what was going on in the ward.
Theme 7 - Student perceived benefits (30)	Students perceived VPs to emphasise and integrate principles from basic science into clinically relevant learning experiences and provided a memorable 'patient' experience that they could apply in the future.	S3: You have all this information but when you actually see someone you think 'I don't know what to do first' and for me that's what VPs are really good for. S2: I just think it's a lot more memorable than having a fact down on a piece of paper . . . even though it's not a real patient I still think it helps you remember things cause it's more like what you face every day when you go on the wards.

analysis. From this we identified 7 key overarching themes before reviewing the descriptive codes across all transcripts to ensure they related accurately to our preliminary interpretation (Table 4).

DISCUSSION

Our findings suggest that student engagement with VPs is not simply based on the quality of the VP resource but how these are perceived as beneficial to the student in relation to both educational and clinical attainment. To promote the role of VPs to the student population it is important for educators to firstly appreciate how VPs are perceived, and secondly to facilitate early student engagement with the resource. We will therefore discuss important aspects of the student feedback with regards to these two considerations.

Themes 1-3: Factors influencing Perception of VPs and prioritisation of demands

It was not surprising that participants commented on the time pressured environment in which they manage competing learning needs. Whether these demands are from other subject areas within the curriculum or deciding which microbiology learning resource to prioritise, the perception of the relative importance of a resource influences the student's decision to engage on a deep level of full integration, as a superficial revision tool or not to use it at all.

Our results highlighted three facets of the curriculum that may have determined how a student engaged with VPs. Failure of faculty to integrate and relate VPs to other course materials and its clinical relevance to other specialties within the course (Theme 1 – Formal curriculum) could promote a perception that VPs are not a resource that requires focus. How the resource is presented to students, reinforced through

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timetabled sessions and the extent to which it is formally examined *implies* the resource's value and the extent to which it can be dismissed (Theme 2 – Null curriculum). Our findings also suggest that the 'Hidden curriculum' (Theme 3), a recognition of the relative importance of the resource which is emphasised through student to peer interaction, also has a significant impact on how VPs were used. Peer opinion, particularly that of students who had recently passed the related exams or from the year above, profoundly impacted upon the perception of any given resource. For our cohort, the 'Hidden curriculum' exerted a *de facto* negative impact as they were the first year to use the VPs and so endorsement from earlier year groups was not possible. We were pleased to note that those who positively engaged with the VPs promoted their use to students in their own year and the year below.

These perceptions were also seen to contribute towards how and when students engaged with the resource. When students perceived the VPs as a revision aid, their engagement was at a superficial level with the expectation that the resource should be brief and directive. When students engaged with VPs as primary learning tools they engaged prior learning and used the resource to associate their current knowledge with what was being presented to them, integrating this knowledge in a more effective manner than if they used other learning tools[3]. In this manner VPs derive a greater benefit than simple didactic learning.

Themes 6 & 7: Application of Microbiology in practice

Students reported that the use of VPs helped them to develop their ability to apply microbiology principles to clinical scenarios in a safe learning environment whilst also providing a memorable learning experience. In keeping with other studies[9], it was found that incorporating clinically relevant media such as x-rays, hospital charts and patient images with multiple choice questions helped the student to integrate the key principles of microbiology and related to what they experienced on the wards. The key design features required to successfully create VPs for this purpose have been described elsewhere[10] but it is important to note that participants provided examples when they recalled answers or envisaged actual images used in the VPs when asked to apply these principles. Students reported instances in both the clinical and examination situations where they relied on their learning experience with the VP to form their response. In doing so, they perceived a benefit from engaging with the resource and were more inclined to recommend their usage to other students.

VP Learning Experience

Our results suggest that there is a cyclical learning experience (Fig. 2) relating how the student interacts with the VP to the environment in which the resource is presented and perceived.

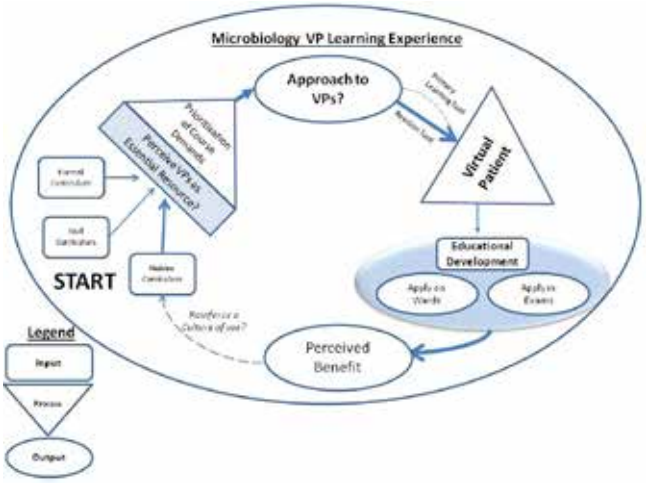

Fig 2. Schematic representation of Student Learning Experience using Microbiology VPs

The student learning experience in relation to microbiology VPs begins with an initial evaluation of whether the resource is an essential resource. It appears that a range of extrinsic and intrinsic influences act upon a student's perception of the resource, the benefits derived and the extent to which it must be prioritised in a demanding course. This perception determines whether the VPs are used early in the course with maximal engagement as an overarching primary learning tool or, as we found more commonly, as a superficial revision resource close to examination time. We noted many examples where students applied knowledge gained from their engagement with the VP in examinations and in clinical contexts to derive a perceived benefit. This perceived benefit was then fed back to their peers and the members of the year below. It is suggested that this positive feedback can have a significant impact upon their peers' decision to use the resources in the future and may encourage a culture of use.

LIMITATIONS

This study only explored one cohort of medical students in one institution so results may not be generalisable to other microbiology undergraduate curricula. It is possible that students who volunteered to participate in the focus groups may have held more positive views on VPs than those who did not volunteer. In an effort to ensure representative groups we purposively selected volunteers of diverse demographic characteristics. Although we recruited a relatively small sample size in phase 2 we believe that we achieved thematic saturation relatively quickly. The triangulation of results identifying and supporting similar themes between both phases of data collection would uphold the veracity of our findings.

CONCLUSION

Student perceptions of curriculum innovations are informed by a number of factors; some are within the control of the teaching institution and some are not. For microbiology education to fully utilise the substantive benefits of VPs, attention has to be paid to their holistic integration into

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the curriculum with integration at an early stage of student learning. With microbiology considered by students to be a topic that is difficult to engage with and apply in a clinically relevant manner, it is crucial to engage with all aspects of the student learning experience to derive the greatest benefit from VP resource integration. Whilst we recognise that further research is required to explore other factors that may be involved in the student learning experience, educators should be mindful as to how they integrate the VP resource with a focus on student perception. It is vital to consider how VPs are presented to students, their implied importance in relation to assessment and feedback, and most significantly how to positively engage peer perception to support a culture of use. We believe that where rounded integration is achieved, students have shown a greater willingness to engage with the resource and an application of its use in clinical scenarios.

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Medical History

Anthony Traill (1838-1914), the first Provost to confer degrees on Women Graduates

Caoimhghin S Breathnach

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ABSTRACT

Anthony Traill was born into a Scotch-Irish family at Ballylough House near Bushmills in county Antrim in November 1838. At the age of twenty he entered Trinity College Dublin to study engineering, but he was a professional student who passed through all the faculties and took legal and medical degrees in 1864-1870. He applied his knowledge of physics when advising his brother William who was building the Portrush-Bushmills electric railway. Though he took time off to indulge his athletic abilities, he steeped himself in College affairs and became Provost in March 1904, a post he held until his death in October 1914. His outstanding contribution whilst holding that post was to welcome women with university training into graduation.

ACADEMIC, ENTREPRENEUR AND POLITICIAN

Anthony Traill would have been called a professional student in my youth. He glided through the faculties: born on the 1st of November in 1838, at Ballylough House, two miles south of Bushmills in county Antrim, he entered Trinity College Dublin to study Engineering, graduated in Mathematics and Experimental Science with the Science Scholarship, then proceeded MA in 1864 and LL.D .in 1865.[1] Even after becoming a Fellow of the College he took the degree of Master of Surgery in 1869, and that of Doctor of Medicine in December 1870, but there is little evidence that he ever practised the healing art.

Traill's knowledge of Physics, not surprisingly, was valuable to his brother William Acheson Traill (1844-1934) who conceived, designed and built the Giant's Causeway, Portrush, and Bush Valley Railway & Tramway Company in 1883. Anthony Traill was its first chairman, and it remained in operation until 1947. At the Berlin Trade Fair in 1879, and on a short (1½ mile) conversion of an existing line in Lichterfelde near Berlin in 1881, Siemens had demonstrated the world's first railway electrification system. This led the Traills to invite the British branch of the company, Siemens Brothers of London, to electrify the new line they planned to build from Portrush to Bushmills, a distance of approximately 7 miles. Opened in early 1883, this was the first long electric railway in the world, the first to be supplied with electric current through a third rail, and the first to be powered by hydroelectricity. This was provided by a generating station built at Walkmill Falls, near Bushmills. The Giant's Causeway extension of the track, completed in 1887, was engineered by Alfred Price (1837-1934), son of James Price the eminent Irish civil engineer. [2]

Fig 1. Portrait of Anthony Traill, by J. Sydney R Rowley, oil on canvas, 141 x 111 cm, Trinity College Dublin Art Collections. Reproduced by kind permission from the Board of The University of Dublin, Trinity College Dublin, Ireland.

Institutional and national politics soon became Traill's chief occupation (in 1884 he was appointed High Sheriff of Antrim, and in April 1901 Commissioner of National Education in Ireland) [3], yet he found time to indulge his interest and his

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immense physical energy in athletics, and he captained the Trinity College Dublin cricket eleven for eleven years and was College racquets champion for fourteen seasons. Though he did not cut an academic figure, he was an Assistant in the Department of Natural Philosophy from 1884 to 1899.[1]

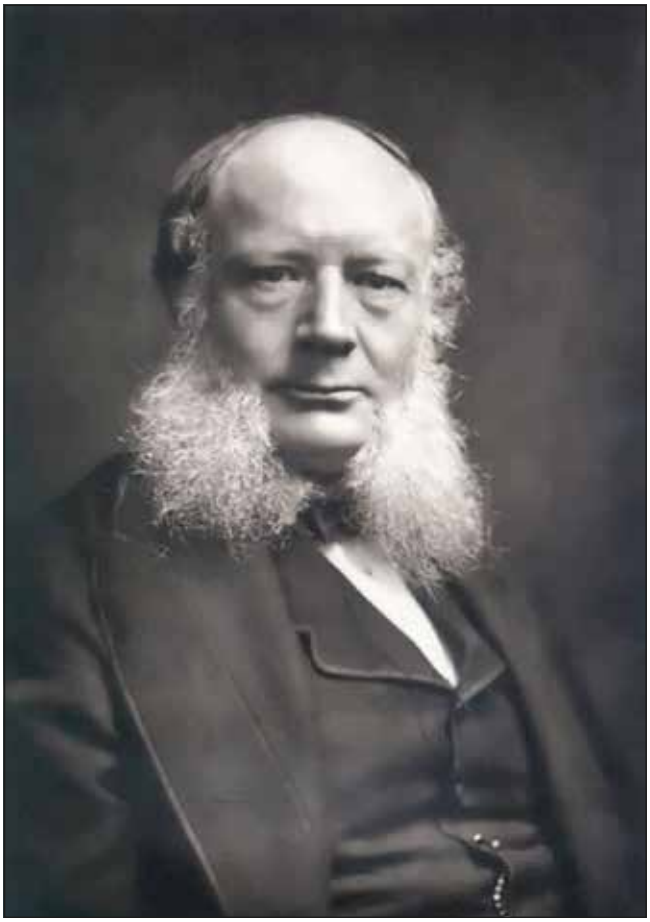

Fig 2. Portrait of Sir William Siemens; reproduced from the website http://commons.wikimedia.org/wiki/File:Wilhelm_Siemens.jpg under Public Domain licence.

From 1865, when he became a Junior Fellow in Trinity College, Anthony Traill worked successfully in the interests of the College, and in 1899 his abilities and dedication were recognised when he was promoted Senior Fellow on the resignation of Thomas Dunbar Ingram (1826-1901). But, whilst still a Junior Fellow, Traill was not averse to self-promotion. In 1880 the Provost of Trinity College, Humphrey Lloyd, was 80 years old and showed signs of deterioration. And there was no precedent for retirement! Fears of a Liberal administration caused alarm and despondency, and those fears were realised when the Conservatives lost an election. Traill came forward with an audacious solution to the problem in Trinity College: he proposed to two Conservative Members of Parliament that he would hand over his private income of £2,000 per annum to pay a pension to Lloyd if the Conservatives, in the last throes of office, were to appoint him as Provost. At the time there were 25 Fellows senior to Traill, whose sole publication was a political speech. His machinations came too late, for Gladstone took office in April 1880, Lloyd lingered into 1881, and Gladstone appointed as Lloyd's successor John Hewitt Jellett (1817-1888), the choice of the Senior Fellows.[1]

Jellett was succeeded as Provost by George Salmon (1819-1904) and, when Salmon died five years after, Traill was promoted Senior Fellow, a bevy of names came up for consideration for the vacant Provostship, among them John Pentland Mahaffy (1839-1919) and Robert Yelverton Tyrrell (1844-1914). On the 22nd of March 1904 Arthur Balfour, the Prime Minister, announced that his choice was Anthony Traill.

Fig 3. Portrait of John Pentland Mahaffy, by Walter Osborne, oil on canvas, 80 x 65 cm, Trinity College Dublin Art Collections. Reproduced by kind permission from the Board of The University of Dublin, Trinity College Dublin, Ireland.

PROVOST OF TRINITY COLLEGE, DUBLIN

Traill's most notable achievement was welcoming women with university training and qualification into graduation. He argued that these women, who were as well educated as any male Dublin BA, should be admitted as candidate Bachelors and allowed to graduate without further examination. The Board of Trinity College passed a resolution in 1903 that "the time had come to admit women to teaching and degrees of Trinity College". A few claimed their degrees in December 1904. But what attracted Irish women also attracted English women and by December 1907, when the concession terminated, 720 'mailboat degrees' had been added to the Trinity College roll. 'Selling degrees to strangers' met with ridicule, but Traill 'simply ignored the barbs and accepted the fees', income always being welcome.[1] The new female undergraduates outnumbered the males – and outshone them, too.

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Constant agitation to secure academic opportunities for Irish Catholics in the University of Dublin met with organised opposition from the authorities and students of Trinity College – epitomised in Traill's paper 'Hands off Trinity' published in the journal *Nineteenth Century* in March 1899. [4] The Robertson Commission of 1901-3 recommended reconstruction of the Royal University as a teaching body with an additional College in Dublin associated with the Queen's Colleges in Belfast, Cork and Galway, and the Fry Commission of 1906-7 recommended the establishment of a College in Dublin acceptable to Catholics, but its members were divided as to whether it should be included in the University of Dublin or not.

That Catholic opinion was divided can be traced back to the time of Cardinal John Henry Newman (1801-1890) who, many years earlier, intimated to Aubrey de Vere (1814-1902):

> "If we fail at present to create a Catholic University, there remains another great benefit which we may confer on Ireland. We can in that case fall back upon a second college in the Dublin University, one on as dignified a scale as Trinity College and in all respects its equal; one doing for Catholics what Trinity College does for Protestants. Such a college would tide over the bad time, and eventually develop into a Catholic University." [5]

'Hands off Trinity' became the rallying cry of the opposition to the proposal. But soon, in 1907, James Bryce (1838-1922) was replaced as Chief Secretary for Ireland by Augustine Birrell (1850-1933), and Birrell and the Royal Commission eventually succeeded in persuading the Government in London to establish the National University of Ireland (leaving out the unblessed Trinity) in 1908.

Though Kirkpatrick dedicated, with permission, his *History of the Medical Teaching in Trinity College Dublin and the School of Physic in Ireland* to Anthony Traill in 1912, that is the sole mention of his name, which appears in neither the text nor the index. [6]

In 1914 Traill was forced by illness to cease active involvement in the affairs of Trinity College, and was confined to his bed for several months before dying, still in office and aged almost 76 years, in the Provost's House. [2] His successor as Provost was John Pentland Mahaffy, who was less than four months younger than Traill. Upon hearing that Traill was ill, Mahaffy was said to have remarked, "Nothing trivial, I hope?". [7]

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Medical History

Battle of the Atlantic: Military and Medical Role of Northern Ireland (After Pearl Harbor)

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INTRODUCTION

After Pearl Harbor[1] I[1] asked whether an American Catalina Pilot had really found the *Bismarck*. I was informed that he was Ensign L.B. Smith, U.S. Navy, stationed with 209 Squadron, R.A.F. Coastal Command at Lough Erne. He sighted the *Bismarck* 550 miles west of Land's End. Two other U.S. Navy Ensign pilots of R.A.F. Catalinas took over shadowing the *Bismarck* on 26 May 1941[2,3]. Much later I learned that Flight Lieutenant Waller of 502 (Ulster) Squadron (based in Limavady) flying a Whitley VII was sent to meet battleship *King George V* after she had helped sink the *Bismarck*. "*King George V* was said to be very short of fuel. We had seen two Heinkel 111 bombers as we approached *King George V* and we signaled by lamp to warn *King George V*. The message was allegedly not received by C in C Home Fleet"[4]. Later Waller, my future father-in-law, received an O.B.E. Military. When, sixteen years later, I went as a junior house officer at Bart's to ask former Wing Commander Waller if I could marry his only daughter, Tessa, he said, "No, your prospects are not good enough." On my return home, my father said, "I'll call up George and remind him of his prospects at Aldergrove and Limavady. You two are made for one another" [5].

EMERGENCY MEDICAL SERVICES PLANNING AND COORDINATION

The strategic role of Northern Ireland in the early years of World War II is reflected in the important role of its hospitals and health care institutions in serving both military and civilian personnel[6]. During the war, 1,900 rescued survivors of U-boat attacks on supply ships or escorts found their way to Londonderry[7] (Fig. 1). If injured or partially drowned, they were generally transferred to Royal Naval medical supervision under the jurisdiction of Sir Gordon Gordon-Taylor, Surgeon in Chief of the Royal Navy[9,10,11] (Fig. 2).

In 1938, prior to the outbreak of war, Northern Ireland's Ministry of Home Affairs sought the advice of the Emergency Committee of the local branch of the British Medical Association, to assure advance preparation for a war emergency and "particularly the possibility of the evacuation of hospitals in Great Britain and the consequent necessity for special arrangements for the care and treatment

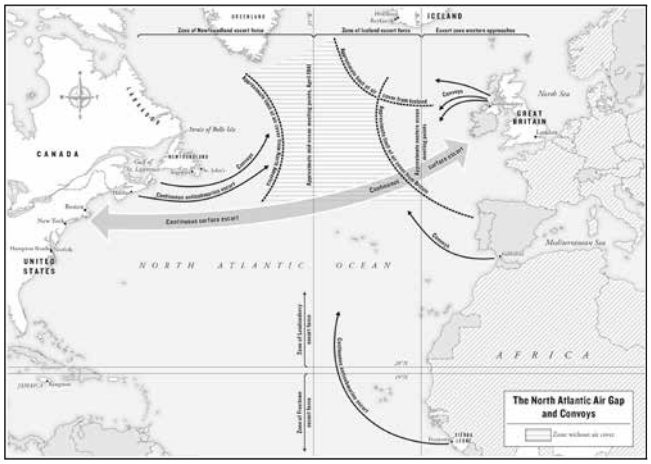

Fig 1. The Air Gap and Convoys[8], reproduced with permission of Prof. Paul Kennedy, ©David Lindroth and reproduced with their permission exclusively for this Medical History. In March 1943 Doenitz commanded 140 operational U-boats with 185 in training. The Allies, by contrast, suffered from inadequate naval protection, poor intelligence, non-existent or minimal air cover and no cover at night. By May 1943 the Allies were able to deploy in the mid-Atlantic 10-centimeter radar, Hedgehog grenades, aerial homing torpedoes and, above all, 2,500 mile-range B-24 Liberator bombers. "The B-24 Liberator was extraordinarily robust American-built…that first made the difference. Above it all was the continuous air cover for the convoys," concludes Professor Paul Kennedy of Yale University[8].

of patients, Service or otherwise, who might come to Northern Ireland"[12]. The Ministry suggested to the Emergency Committee compilation of a registry of medical practitioners and available hospital beds. Dr. F.M.B. Allen, Secretary of the Emergency Committee of the British Medical Association (Northern Ireland Branch), now the Northern Ireland Medical War Committee, was appointed by the Ministry in August 1939 as part-time hospital officer. Allen prepared an Emergency Hospital Scheme which classified all general hospitals in Northern Ireland with regard to casualties. The Scheme was primarily intended for treatment of air raid casualties, but it also was to include other ill and wounded

[1] All first-person references in this paper are to the first author.

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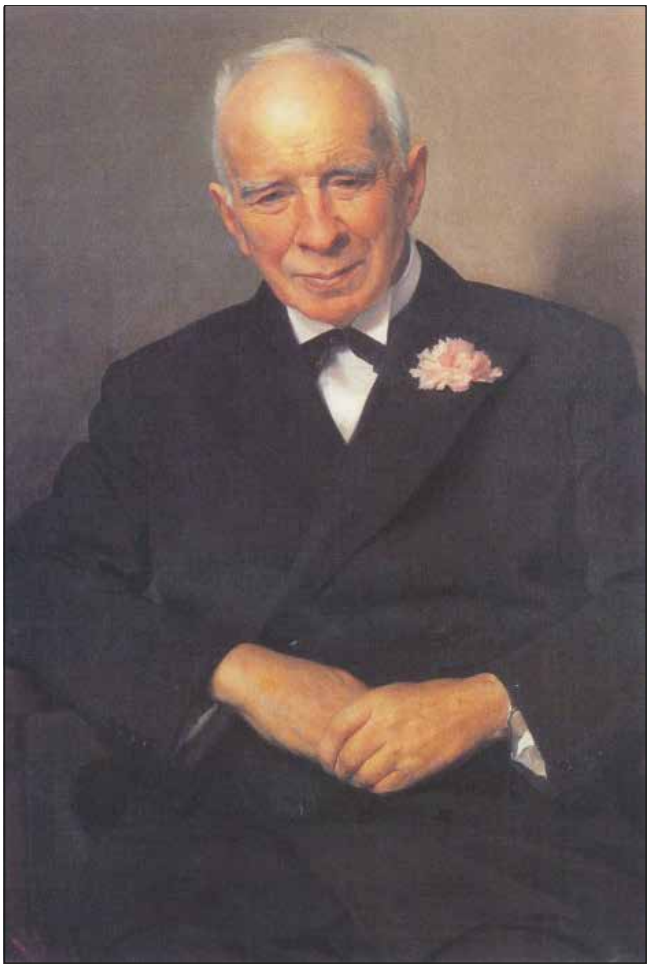

Fig 2. Sir Gordon Gordon-Taylor, CB, KBE, OBE. Portrait, oil on canvas, 91.5 cm x 71 cm, 1960, by Sir James Gunn, RA (1893-1964). Reproduced courtesy of the Royal Australasian College of Surgeons, with their permission, solely for this Medical History. During World War II as Chief Surgical Consultant to the Royal Navy, he became friendly with U.S. Navy Surgeon General Admiral Ross McIntire and with Fleet Admiral Ernest King[1]. Sir Gordon Gordon-Taylor was visiting Professor of Surgery at Harvard in 1941 and 1946 and helped his friend, Robert M. Zollinger, Senior, set up his academic Department of Surgery at Ohio State University[9,10,11]. Gordon -Taylor was examiner in Surgery in Belfast, Cambridge, Durham, Edinburgh, Leeds and London.

members of the British Armed Forces and their Allies[12]. Thus, Hospital Officer Allen acted as the link between the Armed Forces and civilian hospitals. On September 1, 1939 the Ministry issued an official Memorandum, outlining the Emergency Hospital Scheme, followed by a September 4, 1939 Circular requiring all Group I and II hospitals (Table 1A) to keep the Hospital Officer informed of available beds on a daily basis [13].

In May 1940 arrangements were made with the Northern Ireland Road Transport Board for conversion to ambulances of ten Dennis Lancet single-decker buses, which were first used in June 1940[13].

After the fall of France it was clear that a new department was

Table 1A.

Casualty Receiving Hospitals, Emergency Hospital Scheme, September 1939, Modified May 1940[13].

GROUP/ CLASS	HOSPITAL	LOCATION
GROUP I/ CLASS A	Mater Infirmorum Hospital	Crumlin Road,Belfast
	Royal Victoria Hospital	Belfast
	Belfast City Hospital	Lisburn Road, Belfast
GROUP I/ CLASS A_I	Craigavon Hospital	Strandtown, Belfast
	Belfast Children's Hospital	Falls Road, Belfast
GROUP II, CLASS B	Ards District Hospital	Newtownards
	Lisburn and Hillsborough District Hospital	Lisburn
	Bangor Cottage Hospital	Bangor
	Larne District Hospital	Larne
	Massereene District Hospital	Antrim
GROUP III/ CLASS C	Newry	Newry
	Coleraine	Coleraine
	Waterside General Hospital	Londonderry
	Dungannon	
	Dalriada District Hospital	Ballycastle
	Ballymena District Hospital	Ballymena
	Route District Hospital	Ballymoney
	Banbridge District Hospital	Banbridge
	Roe Valley District Hospital	Limavady
	Lurgan and Portadown District Hospital	Lurgan
	Armagh County Infirmary	Armagh
	Down County Infirmary	Downpatrick
	Londonderry City and County Hospital	Londonderry
	Fermanagh County Hospital	Enniskillen
	Tyrone County Hospital	Omagh

needed for civil defense in Northern Ireland, and the Ministry of Public Security was established in June 1940 with the Rt. Hon. J.C. MacDermott, K.C., M.P. as Minister. The branch of the Ministry of Home Affairs responsible for hospital services, and its Hospital Officer were then transferred to the Ministry of Public Security[13]. The Ministry subsequently divided Northern Ireland into four areas, with Dr. F.M.B. Allen, as Hospital Officer, in charge of Belfast and the surrounding areas. Three assistant part-time hospital officers were appointed: (1) Lieutenant Colonel A.H. M. Eaton, F.R.C.S.Ed., R.A.M.C. , Tyrone County Hospital, Omagh for the West area; (2) W.F. Evans, M.A., M.D., Lislea, Colraine,

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Table 1B.

Hospitals Selected for Admission of Evacuees or Patients Evacuated from Casualty Receiving Hospitals to Make Room for Casualties, Emergency Hospital Scheme, Modified from May 1940[13]

**Established November 1941*[13].

***Destroyed in April 15-16, 1941 Air Attack*[14]

ORDER	HOSPITAL	LOCATION
1	Belfast Emergency Hospital*	Belfast
2	Ulster Hospital for Children and Women**	Belfast
3	Samaritan Hospital	Belfast
4	Royal Maternity Hospital	Belfast
5	Belfast Ophthalmic Hospital	Belfast
6	Benn Hospital	Belfast
7	Nervous Diseases Hospital	Belfast
8	Antrim County Hospital	
9	Smiley Cottage Hospital	Larne
10	Armagh Union Infirmary	Armagh
11	Downpatrick Infirmary	Downpatrick
12	Enniskillen Infirmary	Enniskillen
13	Magherafelt Infirmary	
14	Omagh Infirmary	
15	Castlederg Infirmary	
16	Clogher Infirmary	
17	Mourne District Hospital	Kilkeel
18	Strabane District Hospital	
19	Londonderry and North West Eye, Ear and Throat Hospital	Londonderry
20	Mary Ranken Maternity Home	Coleraine
21	Ballymena Cottage Hospital	
22	Cushendall Cottage Hospital	
23	Portrush Cottage Hospital	
24	Robinson Cottage Hospital	Ballymoney
25	Newry General Hospital	
26	Cowan Heron Cottage Hospital	Dromore
27	Coleraine Cottage Hospital	
28	Thorndale Home	Belfast
29	Rescue and Maternity Home	Belfast
30	Throne Convalescent Hospital	Belfast

Co. Londonderry for the North area; (3) N.E.H.P.Williams, M.B., B.Ch., Sandrys Place, Newry for the South. These assistant officers were charged with assisting Dr. Allen in the admission and transfer of casualties and the increasingly important liaison between the civil casualty services and the medical services of the Armed Forces (Table 1A, Table 1B)[13].

A dramatic increase in casualties resulted from the air attacks on Belfast on the nights of April 15-16 and May 4-5, 1941 and their sequelae. The Ulster Hospital for Children and Women and the Belfast Hospital for Diseases of the Skin were destroyed while the Mater Infirmorum Hospital and the Benn Eye, Ear and Throat Hospital remained in operation despite considerable damage [13]. Thereafter the Emergency Hospital Scheme was transferred to the Public Health Division of the Ministry of Home Affairs[13](Table 2).

TABLE 2.

Casualties Admitted to Northern Ireland Hospitals[13]
**Other cases defined as "casualty", e.g. "transferred sick"*

YEAR	AIR RAID	*OTHER	TOTAL
1940	--	--	260
1941	680	2,820*	3,500

In post-bombing recognition of the importance of blood transfusion and the treatment of shock, regional Resuscitation Officers were appointed: Professor of Pathology J.H. Biggart of Queen's University Belfast [15,16], and Dr. J.A.L. Johnston, Pathologist, Londonderry[17,18]. Later in 1941, the Joint War Organisation of the British Red Cross and St. John provided two mobile X-ray vans located at the Belfast Fever Hospital, to be under the supervision of Mr. R. M. Leman, chief radiographer of the Royal Victoria Hospital[13]. In addition, hospital accommodations were supplemented by the provision of pre-fabricated hospital hutments by the War Office to provide beds for 2,500 patients. In November of 1941 the Ministry established the 400 bed Belfast Emergency Hospital at the site of the Belfast Mental Hospital, from which about 500 patients were transferred to other facilities[18] (Table 1B). An Emergency Medical Services Surgeon was appointed, as well as a resident surgical officer and house surgeon, with nursing care provided by members of the Civil Nursing Reserve; all were under the supervision of the Resident Medical Superintendent of the Mental Hospital now acting as Superintendant. The well-equipped Emergency Hospital admitted as many as possible of civilian patients on the waiting lists for voluntary Belfast hospitals, as a large proportion of these patients were employed in essential war industries such as ship-building, aircraft production and engineering[18].

The Civil Defense Casualty Services in Northern Ireland were directed by the same authority as the Emergency Hospital Services [6]. In contrast to England and Wales, there was no separate Ministry of Health until 1944 when Northern Ireland's Ministry of Health and Local Government was established. Prior to that time, the Emergency Hospital Services and other emergency services were directed by Brigadier Beddows[19], in liaison with Hospital Officer Allen for the Public Health Division of the Ministry of Home Affairs[18]. Dr. F.M.B. Allen resigned on April 15, 1942, and was succeeded by W.A. Brown, M.D., D.P.H. [18].

In his Presidential Address to the Ulster Medical Society, 20 October 1960, Dr. J.A.L. Johnston, former Londonderry Resuscitation Officer and President of the Ulster Medical

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Society, reported the only case of typhus he had seen in 1941: the vector had been a cat retrieved from a raft in the Atlantic after the sinking of the Bismarck[17] (Fig. 3). Weekly reports of infectious disease incidence attest to the fact that the war-time threat of a rise in contagious disease did not materialize in Northern Ireland[20]. Of the U.K. in general, the Epidemiological Notes of the *British Medical Journal* were able to report after the final weekly report for 1941, "We may conclude that the nation's health has been and remains satisfactory. In fact, it is better than many anticipated early in the war when considering the possible effects of such adverse conditions of life as herding in shelters, lack of ventilation due to black-out, and dispersal of large sections of the population" [21,22].

Fig 3. The Sinking of the Bismarck 27 May 1941, oil on canvas, by Charles E. Turner (1893-1965), 1941, dimensions 63.5 cm x 76.2 cm, collection item no. BHC0679. Reproduced with permission of the National Maritime Museum, Greenwich, London, exclusively for this Medical History.

The final acts in the May 27, 1941 sinking of the Bismarck were caused by three torpedoes from the Royal Navy cruiser Dorsetshire which closed to within a mile.

Beddows also did well as DDMS Northern Ireland from 1941 to 1944. Later, his high honour "Legion of Merit" of the United States, was published at the same time as that of his direct boss Lieutenant-General Sir Alexander Hood, G.B.E., K.C.B., M.D., F.R.C.S., F.R.C.P., K.H.P.[19,23,24]. Beddows' U.S. citation reads that he

> Distinguished himself by exceptionally meritorious conduct in the performance of outstanding services as Deputy Director of Medical Services for British Troops in Northern Ireland. Brigadier Beddows made all the initial arrangements for the reception of United States Troops in Northern Ireland. He continued to provide for their medical care until United States Army Hospitals could be established; and he caused to be transferred to the United States Army two of the best hospitals under his control. His continued assistance to our medical service has improved the care given to United States Troops sick and injured in Northern Ireland [23].

The 'best hospitals' were Musgrave Park and Waringfield[25]. Beddows graduated in Medicine. from the University of Birmingham in 1911[19].

POST PEARL HARBOR

Come Christmas, 1941, I was allowed to query the Americans now in their uniforms. The Americans were even allowed to marry in Ulster. Three weeks after Pearl Harbor, Charles Francis Jenkins married Miss Mary Ellen Gallagher in Saint Eugene's Cathedral, Londonderry. In August 1942 they returned on the *USS West Point*, the former *SS America*. They were assigned to the best quarters on Sun Deck. On October 2, 1942, their first child was born. They lived just south of Boston in Scituate, Massachusetts, and Charles became Supervisor at the nearby Hingham Shipyard repairing USN and RN warships[26].

I asked my brother's Godfather Major, later Sir Benjamin Rycroft[1,27,28,29] why the eye cases came to him and the Neurosurgical cases were flown to Oxford. "Neurosurgery is harder than the eye business. They are flown with catheters draining their spinal fluid." "Why?" "So they don't burst their brains." "Who thought that up?" "Cushing in Boston. He trained all the head doctors; Cairns at Oxford, Ross at Barts."

"How do the wounded get to Oxford?"

"Harrows become Sparrows and Dakotas help." I asked my father how Harrows became Sparrows. He replied, "When they fly patients" – Harrows were Handley Page HP54 bombers.

"Are they Yanks?" I asked. "Maybe, but it is always the RAF who flies them to Abingdon or Brize Norton if Abingdon has Thames fog."

The summary of allied Neurosurgery in World Wars I and II under the command of U.S. Navy Surgeon General Ross T. McIntire[1], traces the reduction in mortality from head injury. Harvey Cushing halved it from 37% to 20% and his pupil Sir Hugh Cairns halved it again in World War II[30]. Cairns was ably assisted by Calvert of Queen's Belfast[31]. The Cairns protocol for immobilization and transport in all its aspects, slightly amplified, remains a modern standard of care[32,33,34]. Cairns' insistence on the appropriate universal use of crash helmets also reduced fatalities[34].

PRESIDENTIAL RECOGNITION

During November 10-11, 1942, Mrs. Eleanor Roosevelt visited Northern Ireland and met with both civil and military leadership. On Armistice Day she visited the U.S. Naval Base at Londonderry and the Naval Field hospital in Creevagh, as well as the American Fifth General Army Hospital at Musgrave Park. She visited both British and American patients in military hospitals, and expressed sincere thanks on behalf of President Roosevelt and the American people for the warm welcome and excellent EMS medical care the Americans had received[7,35,36].

Over 18,000 Liberators were built between 1941 and the

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end of 1944. Upon the direct orders of Commander-in-Chief Franklin D. Roosevelt and Prime Minister Churchill as Minister of Defense over a thousand B-24 Liberator bombers were diverted to the Battle of the Atlantic [37]. On 9 June 1941 three French-purchased, U.S. designed and built, unmodified Liberators (AM 913, 914 and 922) had been flown into Nutts Corner by Colonel McReynolds of the U.S. Army and Mr. Homer G. Berry of U.S. Consolidated Aircraft. The Liberators also saw combat service from Ballykelly, Limavady, Aldergrove[1], as well as from RAF Station Eglinton, which is now City of Derry Airport. Combat operations began on 20 September 1941 and the Northern Ireland-based Liberator vs. U-boat battles over the Mid-Atlantic began on 4 October 1941 (Fig. 1). These 2,500 mile-range bombers with improved radar and weapons were decisive in the spring of 1943.

In late May 1943 with Hitler's agreement, Admiral Doenitz withdrew his U-Boats from the North Atlantic due to heavy loss[8,38]. The superb organization of medical services in Ulster during World War II contributed greatly to victory in the Battle of the Atlantic. The extraordinary cooperation between civilian medical and surgical services and the British and United States Armed Forces, begun in 1939[1], played a crucial role.

ACKNOWLEDGEMENTS

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Letters

TWIDDLER'S SYNDROME

Editor,

A 38 year old lady with a history of dilated cardiomyopathy with severe impairment of left ventricular systolic function and non-sustained ventricular tachycardia on Holter monitoring underwent implantation of a dual chamber implantable cardioverter defibrillator (ICD) for primary prevention of sudden death.

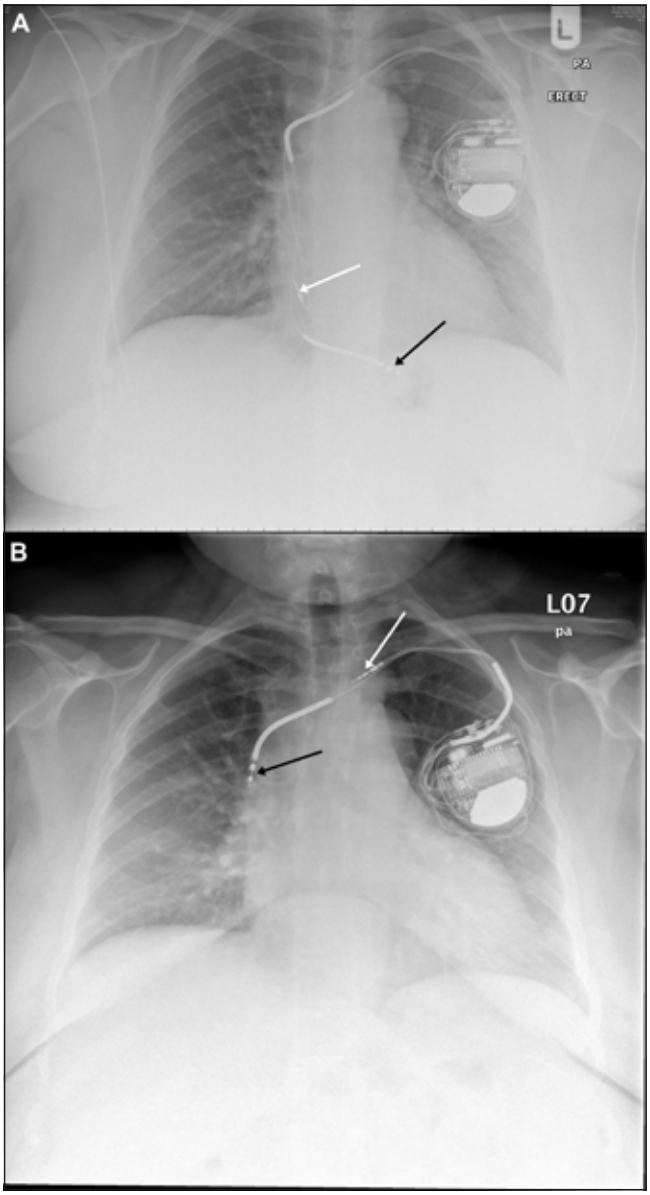

Fig 1. Panel A: Chest X-ray one day after implantable cardioverter defibrillator (ICD) implantation demonstrating satisfactory position of atrial lead (white arrow) and ventricular lead (black arrow). Panel B: Chest X-ray four weeks after ICD implantation demonstrating retraction of atrial lead (white arrow) and ventricular lead (black arrow) and loops of redundant lead in the region of the ICD generator.

An Evera XT DR ICD generator (Medtronic, Minneapolis, Minnesota) was placed in a left pre-pectoral subcutaneous pocket. A Sprint Quattro dual coil active fixation ICD lead (Medtronic, Minneapolis, Minnesota) was placed at the right ventricular apex and a CapSureFix active fixation lead (Medtronic, Minneapolis, Minnesota) was placed in the right atrium. Chest X-ray (Figure 1) and device parameters were satisfactory the following day and the patient was discharged.

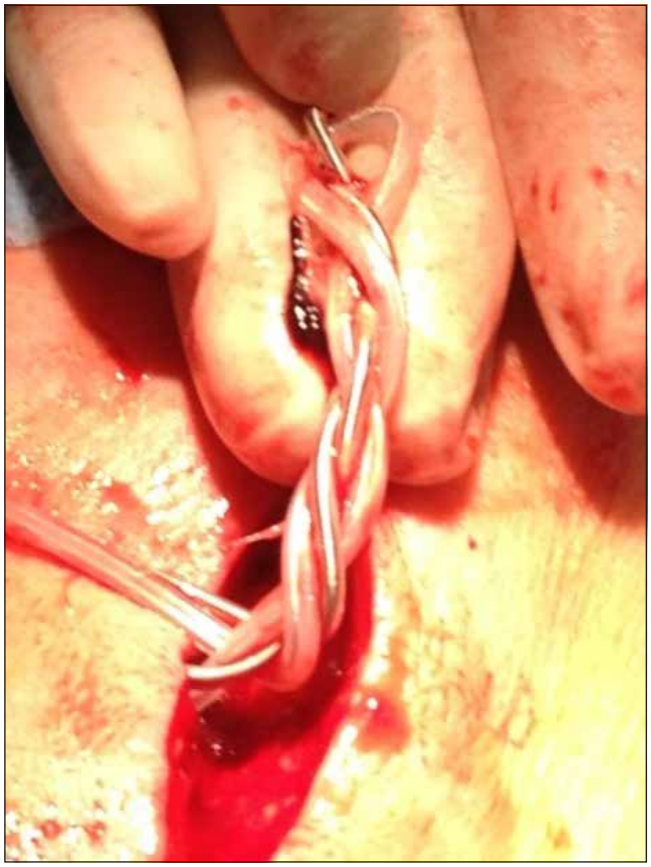

Fig 2. Image taken during ICD system explant demonstrating a large collection of entangled leads.

She presented to the accident and emergency department four weeks after ICD implantation complaining of chest pain and shortness of breath. A chest X-ray at that time revealed marked lead displacement, with the distal tip of the ICD lead in the superior vena cava and the distal tip of the atrial lead close to the left subclavian vein. In addition, there were a number of loops of redundant lead in the region of the ICD generator, in excess of that observed on the chest X-ray early after implantation (Figure 1). Device interrogation revealed no sensing of intra-myocardial electrical activity and inability to capture the myocardium at maximum output on both leads. These findings were felt to be secondary to manipulation of the device by the patient, a phenomenon known as Twiddler's syndrome. The patient proceeded to ICD system explant. During the procedure a large collection of entangled leads was found within the pocket (Figure 2), confirming Twiddler's syndrome.

Twiddler's syndrome represents pacemaker or ICD

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malfunction as a consequence of patient manipulation, usually by way of repeated rotation of the generator within the sub-cutaneous pocket. This results in entanglement of the leads causing lead retraction and device malfunction. The syndrome was first described in 1968[1]. Patient related risk factors include obesity and advanced age; both increase the likelihood of loose sub-cutaneous tissue and therefore make manipulation of the generator within the pocket easier[2]. Lead retraction may lead to stimulation of non-cardiac structures such as the diaphragm and muscles of the chest wall[3]. Management of Twiddler's syndrome usually involves re-positioning of the leads, additional securing of the generator to the sub-cutaneous pocket or placement of the generator within a sub-pectoral pocket and patient education to avoid this behaviour in the future. In the present case the leads were not repositioned because of concerns regarding a recurrence of the causative behaviour.

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COST IMPLICATIONS OF UNNECESSARY COAGULATION SCREENS IN SURGICAL PATIENTS – A MULTI-CENTRE STUDY

Editor,

Coagulation screens in surgical patients are routinely requested, often inappropriately. This can delay surgery, and cause unnecessary concern for the patient.[1] It is also associated with a significant cost to the hospital concerned, and often does not alter management. Coagulation screens in the two district general hospitals involved in this study cost £4.81 and £7.07 respectively. We performed five sampling periods of surgical inpatients in two district general hospitals, comparing with local and NICE guidelines[2], to establish if coagulation screen requests were appropriate and to identify cost implications. Both elective and emergency patients were included in the study.

Local guidelines for requesting a coagulation screen include a personal history suggestive of a bleeding disorder, acute bleeding with clinically suspected coagulopathy, patients with liver disease or chronic renal impairment whom require an invasive procedure, obstructive jaundice, severe sepsis, and paracetamol overdose.

NICE guidelines[2] for pre-operative assessment of patients state there is no indication for routine coagulation preoperatively for any type of surgery, from Grade 1 – minor, to Grade 4 – major+. A coagulation screen should only be performed if clinically indicated.

All coagulation screen requests in surgical inpatients over two to five week periods were analysed and compared with local and NICE Guidelines. Medical notes and laboratory results were reviewed to determine whether or not the coagulation requests were appropriate. This was repeated five times over a 4-year period (15 weeks in total) in two district general hospitals.

343 coagulation screen requests were made over the five audit periods. Only 36.7% requests were indicated as per guidelines. Inappropriate requests included: routine at admission, pre-operative, pre-procedure bloods (53.9%), radiology requests (6.5%), repeated samples (5.1%), patients on warfarin (1.4%), and no documented reason (33.2%). Interestingly, only 3 unexpected coagulopathies were found (1.38%), which did not alter the management of the patient. Over the five sampling periods, the total cost of inappropriate coagulation screens performed to the two hospitals concerned was £1095.75.

These data show, despite guidelines, there are a large number of unnecessary coagulation screens performed. Extrapolating our data over the 4-year study period, approximately £13,934.57 is spent on inappropriate coagulation screens. It would be helpful if a summary of these data with the indications for requesting a coagulation screen were reinforced with each change-over of medical staff, especially during the induction period of new F1 doctors.

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POST OPERATIVE RECOVERY TIME: AN INTERNATIONAL SURVEY OF ENT SURGEONS ADVICE.

Editor,

Ill health in workers cost the UK tax payer £14.2 billion in 2013[1]. While the majority of these cases are related to long term incapacity a small percentage will be due to those convalescing after a wide number of procedures. One of the most frequently asked questions peri-operatively is "how long will I be off work?" and part of our role is to create realistic

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expectation for recovery time. The advice given to patients is frequently based upon personal experience rather than firm scientific evidence. In addition, the development of innovative surgical techniques has meant that the traditional teachings with regard to time taken for convalescence following surgery are somewhat outdated[2].

ENT UK provides a selection of leaflets for common ENT procedures which include details on expected recovery times[3]. Anecdotal evidence suggests that there is a degree of variability in the advice given by individual surgeons and departments across the country. We aimed to assess the variability in advice given by surgeons in the United Kingdom (UK) and the Republic of Ireland (RoI) using an internet based questionnaire. Surgeon grade and location as well as post operative recovery time advised was collated for eight routinely performed procedures.

Questionnaires were sent to 48 surgeons in the UK and 32 surgeons in the RoI. A response rate of 15/32 (47%) in the RoI and 29/44 (65%) in UK was obtained. Respondents consisted of 56% consultant grade, 21% specialist registrar (SPR), 19% senior house officer (SHO) and 4% staff grade. The main centres responding were Belfast (23%), Craigavon (20%), Antrim (16%), Dublin (14%) with smaller contributions from Derry, Cork, Waterford, Sligo and Galway.

The average recommended time off following tonsillectomy was 13.8 days (7-28), tympanoplasty 10.8 days (3-28), thyroid lobectomy 13.2 days (5-42), Microlaryngoscopy 3.6 days (0-7), Oesophagoscopy was 2.1 days (0-7), Septoplasty 10.8 days (1-28), Functional Endoscopic Sinus Surgery 11.1 days (3-42), Bilateral Myringotomy and Vent 1.5 days (0-7). The majority of departments recommended similar periods of time for patient convalescence however a few had significantly different recommendations. The longest recovery periods were recommended by staff grades recommending an average of 16 days off across all procedures, with SHO's, SPR's and consultants recommending a period of 7.5, 8 and 8 days off respectively. This may reflect the closer supervision of junior staff and as a result post operative instructions given by junior staff may simply be an indirect version of the consultants advice. While consultant advice was generally similar across all the departments surveyed, smaller peripheral units had a wider variation in the recommendations provided than central teaching hospitals.

In conclusion we found that the average time recommended for post operative recovery across ENT surgeons in both the RoI and UK is very similar to that which is recommended by ENT UK. There is however wide variations both between departments and between different grades of doctors. This may reflect regional variations in patient expectations or indeed the different levels of doctors' experience and supervision. There is limited information in the literature regarding post operative recovery time from both the doctor and the patients perspective. This likely represents the vast differences in both the procedures carried out and the fitness of the patients undergoing these procedures. Despite this, it is essential to have some degree of standardisation regarding post operative recovery times for common procedures in all surgical specialities. The provision of consistent and adequate information to both patients and general practitioners ensures appropriate recovery time is received by the patient, potential unseen complications are detected and unnecessary cost to employers is avoided.

The authors have no conflict of interest.

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RIVAROXABAN ASSAY: A SINGLE CENTRE EXPERIENCE MEASURING RIVAROXABAN LEVELS WITH A SPECIFIC ANTI XA ASSAY AND THE EFFECT ON THE STANDARD COAGULATION SCREEN.

Editor,

Traditional anticoagulants including Vitamin K antagonists (VKA), unfractionated heparin (UFH) and Low Molecular Weight Heparins (LMWH) have been in use in clinical practice for a long period of time. Each have readily encountered limitations from their route of administration, need for monitoring with narrow therapeutic windows as well as their complications including heparin induced thrombocytopenic thrombosis.

Rivaroxaban inhibits free factor Xa and hence prothrombinase activity as well as clot bound Xa, thus effectively blocking thrombin generation. One advantage over VKA is that blood coagulation monitoring is not necessary. However introducing a static change into a dynamic cascade always raises concern. The concentration may **potentially** need to be measured in certain clinical situations. These may include urgent surgery, perioperative management, thromboembolic events, bleeding events and suspected overdose.

We performed a study to assess the effect of rivaroxaban on the current coagulation screen to help aid clinicians in making decisions as and when these circumstances arise. All routine coagulation screens through Northern Ireland are undertaken on a Sysmex Coagulaometer using the Innovin reagent. The Regional Specialty Coagulation Laboratory uses a Stago analyser and the STA Neoplastine CI+ reagent.

By taking thirty samples from patients on rivaroxaban,

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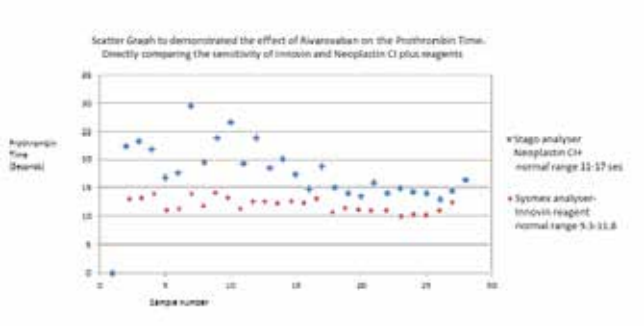
recording the dose and time from last drug ingestion we were able to measure the effect on the standard coagulation screen with both analysers. On the same samples the rivaroxaban concentration was measured with the specific anti-Xa rivaroxaban assay.

RESULTS

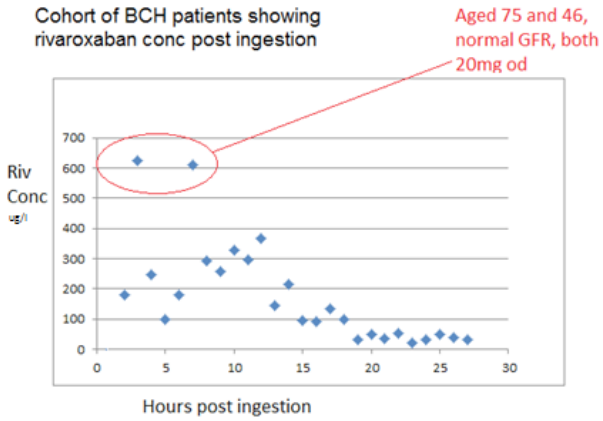
The effect on the PT and APTT was variable between analysers. The PT, in line with previous publications, was more sensitive than the APTT at smaller drug concentrations.



The Neoplastine CI plus reagent on the Stago analyser was more sensitive than the Innovin reagent to rivaroxaban concentrations.

The Neoplastine CI PT was prolonged in all samples taken within 17 hours of rivaroxaban ingestion.

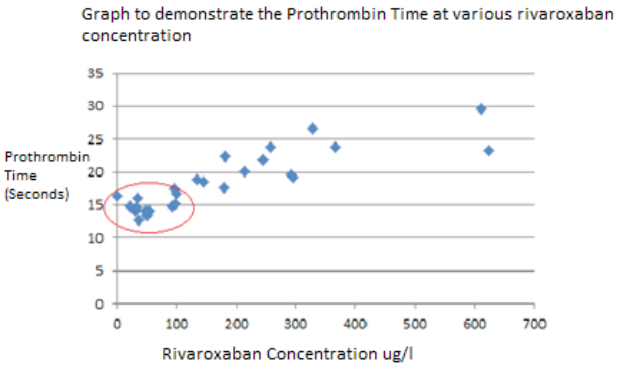
On each of the samples we ascertained the rivaroxaban concentration with a manufacturer's specific anti Xa reagent. As a control, healthy volunteers on no anticoagulation had their rivaroxaban levels measured. The volunteers' rivaroxaban levels ranged from 15-21ug/l and therefore we assume no drug is present when levels fall into, and below, this range.



Our results compare with University Hospital Hotel Dieu (Paris) which found peak concentrations up to 400ug/l and trough concentrations up to160ug/l.

However as you can see from our results two patients have a higher rivaroxaban level than expected. These patients were also taking verapamil. We noted the SPC advises rivaroxaban not to be used in patients who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors unless the potential benefit justifies the potential risk.2

There is a positive correlation between rivaroxaban concentration and Neoplastine CI PT reagent with prolongation up to a certain concentration and beyond this the effect on Neoplastine CI PT appears to plateau.



This may indicate that higher doses particularly in overdose or co prescribed CYP3A4 inhibitors may not necessarily have a directly proportional additional anticoagulant side effect.1

CONCLUSION

There is a choice of laboratory tests available to aid clinicians when it is necessary to measure rivaroxaban. Rivaroxaban anti Xa assay will quantify the drug concentration however turnaround time is within four hours. The PT, provided it is sensitive to rivaroxaban, is a quicker test and may be useful to ascertain rivaroxaban presence. However given the demonstrated plateau effect on PT at higher rivaroxaban concentrations, the PT will not give reassurance that levels are not excessive. Although smaller amounts of rivaroxaban(<100ug/l) may still be present when the PT is normal its clinical significance and its anticoagulant ability needs to be judged on a case by case basis.

The tests must be interpreted with timing of blood sample to drug ingestion making reference to known drug pharmacokinetics being mindful that assessment of the sensitive PT may be normal if checked within two hours from ingestion.

Decisions need to be made as to how this information is disseminated throughout the routine coagulation laboratories and whether the reagent current utilised needs changing in light of these findings.

Dr A Niblock, P Murray, A.M Kearney, Dr G Benson

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Corresponding author: Dr Aaron Niblock. E-mail aaronnibock@doctors.net.uk

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INFLUENCE OF ETHNIC ORIGIN ON VZV SEROPREVALENCE IN WOMEN OF CHILD-BEARING AGE.

Editor,

Chickenpox is estimated to complicate 0.7–3/1,000 pregnancies in the UK[1] with potential for severe adverse consequence to both mother and baby. Susceptibility to chickenpox can be assessed by IgG testing although this is not currently done as part of routine antenatal screening in UK. Less than 10% of women of child bearing age in Northern Ireland are susceptible to chickenpox[2] however this may vary on basis of ethnic and geographical origin. The ethnic and geographical origin of the Northern Ireland population has changed over recent decades and we wished to investigate the effect of ethnic origin on VZV seroprevalence locally using names as an indicator of likely ethnicity/geographical origin.

We reviewed Northern Ireland laboratory test requests for the time period from January 2008 to April 2015. The criteria for inclusion in the analysis were: age 16-40, female, known test result, full name recorded on test request. A total of 15,471 blood samples tested routinely for VZV IgG fulfilled these inclusion criteria.

Categorisation of names and surnames by presumed geographical origin was performed by a Medical Microbiology registrar from Belarus who had good familiarity with Eastern European names. The names were allocated to 3 groups **Group A**: Asia, Africa and Middle East **Group B**: Baltic and Eastern European, and **Group C**: UK and Western European.

Of the 15,471 blood samples, 14818 (94.1%) were categorised as Group C while Group A and B accounted for 1.6% and 2.6% of the samples respectively. Results are shown in Table 1.

Group	Non immune (negative or equivocal) / total tested (% seronegative)
Group A Asia, Africa or Middle East	51/246 (20.73%)
Group B Baltic and Eastern European	55/407 (13.51%)
Group C UK/Western European	1324/14818 (8.9%)

The proportion of non-immune samples was significantly lower in the group C samples and was highest in Group A (χ^2 test $p< 0.00001$).

These data demonstrate that varicella non-immune rates in our local population vary with ethnic/geographical origin.

The higher proportion of non-immune patients in Group A is in accordance with previously reported evidence of lower varicella seroprevalence in people brought up or living in tropical areas.[3] This has been suggested as being related to climatic differences in humidity and temperature that may affect virus survival and transmission.[4] However it is rather more difficult to postulate a mechanism for reduced seroprevalence in Eastern European female population compared to the rest of Europe. Socioeconomic and social contact factors may play a role in explaining differing varicella transmission dynamics in different European countries but this has proven difficult to elucidate.[5]

It is important to consider differences in immunity rates within populations when modelling health economic approaches to antibody screening and/or vaccination to prevent the consequences of varicella infection in pregnancy as thresholds for intervention may vary with ethnic/geographical origin.

Dr Yura Protaschik MB BCh, Registrar

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CHEMICAL BURN FROM CONTACT WITH SCRUBBING SOLUTION

Editor,

Following hand washing with Videne surgical scrub prior to administration of a spinal anaesthetic, sterile gloves were worn for approximately 20 minutes. Symptoms of itch and irritation between middle and index fingers were noticed within two hours then progression to a delineated raised erythematous area within 24 hours. Figure 1. Extensive blister development occurred over the next 48 hours. Figure 2. There was no contact with any other substances and no previous history of skin sensitivity or allergy. Following attendance at Accident and Emergency and review by the burns clinic, a diagnosis of chemical burn in the interdigital area was made.

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This was presumed to be caused by incomplete rinsing of the fingers, leaving a thin film of Videne in contact with the skin

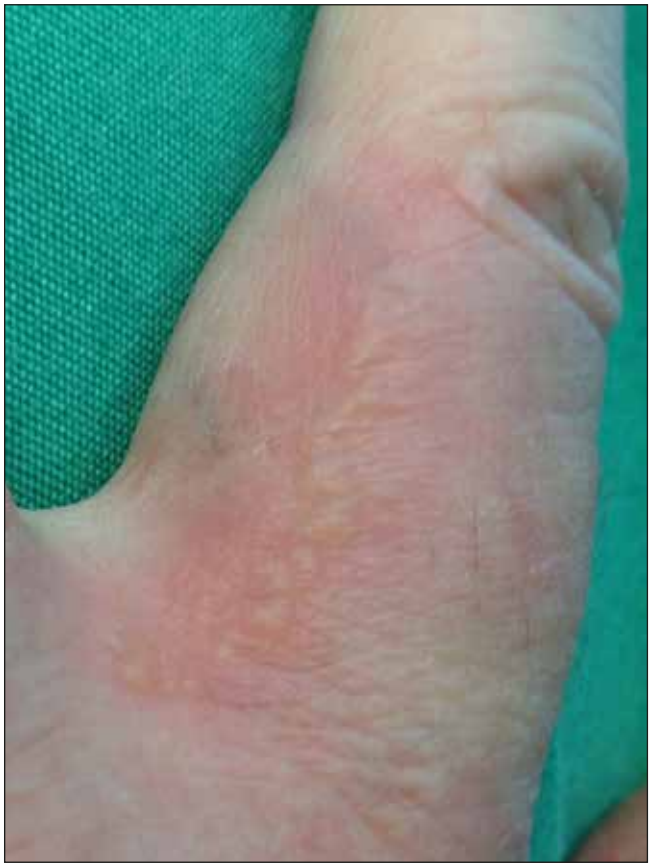

Fig. 1.

Videne surgical scrub is commonly used for pre-operative hand cleansing, or for disinfecting the incision site prior to surgery. It is manufactured by Ecolab Ltd. as an antiseptic solution and offers activity against a broad range of bacteria, viruses, fungi and some bacterial spores. [1]

Videne contains 7.5% w/w Povidone-Iodine which gives 0.75% w/w available Iodine. It is a dark brown solution similar to Bethadine, but with a variation of excipients. This results in a difference in pH of 3-5.5 (Videne) compared with pH 4-6 (Bethadine). The presence of the aluminium salt of alkylphenol ether in Videne has been suggested as the reason why Videne may be more irritant than Bethadine. [2]

Manufacturer's advice for preoperative surgical scrub is to apply approximately 3.5ml of Videne after first wetting the hands and arms with water. The Videne is then rubbed thoroughly onto these areas. A brush may be used to scrub the nails. A little water is then added to develop a lather and finally, this is rinsed off with running water [3]. Side effects are rare, but include skin reactions in Iodine sensitive patients. Both allergic and irritant contact reactions to Povidone iodine are recognised in patients. Such reactions can cause redness, induration and multiple small blisters.

Povidone-iodine in the form of Bethadine antiseptic solution has been reported to cause a chemical burn in an eight year old boy undergoing appendicectomy. The proposed mechanism was irritation from iodine coupled with maceration, pressure and friction[4].

The Pennsylvania Patient Safety Authority reports similar cases of patient burns following Bethadine application, caused by pooling of the solution beneath the patient, in intertriginous creases, or around the drapes during the surgical procedure.[5]

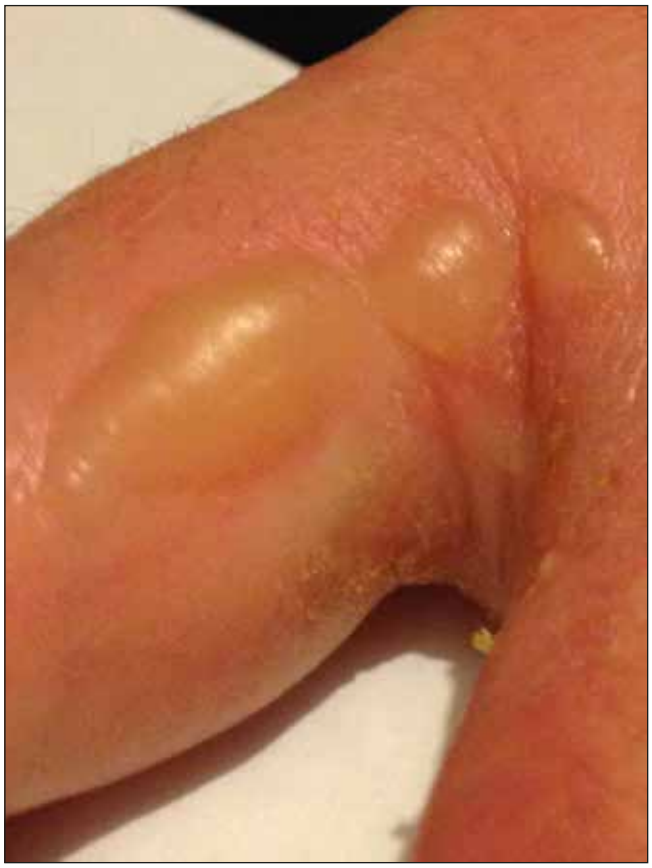

Fig. 2.

This case was unusual in that the burn developed after a short exposure time i.e. about 20 minutes, and it affected the anaesthetist rather than the patient. There was no obvious collection of Videne in the glove and therefore the volume of solution responsible for the burn must have been quite small. When the manufacturer's helpline was contacted, there were no previous reports of such injury among medical personnel.

On the advice of Occupational Health, direct patient contact was avoided until the blisters had dried completely which took approximately one week. This case serves as a reminder of the irritant nature of scrubbing solution to operating theatre personnel, following even short periods of skin contact and the importance of complete rinsing of the skin before applying surgical gloves.

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MESOTHELIAL INCLUSIONS MASQUERADING AS METASTATIC CARCINOMA.

Editor

A 35 year old female presented with a two week history of exertional breathlessness, cough and hoarseness with no reported weight loss, night sweats or fever. The patient underwent a chest x-ray and subsequent CT examination which illustrated a large right paratracheal mass.

The patient underwent a number of radiologically guided CNBs and despite raising the possibility of a diagnosis of CHL a definitive diagnosis was not possible due to the poor representation of tumour in limited tissue samples

Biopsies obtained by thoracotomy from an internal mammary artery LN and anterior mediastinal LN were submitted and felt to represent sampling from metastatic carcinoma due to a population of abnormal single epithelioid cells which were found in LN sinuses. A panel of immunohistochemistry demonstrated strong positivity of these cells with CAM 5.2, CK7 and diffuse weak positivity with ER. The cells were negative with PAX 8, TTF1, CK20, CDX2, CD68 and CD30. The morphological appearances and immunophenotype favoured a breast or upper gastrointestinal primary origin.

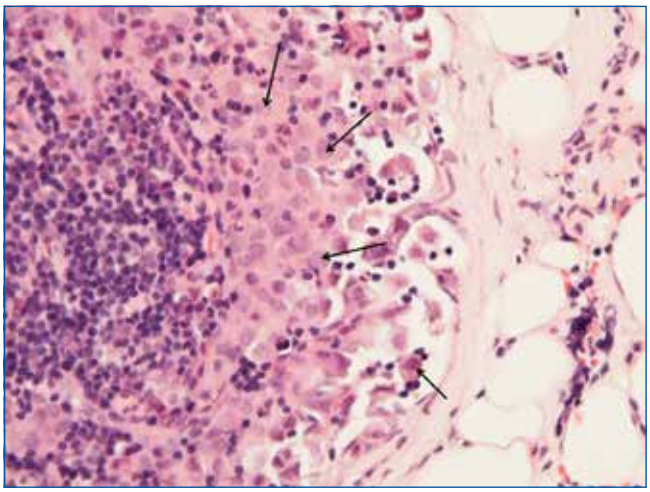

Fig 1

Extensive imaging failed to identify an occult primary carcinoma and it only became apparent at the MDT that the samples did not correspond to radiological sites of disease. Pathological review of the mediastinoscopic biopsies led to the correct identification of a rare but benign entity which can be seen when sampling LNs from the mediastinal region (mesothelial inclusions). Further immunohistochemistry performed demonstrated positivity of the epithelioid cells with WT1 and calretinin, confirming that they were indeed mesothelial in origin. Three months after the initial diagnostic procedure a final larger CNB of the mediastinal mass confirmed the previous suspicion of NSCHL. The patient has since finished the standard regime of ABVD and is currently asymptomatic and in remission.

Primary mediastinal lymphomas are most frequently of three histological varieties; NSCHL, PMBCL and lymphoblastic lymphoma. Mediastinal B cell lymphoma occurs in the third to fifth decade with a female predominance. Approximately 60% of all CHL and 20% of NHL involves the mediastinum at presentation.[1] Interestingly there are clinicopathologic and molecular similarities between PMBCL and NSCHL.[2] In addition, distinguishing CHL from PMBCL can be challenging as some patients have overlapping histological features similar to CHL and PMBCL.[3] Diagnosis is further hindered as the diagnostic RS cells in CHL range from 1-10% of all cells and may not be represented in a limited sample. Therefore it is important to have adequate tissue for morphological assessment as treatment is disease specific.

This was a complex case due to a number of factors. There are multiple possible pathologies which involve the mediastinum and even when narrowed down to lymphoma it is difficult to provide a clinically meaningful subtype due to tumour heterogeneity and poor representation in fragmented needle core biopsies. Furthermore a diagnosis of benign inclusions as a mimic of metastatic tumour was not initially considered until after MDT discussion.

There are a number of case reports recognising the pitfalls of mesothelial inclusions mimicking metastatic carcinoma and diagnostic difficulties in interpreting limited or non-representative tissue sampled from sites poorly characterised by radiological or clinical examination.[4] Benign inclusions are foci of non-neoplastic ectopic tissue in lymph nodes and they are classified into three types: epithelial, nevomelanocytic and decidual. It is important to recognise and identify this benign entity and not mistake these appearances as metastatic tumour.[5]

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ERRATUM

The editor has been informed that there is an error in the following paper:

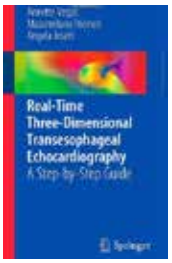
The fortunes of the legal and medical professions during the "Troubles" – Presentation to the Northern Ireland Medicolegal Society – October 14, 2014

Philip McGarry
Ulster Med J 2015; 84(2): 119 – 123,

Page 121 refers to Gordon Blair of the School of Dentistry – the correct name is George Blair. We apologise for any inconvenience caused.

Book Review

REAL-TIME THREE-DIMENSIONAL TRANSESOPHAGEAL ECHOCARDIOGRAPHY. A STEP BY STEP GUIDE.



Annette Vegas, Massimilano Meineri, Angela Jerath

Publisher: Springer, 2012. ISBN-13: 978-1-4614-0664.8. RRP £40.99

This is a richly illustrated reference book of 234 pages that has been condensed into a spiral-bound pocket book format that can sit on the patient's bed as you are performing a trans-oesophageal echo (TOE) study! The authors are anaesthetists based in Toronto General Hospital – a major Canadian cardiovascular centre.

Their cardiac surgical expertise is reflected in extensive sections on native and prosthetic valve assessment as well as transcatheter aortic valve replacement, inter-atrial septum occlusion, ventricular assist devices and cardiac masses.

The book is well suited for someone learning or performing TOE in a tertiary centre or referring patients to such a centre for cardiac valvular or device interventions.

The acquisition of images and image interpretation is well explained and there are extensive notes on the pathology of each disease as well as classifications of the different types of valves and devices with their characteristic findings on TOE. This extends to notes about the "washing jets" – small leaks associated with the movement of metallic valve leaflets that can be confused with paravalvular leaks by the unwary.

The book does not delve into post-processing of 3D images which can be time-consuming and frustrating, but the golden rule of post-processing is that you need good quality data in to get an excellent image out and the guidance offered in this book should help greatly with that.

I always take this handy pocket book into the echo lab during my TOE sessions – I can't think of a higher recommendation than that.

Dr John Purvis
Consultant Cardiologist

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Ulster Med J 2015;**84(3):**196-199

Abstracts

Ulster Society of Internal Medicine
93rd (Spring) Meeting Friday 15th May 2015

Antrim Area Hospital

PROGRAMME:

2.00 pm **Prevalence and outcome of STeMI equivalent ECGs in the primary percutaneous intervention turndown cohort.** McCarrick L, Tweedie J, Linden K, Devlin P, McGeough M, Herity N. Eastern Heart Attack Centre, RVH.

2.15 pm **Endoscopic Duodenal Stent Placement in Adults with Cancer.**

JJ McGoran, PSJ Hall, RM Mitchell, I Mainie.

Department of Gastroenterology, Belfast City Hospital, Belfast HSC Trust.

2.30 pm **Two cases of SLE complicated by macrophage activation syndrome.**

C Masih, S McDonald, N Liggett. Department of Rheumatology, Craigavon Area Hospital, Craigavon, N. Ireland

2.45 pm **Guest Lecture: "Diabetes arising from chronic pancreatitis: current and future strategies for beta cell preservation."** Dr. Philip Johnston, Consultant Endocrinologist, Belfast HSC Trust.

3.15 pm **Afternoon Tea** and **Poster Viewing**

Refreshments sponsored by **Merck, Sharp and Dohme.**

Poster 1 **A case of 'crazy paving' and treatment pitfalls.**

I Moore, N Chapman, L Polley, R Convery.

Craigavon Area Hospital, Southern Health and Social Care Trust.

Poster 2 **Bosentan-induced cholestatic hepatitis in a patient with HIV-related pulmonary hypertension. Where do we go from here?** M Monaghan[1], M Riley[2], L Jackson[1], CM Wilson[1]. 1. Cardiology, RVH 2. Respiratory Medicine, BCH

Poster 3 **Acute cardiomyopathy due to Systemic Lupus Erythematosus; A case report and discussion.** A.Gray, J. Burns, V. Moohan. Depts of Cardiology/ Rheumatology, Antrim Area Hospital, Northern HSC Trust.

3.40 pm **Grand Rounds: Cases from Antrim Area Hospital.**

Facilitator: Dr Camille Harron, Consultant Renal Physician, Northern HSC Trust.

4.10 pm **Managing an unplanned pregnancy in end stage renal failure: a stormy road ahead.** D Keenan, G Shivashankar, S Bolton.

Renal Unit, Altnagelvin Area Hospital, Londonderry. Western HSC Trust.

4.25 pm **Langerhans cell histiocytosis: Two cases reports and treatment pathways.** C Hagan, D NcNicholl, N Chapman, RP Convery. Department of Respiratory Medicine, Craigavon Area Hospital, Craigavon, UK

4.40 pm **Guest Lecture: "Investigation and management of stroke in the younger patient."** Dr Mark McCarron, Consultant Neurologist, Altnagelvin Hospital, Western HSC Trust.

5.10 pm Presentation of prize for the best abstract.

2PM ORAL

PREVALENCE AND OUTCOME OF ST ELEVATION MYOCARDIAL INFARCTION EQUIVALENT ELECTROCARDIOGRAMS IN THE PRIMARY PERCUTANEOUS INTERVENTION TURNDOWN COHORT.

McCarrick L, Tweedie J, Linden K, Devlin P, McGeough M, Herity N.

Eastern Heart Attack Centre, Royal Victoria Hospital

Since 30/09/13, the Belfast Trust has provided a PPCI service. ECG's of suspected STEMI patients are faxed to a central hub with patients being accepted or declined for PPCI utilising a regionally-agreed protocol.

STEMI equivalent ECG are those without classical ECG changes but with an acutely occluded artery;

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1. Isolated Posterior MI
2. LBBB with Sgarbossa criteria
3. ST elevation in lead aVR

We evaluated the frequency and outcomes of STEMI equivalent ECG in a cohort of patients declined for PPCI.

Criteria for activation of pathway is chest pain less than twelve hours plus either contiguous ST elevation of ≥2 mm in chest leads or ≥1mm ST elevation in limb leads. Data was collected retrospectively from 30/09/2013 to 31/03/14. Overall 557 patients were declined. 25 (4.4%) of patients within this cohort were found to have a STEMI equivalent ECG. The most common finding was an isolated posterior MI (Table 1).

TABLE 1.

Frequency and angiographic findings of patients presenting with STEMI equivalent ECG

	Patients with STEMI equivalent ECG	Proceeding to coronary angiogram	Culprit lesion at angiogram (%)
Posterior MI	14	14	100
STeAVR	7	6	100
LBBB	4	3	100

STEMI equivalent ECG are currently not incorporated within the PPCI activation pathway. Awareness and prompt recognition should prompt urgent angiography. Six month mortality within this group was 28% compared with 12% overall.

215PM ORAL

ENDOSCOPIC DUODENAL STENT PLACEMENT IN ADULTS WITH CANCER

JJ McGoran, PSJ Hall, RM Mitchell, I Mainie

Department of Gastroenterology, Belfast City Hospital, Belfast HSC Trust

Duodenal stenting has been used as an effective palliative treatment of gastric outlet obstruction (GOO).[1] A retrospective assessment of patients with duodenal stent placement since 2012 in Belfast City Hospital was carried out. We identified eighteen patients who had duodenal stenting from January 2012 to March 2015.

All patients had cancer, with gastric carcinoma comprising half of cases (9/18), four patients with pancreatic cancer, two with gallbladder carcinoma and one patient each with oesophageal, renal and cervical malignancies. Complications occurred in 16.7 % (3/18) of patients, a figure which is comparable with current literature.[2] These complications included gastroduodenal perforation (1), bleeding (1) and aspiration pneumonia (1). Only the patient with the post-procedure gastrointestinal bleed died within 30 days (cause of death not secondary to the stent insertion). Two other patients died within 30 days, secondary to infection. The hospital reporting system was used to give details regarding postoperative care. Appropriate and comprehensive advice, which involved fasting for four hours and dietary advice, was given for 66.7 % (12/18) of patients.

This study shows that duodenal stent placement is an effective palliative treatment of GOO, with involvement of the whole multidisciplinary team. Suggestions for development include centralising the service in a high volume unit and standardising postoperative advice.

1. Boskoski I; Tringali A; Familiari P; Mutignani M; Costamagna G. Self-expandable metallic stents for malignant gastric outlet obstruction. *[Review] Advances in Therapy*. **27(10)**:691-703, 2010 Oct.
2. Maire, F; Sauvanet, A. Palliation of biliary and duodenal obstruction in patients with unresectable pancreatic cancer: endoscopy or surgery? *[Review] Journal of visceral surgery*. **150(3 Suppl)**:S27-31, 2013 Jun.

230PM ORAL

TWO CASES OF SLE COMPLICATED BY MACROPHAGE ACTIVATION SYNDROME

C Masih, S McDonald, N Liggett

Department of Rheumatology, Craigavon Area Hospital, Craigavon, N. Ireland

Case 1. A 22year old man with a 6 month history of leucopaenia was admitted with pyrexia, rigors and lymphadenopathy. Antinuclear antibodies were strongly positive and a diagnosis of SLE was made. Streptococcus pneumonia, RSV and EBV were isolated and the patient deteriorated with chest sepsis and required ICU admission. With ongoing pyrexia, rash and cytopaenia macrophage activation syndrome was considered. Ferritin of 35000 and bone marrow biopsy showing haemophagocytosis were supportive. An initial response to pulsed methylprednisolone was not sustained and he required treatment with rituximab and responded well. He was maintained on a reducing dose of prednisolone and hydroxychloroquine and further treatment with rituximab is planned.

Case 2. A 28year old man with a diagnosis of SLE from Lithuania was admitted with pericarditis. He had been off all treatment since arriving in UK six years ago. Shortly after admission he had two seizures associated with atrial fibrillation with fast ventricular response and required admission to ICU. He developed chest sepsis with Klebsiella and Staphylococcus aureus, as well as partial bilateral ulnar nerve palsy. Despite intensive antimicrobial therapy and reducing doses of steroid he remained pyrexic, and had paranoid ideation. When his haemoglobin fell to 65mg/dL and a rash emerged a diagnosis of macrophage activation syndrome was considered. Ferritin was raised at 8049 though bone marrow biopsy was non-diagnostic. He responded to pulsed methylprednisolone and immunoglobulin therapy and maintenance is planned with oral prednisolone and hydroxychloroquine.

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410PM ORAL

MANAGING AN UNPLANNED PREGNANCY IN END STAGE RENAL FAILURE: A STORMY ROAD AHEAD

D Keenan, G Shivashankar, S Bolton

Renal Unit, Altnagelvin Area Hospital, Londonderry. Western HSC Trust.

This case report reviews some of the challenges presented by pregnancy in end-stage renal failure. The patient, a 29 year old female with CKD secondary to diabetic nephropathy had been progressing rapidly towards dialysis and transplantation. She had poor glycaemic control despite the use of an insulin pump and uncontrolled hypertension on four antihypertensive agents.

In 2014, her urine pregnancy test was positive and a trans-vaginal ultrasound confirmed an intrauterine pregnancy. This unplanned pregnancy was high risk both to her own health and that of the foetus. There was a high risk of miscarriage due to her diabetes, hypertension and CKD. There were also concerns about her diabetic retinopathy worsening as well as requiring intensive dialysis and impact on transplant status. At the time of conception, she was pre-dialysis (GFR 10mls/min).

Significant adaptations were needed to the dialysis programme to account for acidosis, hypophosphataemia and minimization of fluid shifts, all of which are bad for foetal development. With a well-coordinated multi-disciplinary approach, we were able to successfully manage all her risk factors during pregnancy, leading to a favourable obstetric outcome.

Managing pregnancy in dialysis patients is challenging, not least because it is a rare event. In 1984 the European Dialysis and Transplant Association recorded a surviving infant in pregnant dialysis patients being 22.9% 1. Recently though; this is higher with centres reporting a success rate greater than 70%2. We will explore some of the challenges that arise when managing the pregnant dialysis patient.

1. Successful pregnancies in women treated by dialysis and kidney transplantation: Report from the Registration Committee of the European Dialysis and Transplant Association. *Br J Obstet Gynaecol* 1980: **87**:839-835

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425PM ORAL

LANGERHANS CELL HISTIOCYTOSIS: TWO CASES REPORTS AND TREATMENT PATHWAYS.

C Hagan, D NcNicholl, N Chapman, RP Convery.

Department of Respiratory Medicine, Craigavon Area Hospital, Craigavon, UK

Pulmonary Langerhans cell Histiocytosis (LCH) is a rare Interstitial Lung Disease characterised by infiltration of the lung with histiocytes. Studies suggest an incidence of 2 per million/population and a strong association with cigarette smoking. Clinical features comprise exertional breathlessness, cough and systemic symptoms with an increased risk of pneumothorax. High Resolution Computed Tomography (HRCT) features include diffuse centrilobular nodules and widespread cystic lesions which typically spare the costophrenic angles. Diagnosis is usually based on a combination of clinical and radiological findings. Confirmation by histology from an open lung biopsy demonstrates abnormal proliferation of Langerhans cells, characterised by the presence of Birbeck granules on electron microscopy.

We report the presentation and treatment pathway up of two cases of LCH.

Case 1: 59 year old male smoker presented with dyspnoea and cough. HRCT showed widespread nodular opacities, bilateral cavities and widespread pulmonary infiltrates. Management included smoking cessation and a combination of prednisolone and azathioprine resulting in clinical and radiological improvement.

Case 2: 46 year old male ex-smoker presented with dyspnoea and wheeze following a recent admission with pneumonia. HRCT demonstrated multiple cysts with basal sparing. He was commenced on steroids; resulting in symptomatic and physiological improvement.

Conclusion: We describe the use of immunosuppressant therapy in a rare interstitial lung disease with the view to preventing disease progression and the requirement for lung transplantation.

POSTER 1

A CASE OF 'CRAZY PAVING' AND TREATMENT PITFALLS

I Moore, N Chapman, L Polley, R Convery

Craigavon Area Hospital, Southern Health and Social Care Trust

A 49-year-old male with a history of significant alcohol misuse presents with progressive cough and dyspnoea over a 6 month period. There had been little improvement with antibiotic or inhaler therapy. He is a life-long smoker with no previous respiratory history. Routine CXR identified marked alveolar shadowing over both midzones with relative apical and basal sparing. After assessment at respiratory clinic he proceeded to CT Chest which demonstrated a 'crazy paving' pattern of interstitial infiltrate with no significant adenopathy or mass lesion. Subsequent bronchoscopy was unremarkable and culture negative. After multi-disciplinary discussion this patient proceeded with surgical lung biopsy. A histological diagnosis of pulmonary alveolar proteinosis was confirmed.

Pulmonary alveolar proteinosis (PAP) is a rare condition with an estimated incidence of 0.2 per million of the population1. The condition results in the abnormal accumulation of

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surfactant within the alveoli. The majority of cases are felt to be autoimmune in nature with granulocyte macrophage-colony stimulating factor (GMCSF) proving to be a key cytokine in this pathophysiology2. Total lung lavage is currently gold standard treatment.

Attempts to arrange the recommended treatment of total lung lavage in this case had been initially hampered due to social circumstance. In the last few months however due to a general deterioration in his symptoms and pulmonary function extra efforts have been made to facilitate treatment with an elective admission at the end of April.

1. Borie et al. Pulmonary alveolar proteinosis, *Eur Respir Rev*, 2011;**20**:98-107

2. Mani et al. Exogenous Granulocyte-Macrophage Colony-Stimulating factor administration for Pulmonary Alveolar Proteinosis, *Am J Respir Crit Care Med*, 2000;**161**:1143-1148

POSTER 2

A CASE OF BOSENTAN-INDUCED CHOLESTATIC HEPATITIS IN A PATIENT WITH HUMAN IMMUNODEFICIENCY VIRUS-RELATED PULMONARY ARTERIAL HYPERTENSION (HIV-PAH).

WHERE DO WE GO FROM HERE?

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HIV-PAH is a rare life threatening complication of HIV infection, occurring in approximately 1 out of every 200 HIV-infected patients (0.5%) .[1]

Bosentan is an oral nonselective endothelin-1 receptor antagonist (ERAs) used for the treatment of HIV-PAH.

Patient A was diagnosed with both HIV and associated PAH in 2004. At this time she was WHO FC IV with a mean PAP of 51 mmHg (78/35) and CI 2.35 by right heart catheterisation. Echocardiogram showed a moderately dilated right ventricle (EDD 37mm) with moderate impairment of right ventricular systolic function.

She was commenced on Bosentan in addition to Warfarin and anti-retroviral medication. Her WHO FC improved to class I-II with a concomitant improvement in RV dimensions and function and normal NT-pro BNP.

In June 2014 she had significant derangement of her LFTs (AST

198, GGT 1353, ALT 239, ALP 448). Hep B, C, Copper, alpha-1-antitryspin and AFP returned as normal. MRCP showed normal bile ducts and no cholangiopathy. CT and MRI liver were normal. Bosentan was withdrawn and liver function normalised.

The patient reported a decline in functional capacity with a measured rise in NT-pro BNP. Catheterisation showed a mean PAP of 36 mmHg (67/22) and CI 2.86. She was commenced on the phosphodiesterase type-5 inhibitor, Sildenafil 25 mg TID.

While transaminitis is a recognised side-effect of Bosentan a cholestatic picture is less recognised. There is limited information available on the safety and efficacy of Sildenafil in HIV-PAH.

This case illustrates the importance of on-going monitoring of LFT's in patients on ERA's and that aggressive treatment of PAH in the setting of HIV infection may have a good prognosis.

1. Sitbon O, Lascoux-Combe C, Delfraissy JF, Yeni PG, Raffi F, De Zuttere D, Gressin V, Clerson P, Sereni D, Simonneau G Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med*. 2008;**177(1)**:108.

POSTER 3

ACUTE CARDIOMYOPATHY DUE TO SYSTEMIC LUPUS ERYTHEMATOSUS; A CASE REPORT AND DISCUSSION.

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Systemic Lupus Erythematosus is a multisystem autoimmune disease with cardiac involvement being the second most common manifestation after renal disease. Whilst valvular disease, coronary artery disease and pericardial disease are common cardiac manifestations, lupus cardiomyopathy is an uncommon but severe complication that can lead to acute severe bi-ventricular failure. Treatment considerations are predominantly based on evidence from case reports with a lack of consensus opinion on optimal management.

Here we present the case of a 35 year old male who initially presented to the out-patient department with symptoms, clinical signs and serology in keeping with systemic lupus erythematosus. Following initial treatment his symptoms continued to progress and he was admitted to hospital for further treatment and investigation. Despite appropriate management his condition deteriorated further requiring admission to the intensive care unit for ventilatory and inotropic support. Chest imaging indicated a pneumonitis and additionally echocardiography revealed severe impairment of left and right ventricular function. A diagnosis of acute cardiomyopathy due to lupus myocarditis was suspected and he was commenced on high dose intravenous steroids and immunoglobulin. Follow up imaging at day 5 and 12 revealed significant improvement in cardiac function.

The case concludes with a discussion of the presumed aetiology of lupus myocarditis, investigation, differential diagnosis, findings from previous case reports and suggested treatment options.

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Abstracts

18th Meeting of the Irish Society of Human Genetics, Friday 4th September 2015.

Dublin City University.

PROGRAMME:

10.00 – 10.55	Registration / Tea and Coffee.
10.55 – 11.00	Welcome.
11.00 – 12.15	Oral Presentations. Plenary I: clinical research.
12.15 – 13.15	**Keynote address:** *"The 100,000 Genomes Project"* Prof. Mark Caulfield, William Harvey Research Institute, Bart's and The London School of Medicine and Dentistry, Queen Mary University of London, UK.
13.15 – 14.15	Lunch (Provided) and Poster viewing.
14.00 – 14.15	Council Meeting
14.15 – 15.30	Oral presentations. Plenary II: Basic research.
15.30 – 16.00	Tea and coffee / Poster viewing.
16.00 – 16.15	ISHG AGM.
16.15 – 17.15	**Keynote address**: *"Clinical Implications of 2-day whole genome sequencing of acutely ill infants"* Prof. Stephen Kingsmore, Dee Lyons/ Missouri Endowed Chair in Genomic Medicine, Children's Mercy - Kansas City, USA.
17.15 – 18.00	Wine reception / Presentation of Prizes / Meeting close.

SPOKEN PAPERS:

S01. Diagnostic Yield of the Microarray in Paediatric Practice

HA Deeny[1], AM Murphy[1], D O'Rourke[2], S Gallagher[1]

[1]Paediatrics Department, University Hospital Limerick, [2]Department of Laboratory Medicine, University Hospital Limerick

Comparative Genomic Hybridisation (CGH) Microarray has been available in Ireland to Paediatricians from the year 2011. Guidelines for investigation of infants and children with features of developmental delay, dysmorphic features and some cases of epilepsy, recommend the use of CGH Microarray as part of a series of investigations[1].

Our study focused on infants and children screened over the 36 month period from July 2011 to July 2014. Any parent samples sent were excluded and data was entered anonymously on to an excel spreadsheet. Data extracted included; Patient demographics, requesting speciality and indications for testing (Global Developmental delay (GDD), Autism (ASD), Dysmorphic features, Epilepsy and other).

The results showed n=303 children and infants had a microarray sent during the 36 month period chosen. Of these 248 were available for processing. Indications were 46% for Developmental delay, 22.5% for ASD, 14% for dysmorphic features and 12% epilepsy. 23% overall were returned with abnormal Microarray with 14.5% BCNV. Diagnostic yield was 7.3% overall with a 9.5% yield in GDD and 10.9% in ASD. This correlates with previous studies showing a diagnostic yield of 7.8% in GDD and 10.6% in dysmorphic children[2]. In conclusion the Microarray is an investigation in limited selection of disorders and can aid clinicians in obtaining a diagnosis in previously extensively investigated children with no definitive diagnosis.

References: 1. Miller DT *et al*. Consensus statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies. *Am J Hum Genet*. 2010;**86(5):**749. 2. Ellison JW *et al*. Clinical Utility of Chromosomal Microarray Analysis. *Pediatrics* 2012;**130(5)**:e1085-95.

S02. The Next Step in Cardiac Genetics: Targeted gene panels and next generation sequencing in inherited cardiac conditions

G Rea[1,2], JS Ware[1,2], EG Lightman[2], R Walsh[1,2], S John[2] ,T Homfray[3], J Till[3], S Prasad[3], R Buchan[2], S Wilkinson[2], PJR Barton[1,2], SA Cook[1,2,4]

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Inherited cardiac conditions (ICCs) represent a significant cause of morbidity and mortality. Wide variability in expression and penetrance limit the utility of clinical cascade screening in families, whilst the role of molecular diagnosis has traditionally been hampered by the genetic heterogeneity of many ICCs. Currently, new genomic sequencing technologies are transforming the role of molecular genetic testing in ICCs, substantially increasing the diagnostic yield, allowing accurate diagnosis, risk stratification, targeted therapy and cascade molecular screening. We report selected cases from our experience with targeted gene panels coupled with next generation sequencing (NGS) in families with suspected ICC's. Advantages of NGS include the ability to comprehensively sequence large genes such as TTN and RyR2 and the ability to simultaneously sequence multiple genes implicated in disease, including genes for phenocopies, reducing the need to multiple stage testing. We illustrate the impact that targeted gene panels coupled with NGS are having on patient care with respect

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to ICCs, using illustrative cases of Dilated Cardiomyopathy, Catecholaminergic Polymorphic Ventricular Tachycardia and Sudden Unexplained Death. The molecular aetiology in these cases would not have been identified using conventional approaches. By demonstrating the transformative potential of this approach we seek to motivate clinicians to move to comprehensive gene panels as a first line for genetic testing in ICCs, to 're - test' previously 'genotype negative' ICC samples and to consider broad based molecular genetic testing in selected novel situations.

S03. An overview of the incidence and impact of MYH polyposis gene mutations in an Irish Cohort

TP McVeigh[1], N Cody[1], M Meany[1], C Carroll[1], R O'Shea[2], DJ Gallagher[2], C Clabby[1], AJ Green[1]

[1]Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin, [2]Mater Misericordiae University Hospital

The MYH gene encodes a DNA-glycosylase enzyme, which is involved in base excision repair. Bi-allelic mutation of MYH confers predisposition to polyposis and gastro-intestinal malignancies, and is distinct genetically and clinically from autosomal dominant adenomatous polyposis coli. In Europe, two common mutations (G382D and Y175C) are reported in 90% of MYH-associated polyposis. We aimed to examine the incidence and impact of MYH mutations in an Irish cohort. A retrospective cohort study was undertaken. Patients tested for MYH mutations were identified by searching electronic patient databases iGene and Crumbase using terms "MUTYH" and "MYH". Patient charts were reviewed for details regarding phenotype and genotype.

Ninety-four patients from forty-one families were tested for MYH mutations. Bi-allelic mutations were identified in eighteen individuals (14 families), and mono-allelic mutations in another 28. At least one of G382D or Y175C was detected in bi-allelic cases. Nine families had bi-allelic status for one/both common European mutations. There was no age difference between mono- and bi-allelic mutation carriers (51±16–v-56±13years, p=0.244). Nine (50%) bi-allelic mutation carriers developed cancer of colon/rectum, compared to 1(4%) patient with mono-allelic mutation. The average age at diagnosis was 49 years (±13). Polyposis was reported in eleven (61%) bi-allelic and 3(11%) mono-allelic mutation carriers.

Mutations were detected in 14/41(34%) families. Bi-allelic MYH mutations confer a strong risk of early-onset colorectal cancer, while risk in mono-allelic carriers reflects that of background population. Screening of bi-allelic mutation carriers is recommended, while screening mono-allelic carriers may not be of any extra benefit over routine national screening programs.

S04. When it comes to exomes, expect the unexpected

J Casey[1], E Crushell[2], J Hughes[2], E Losty[2], D Slattery[3], A Green[4], S Ennis[5], SA Lynch[1]

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Consanguinity, or cousin marriage, is widely practised in several global communities. It is well known that consanguinity increases the risk of having a child with an autosomal recessive disorder. Our exome sequencing studies involving consanguineous Irish Traveller families have led to some additional unexpected findings.

Firstly, we found that the risk of incidental findings in consanguineous families is skewed; there is a reduced risk of identifying dominant disorders and carrier status but an increased risk of identifying additional recessive disorders. On average, we analyse <1% of the total exome variants after implementing filtering criteria which should minimise/eliminate the risk of incidental findings. Nevertheless, we have made an incidental finding in 10% of families which is much higher than the expected 3% in non-consanguineous families.

Secondly, we found that 26% of patients who underwent exome sequencing had more than one recessive disorder. In some cases, a second recessive disorder was suspected prior to sequencing. In others, it was unexpected. The presence of two recessive disorders results in unusual phenotypes which complicates making a diagnosis. In most cases, the mutations causing the two recessive disorders are on different chromosomes. However, in some families, the causative mutations are in linkage disequilibrium and co-segregate. It is important to determine whether the two disorders are linked or not as it has important implications for genetic counselling.

In conclusion, our exome studies have raised the interesting observation of patients having multiple recessive disorders, highlighting the need for careful clinical workup and data analysis.

S05. Translating research exome analysis into clinical practice – the Belfast-DDD experience

CW Kirk, S McKee, DDD Project

Northern Ireland Regional Genetics Service

Rare genetic syndromes causing dysmorphism and disability in childhood pose a significant diagnostic challenge, and traditional "one gene at a time" methods result in a diagnostic odyssey that can be time consuming and expensive. The DDD ("Deciphering Developmental Disorders") Study has recruited almost 14,000 cases of rare, presumably genetic, disorders into a pipeline to deliver full exome data as well as copy number analysis, in an effort to identify new disease genes and advance the use of next generation sequencing in diagnostics.

Since the project started in 2012, the NI Regional Genetics Service has recruited over 700 families, making it the second-highest recruiter per capita in the UK. We have received results in 34 cases so far, and analysis is on-going in the others.

Among the genes identified are: ANKRD11, PPP2R1A, PPP2R5D, SATB2, SYNGAP1 and GRIN2B. Many of these diagnoses were unexpected, or the genes unavailable for testing via the routine clinical service.

Feedback from the families has been universally positive, allowing several families to achieve "closure" in relation to the diagnosis in a deceased child, or to appreciate recurrence risks for future pregnancies.

Challenges remain in moving this research pathway into the routine clinical arena, and larger studies such as the UK 100,000 Genomes

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Project demonstrate that each new advance is a stepping stone on a long road. We require robust analyses of the clinical and financial benefits of these new technologies, and a clear commitment from health service providers that this is the direction we should be taking.

S06. NRXN1 (Neurexin-1) deletion; A common finding with advent of array but what are its effects?

M Al Shehhi[1], S Shen[2], L Gallagher[3], DR Betts[1], L McArdle[1], A Green[1], SA Lynch[1]

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Recently both point mutations and deletions of neurexin-1 (NRXN1) have been described as a common cause of Autism spectrum disorder (ASD) and other neurodevelopmental disorders. We have identified 37 individuals with NRXN1 deletions in our database of which 22 were index cases. We sought to ascertain the presenting features of index cases and the phenotype, if any, in their relatives.

The cohort was identified by database review of patients referred to our department in whom a neurexin-1 deletion was identified. Chromosome array testing was performed at the cytogenetics laboratory at OLCHC and Guys Hospital London. Genomic data and clinical phenotype information was extracted and analysed.

18/22 (82%) probands were investigated because of developmental delay particularly in speech and language. 4/22 (64%) patients had ASD, 13 had learning difficulties, 4 had seizures. Interestingly, 6/22 were tested because of malformation including congenital heart defect. 8/22 had intronic deletions. 3/22 cases arose de novo. Of the 15 inherited deletions, 2 relatives had a mild ASD phenotype. The majority 13/15 of relatives identified as deletion carriers had a normal phenotype.

Our data suggest that neurexin-1 deletions present with a variable phenotype and are not fully penetrant. Whilst, a parent that carries the deletion has a 50% risk of passing the deletion on, the risk of a child developing ASD is unknown. Genetic Counselling is problematic as the additional factors that trigger the phenotype are unclear. Cascade screening is currently not recommended as it is not possible to predict development of ASD accurately. Intron 5 deletion is pathogenic and further genotype-phenotype correlation studies may help us understand the variability observed.

S07. Transcriptome analysis of CD4+ T cells in coeliac disease

EM Quinn*, C Coleman*, B Molloy, P Dominguez Castro, V Trimble, N Mahmud, R McManus

Department of Clinical Medicine, Trinity College Dublin, St James Hospital, Dublin 8.

Genetic studies have to date identified 43 genome wide significant coeliac disease susceptibility (CD) loci comprising over 70 candidate genes. However, how altered regulation of such disease associated genes contributes to CD pathogenesis remains to be elucidated. Recently there has been considerable emphasis on characterizing cell type specific and stimulus dependent genetic variants. Therefore in this study we used RNA sequencing to profile over 70 transcriptomes of CD4+ T cells, a cell type crucial for CD pathogenesis, in both stimulated and resting samples from individuals with CD and unaffected controls. We identified extensive transcriptional changes across all conditions, with the previously established CD gene IFNy the most strongly up-regulated gene (log2 fold change 4.6; $P_{adjusted} = 2.40x10^{-11}$) in CD4+ T cells from CD patients compared to controls. We show a significant correlation of differentially expressed genes with genetic studies of the disease to date ($P_{adjusted} = 0.002$), and 21 CD candidate susceptibility genes are differentially expressed under one or more of the conditions used in this study. Pathway analysis revealed significant enrichment of immune related processes. Co-expression network analysis identified several modules of coordinately expressed CD genes. Two modules were particularly highly enriched for differentially expressed genes ($P<2.2x10^{-16}$) and highlighted IFNy and other genetically associated transcription factors which showed significantly reduced expression in coeliac samples as key regulatory genes in CD.

S08. Oestrogen withdrawal, breast cell transformation, and breast cancer risk in women with the KRAS-variant

TP McVeigh[1], S Jung[2], D Salzman[3], MJ Kerin[1], S Nallur[3], M Dookwah[3], AA Nemec[3], J Sadofsky[3], T Paranjape[3], O Kelly[3], E. Chan[3], N Miller[1], KJ Sweeney[1], D Zelterman[3], J Sweasy[3], R Pilarski[4], D Telesca[2], JB Weidhaas[2]

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The KRAS-variant rs61764370 is a single nucleotide change in the let7a-binding site of the KRAS gene. It has been previously associated with increased risk of cancer of the breast and ovary. This risk may be modified by environmental factors such as HRT use.

We aimed to evaluate the effect of oestrogen exposure and withdrawal on development of breast cancer in patients with the KRAS-variant.

Isogenic mammary (MCF10A) cell lines with and without KRAS-variant were cultured and observed for oncogenic transformation in charcoal-stripped media following withdrawal and restoration of oestrogen. In vivo investigation was performed by case-control analysis. Data was collected with respect to pathological characteristics, reproductive risk factors and anthropomorphic measurements from a cohort of patients with breast cancer and an unaffected control group of variant carriers.

Addition of tamoxifen to charcoal-stripped media led to 7.9-fold increase in oncogenic transformation in isogenic cell lines with the KRAS-variant, with reduction in colony formation after restitution of oestrogen. In vivo, affected carriers were significantly more likely to have had an oophorectomy pre-diagnosis than wild-type patients ($p=0.033$), and had lower median BMI ($p<0.01$) than unaffected participants with the variant . HRT-discontinuation in variant carriers was significantly associated with post-menopausal triple negative breast cancer ($p<0.0001$), and with cancer of higher grade ($p<0.0001$).

Oestrogen withdrawal in vitro and a low oestrogen state in vivo appear to increase risk of breast cancer and predict aggressive tumour biology in women with the KRAS-variant.

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S09. Identifying genetic predictors of skin cancer in renal transplant populations

CP Stapleton[1], M McCormack[1], D Connaughton[2], PJ Phelan[3], GL Cavalleri[1], PJ Conlon[2]

[1]Department of Molecular and Cellular Therapeutics, RCSI, Dublin, [2]Beaumont Hospital Kidney Centre, Dublin, [3]Department of Nephrology, Royal Infirmary of Edinburgh, NHS Lothian.

Renal-transplant recipients have a 33-fold increased risk of developing non-melanoma skin cancer relative to an age-matched non-transplanted individual. In this study we set out to map germline genetic variations influencing the development of skin cancer in our cohort of 325 renal-transplant recipients, using a genome-wide association study (GWAS) and candidate gene study design.

Both logistic regression and survival analysis was applied in our GWAS. Survival analysis was used in our candidate gene study. Multiple robust genetic loci for skin cancer in non-transplant populations have been identified via large GWAS. These genetic predictors of skin cancer (n=21) were examined to see if they have a higher effect size in renal-transplant recipients compared to non-transplant populations.

For the candidate SNP analysis, a nominally significant association was found with a SNP in the MC1R gene (p= 0.0157). The variant was found to have the same direction of affect as described in the original study and the odds ratio was higher. The presence of one or more copies of the minor allele caused a significant decrease in time to developing skin cancer post-renal transplantation (hazard ratio = 2.06). We found a significant association in our GWAS between time to developing skin cancer post transplantation and a variant in SPOCK1 ($p = 4x10^{-8}$). We found that heterozygote individuals developed skin cancer 7 times faster than wild type homozygotes. We will be carrying out further testing in other cohorts for validation of results.

This work is funded by Irish Research Council for Science, Engineering and Technology.

S10. The Irish DNA Atlas– a Study of Genetic Diversity in Ireland

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Aims: The Irish DNA Atlas is a DNA collection being assembled with the aim of describing the fine-scale population structure in Ireland. Understanding such structure can inform on optimal design of clinical genetic studies as well as the history of the Irish population. We will present an overview of and the preliminary findings from the study.

Methods: We are recruiting individuals with all eight great-grandparents born in Ireland, within 30 kilometres of each other. Participants are asked to complete a detailed birth-brief, which records place and date of birth of three generations of ancestors. We also collect some basic health-related details. DNA is extracted from a saliva sample. We have genotyped using an Illumina OmniExpressdense SNP genotyping platform. We present a number of analyses designed to visualise genetic structure, including; Principle Component, ADMIXTURE, and Runs of Homozygosity analysis.

Results: To date we have recruited 162 participants. The mean great-grandparental area is 32 kilometres, with an average great-grandparental date of birth of 1850. Therefore the individuals in the Atlas provide insight to the genetic landscape of Ireland before significant movement of people from the 20th century onwards. An analysis of dense genotyping data from 142participants shows that the Atlas participants cluster closely with British individuals in a Europe wide PCA, but present different ancestral population components when compared with British, and other European populations. Irish individuals also present slightly higher levels of homozygosity relative to mainland European levels. PCA targeted at specific areas of interest within Ireland also hint at fine-scale substructure.

Conclusion: Ireland shows typical features of a homogenous population, well suited to the study of rare variation in disease risk.

S11. Clinical and genetic predictors of patient response to lacosamide

SB Heavin[1], M McCormack[1], L Slattery[1], N Walley[2], A Avbersek[3], J Novy[3], S Sinha[2], N Alarts[4], B Legros[4], R Radtke[2], C Doherty[4], C Depondt[5], S Sisodiya[3],D Goldstein[6], N Delanty[1,7], GL Cavalleri[1]

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There are ~37,000 people in Ireland living with epilepsy. Anti-epileptic drugs (AEDs) control seizures in up to 70% of patients. Lacosamide (LCM) is an AED that is licenced for the treatment of focal-onset seizures. We aimed to determine the clinical and genetic predictors of LCM responsive and non-responsive patients. A total of 483 patients, who were previously refractory to medication, were recruited from four tertiary epilepsy referral centres: Dublin, Ireland; London, UK; Brussels, Belgium; North Carolina, USA. Response to LCM was determined according to four categories; (i) seizure freedom, (ii) ≥75% reduction in seizure frequency, (iii) seizures worsening and (iv) no response. Overall, 13% of patients showed a positive response (seizure freedom or ≥75% reduction in seizure frequency) to LCM treatment. Response varied depending on epilepsy diagnosis, with idiopathic generalised epilepsy (also known as genetic generalised epilepsy) emerging as a potential target group for LCM treatment. An adverse drug reaction causing discontinuation of LCM treatment was recorded in 19% of patients. Genome wide association (GWAS) and whole exome sequencing (WES) was used to investigate the importance of genetic variation in predicting LCM response. Analysis of common variation via GWAS pointed to a locus containing the KALRN gene as potentially predictive of membership to the seizures worsening group. Analysis of rare variation via WES did not identify any additional variant or gene associated with particular LCM response groups.

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S12. Unfolded Protein Response in a mouse model of Messmann's Epithelial Corneal Dystrophy

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Corneal dystrophies are a group of blinding inheritable conditions with a collective worldwide incidence of 1 in 2,000. Meesmann's epithelial corneal dystrophy (MECD) is a rare autosomal dominant disorder with phenotypes of varying severity ranging from asymptomatic to foreign body sensation, photophobia, presence of anterior epithelium microcysts and corneal scarring. It is caused by dominant-negative heterozygous missense mutations found within the KRT3 or KRT12 genes encoding the cytoskeletal keratins K3 and K12. To investigate the pathomechanism of this disease we generated and characterized a novel knock-in humanised mouse model carrying the MECD-associated Leu132Pro mutation.

Although no overt changes in corneal opacity were detected by slit-lamp examination, heterozygous mice exhibited a subtle histological and ultrastructural phenotype of cell fragility within the corneal epithelium, which was greatly exaggerated in homozygous animals. Mutant corneal epithelial cells were larger, contained prominent intracellular spaces and showed overt cytolysis with occasional cell rupture at the corneal surface.

Immunohistochemical analysis showed that the humanized mutant K12 protein was expressed specifically in the anterior corneal epithelium and revealed an altered keratin expression profile in the cornea of mutant mice that was confirmed by quantitative Western blot analysis.

Analysis of expression of unfolded protein response (UPR) markers, Caspase 12 and DDIT3, revealed up regulation of both markers in homozygous mice and DDIT3 in the heterozygous mice. A TUNEL assay revealed that the apoptotic rate in the mutant cornea was increased 17–fold compared to the wild type ($p<0.001$).

Thus, we have developed a novel mouse model for MECD, which up-regulates UPR pathways that will be a valuable resource for development of therapeutics targeting dominant-negative corneal dystrophies.

POSTER PRESENTATIONS:

P01. A Neurofibromatosis type 1 database for ROI

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Neurofibromatosis type 1 (NF1) is a multisystem variable genetic condition that causes benign tumours in various organs, mainly the skin, eyes and brain. Other associated health complications are epilepsy, scoliosis, learning difficulties and autism. Our aim was to set up a database of the NF1 patients who had been through our Service since it was set up in 1995, detailing how they were affected by the condition. We run a fortnightly NF clinic that is funded by NF Ireland. We used the database template that is used in the Belfast NF clinic.

A cohort of 575 patients with NF1 was recorded on the database on 20/02/2015. The prevalence of NF1 is reported to be 1/3000 live births and based on the estimated population there should be 1,600 individuals with NF1 in ROI.

We identified 13 women with NF1 who were in their 40's and warranted breast surveillance. With their permission, we wrote to their GPs requesting that this be put in place.

We also identified 24 individuals who would be transitioning from Paediatric to Adult services. We wrote to them offering a Genetics Consultation to discuss screening for adults with NF1 and the genetics of the condition. So far, 5 have accepted this offer.

Already this database is proving to be a useful tool for monitoring and identifying NF1 patients who may benefit from screening and/or Genetics review. Also, recording the clinical features of NF1 patients will help us to identify those patients with complex NF1 who require Specialist input.

P02. Titin Truncating Variants are common in patients with myocardial infarction and low ejection fraction

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The Titin gene is a major determinant of myocardial function and its importance in familial and 'idiopathic' Dilated Cardiomyopathy (DCM) has recently been ascertained. We hypothesize that patients with pronounced left ventricular dysfunction following myocardial infarction (MI), when controlling for infarct parameters and coronary anatomy, may have a high burden of TTN truncating variants (TTNtvs). We studied a large cohort (n=335) of post-MI patients. Gadolinium-enhanced Cardiac Magnetic Resonance (CMR) was used to characterise cardiac dimensions, function and tissue properties, the size and thickness of MI were quantified using a standard 17-segment model. Targeted re-sequencing of TTN was performed. Genetic variation in TTN in 430 ethnically matched healthy volunteers along with public repositories, were used for variant annotation and comparison. Our analyses show that out of the 335 post-MI patients, nine (2.7%; ~1 in 35 post-MI cases) had a TTNtv. Patients with a TTNtv had a significantly lower LVEF than those without (31.2±13.9% vs. 41.2±14.7%; p=0.026). An LVEF <30% is used to guide device therapy in post-MI patients and as hypothesized, TTNtv were significantly enriched in this group compared to MI patients with higher LVEFs (6.98% vs. 1.21%, p=0.01). These data identify a novel role for truncating variants in TTN, a DCM gene, in post-MI systolic dysfunction. Intriguingly, the effect size of the TTNtv is equal or greater than many of the infarct covariates used to guide re-vascularisation therapy. Based on these findings it will be important to explore if genetic stratification of the post-MI patient can inform treatment strategies.

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P03. The extent of Lymphangioleiomyomatosis (LAM) in the Tuberous Sclerosis (TS) population in NI

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Lymphangioleiomyomatosis (LAM) is a multisystem disease affecting, almost exclusively female, TS patients. It is characterised by cystic lung destruction and symptoms occur from the 2nd or 3rd decade onwards. Recently, new treatments, e.g. mammalian target of rapamycin (mTOR) inhibitors, have been found to be effective. It is important that women are screened for symptoms for this condition to allow for early intervention. We have 43 women with TS over the age of 18 years. All were sent out a questionnaire regarding respiratory symptoms, treatment and follow-up to determine the extent of LAM in our population. We aim to use this data to improve screening for LAM in our regional TS clinic.

P04. Connexin 26/30 & deafness: our experience of 5 years

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Congenital hearing loss is the most prevalent and genetically heterogenous sensorineural disorder. Around 50% congenital hearing loss in genetic in nature and can be syndromic (30%) or non syndromic (70 %). Autosomal recessive non syndromic deafness is the commonest cause of genetic hearing loss predominantly related to connexin 26/30 genes. The genetic forms of hearing loss are diagnosed by otologic, audiologic, and physical examination, family history, ancillary testing (e.g. temporal bone CT, ECG), and molecular genetic testing. In the absence of a specific diagnosis, empiric recurrence risk coupled with connexin 26/30 results is used for genetic counselling. We analysed our data of past 5 years (2010-14) of connexin 26/30 gene mutation analysis. Connexin 26/31 gene mutation analysis was done in 61 individuals. Fifteen had developmental delay and/or dysmorphism and eighteen had other genetic investigations either pre or post connexin 26/30 testing. Temporal bone imagining and ECG was not done routinely .Three had array CGH identified chromosomal abnormality, two had confirmed diagnosis of Pendred syndrome and three were investigated for Waardenburg syndrome. Connexin 26/30 mutation related deafness was identified in 8 individuals (13%). Five were homozygous for 35delG and three were compound heterozygous. All the mutation positive individuals had bilateral, prelingual, severe to profound SNHL with no dysmorphism or developmental delay excluding the speech. The antenatal and postnatal history was not significant and the inner ear imaging was normal. When these characteristics were taken into consideration the diagnostic yield improved to 22 % highlighting the phenotype associated with Connexin 26/30 related hearing loss.

P05. Initial experience on transportation based PGD/PGS in Ireland

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Preimplantation genetic diagnosis/screening (PGD)/ (PGS) is a reproductive option for couples at risk of a genetically abnormal pregnancy. This study reviews the outcome of all biopsy cycles performed at Cork Fertility Centre (CFC) since the programme began.

Embryo biopsy and embryo transfer procedures were performed at CFC while genetic analysis of the biopsy cells was carried out at Reprogenetics, UK. Biopsied embryos were cryopreserved by vitrification. Unaffected embryos were warmed and transferred in a subsequent frozen embryo transfer (FET) cycle. Seven couples have completed a PGD/PGS cycle at CFC, five for single gene disorders, (cystic fibrosis-3 cases, Mucolipidosis and Smith-Lemli-Opitz Syndrome). The other two couples underwent PGS.

In total, 39 embryos were biopsied, 15 on day 3 (one cycle) and 24 on day 5/6.No logistic failures were found during the biopsy sample transportation. Genetic defects were detected using multiplex-PCR, karyomapping, and array CGH. Polymorphisms were used to confirm diagnosis, and detect chromosome abnormalities. Genetic testing identified 15 unaffected and 19 affected embryos with single gene disorders. 12 blastocysts (54.5%) were chromosomally euploid.

Seven out of eight unaffected embryos survived after warming and were transferred in 6 FET cycles. Four pregnancies resulted -two live births, two ongoing pregnancies- an implantation rate of 57%.

Combining blastocyst biopsy with vitrification appears to be an effective strategy for transportation PGD/PGS. The on-going pregnancy rate suggests that a transport PGD/PGS programme can be an effective reproductive option for couples seeking genetic testing of embryos prior to implantation.

P06. Investigating the role of a single nucleotide polymorphism at 9q22.23 in Thyroid Cancer Predisposition: A Case-Control Study

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FOXE1 is an intronless gene located on chromosome 9q22.23. FOXE1 plays a crucial role in thyroid morphogenesis. Mutations in FOXE1 are associated with a number of thyroid pathologies, namely hypothyroidism, athyroidism and thyroid cancer.

This study aims to investigate the frequency and impact of a single nucleotide polymorphism G>A at 9q22.23 in a Western European cohort of patients with thyroid cancer compared to controls.

DNA was extracted from buccal swabs or whole blood of patients with differentiated non-medullary thyroid cancer by ethanol precipitation. Patients were recruited from two tertiary referral centres in Ireland and France. Cancer-free controls were recruited from the community. Genotyping was performed using Taqman-based PCR. Data was analysed using SPSS V22.

One hundred and eighty one cases and eighty-three controls were genotyped for the variant. The frequency of the minor allele among cases was 0.46 compared to 0.30 among controls. Genotypic frequencies and odds ratios are outlined in the table. The variant was identified in patients with thyroid cancer significantly more frequently than controls in both heterozygous and homozygous forms. This supports the role of this variant in thyroid predisposition.

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	Common Homozygote	Heterozygote	Rare Homozygote
Control	41	34	8
Case	49	98	34
Odds Ratio	-	2.41 (1.36-4.26)	3.56 (1.48-8.53)
	-	0.002	0.003

P07. A qualitative analysis of the attitudes of Irish patients towards participation in genetic-based research

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Background: Progress in diagnostic and therapeutic strategies in medicine is dependent upon high-quality biomedical research. Translation of research findings into the clinic relies on patient participation in innovative clinical trials. We investigated attitudes to genetic research in Ireland, in particular with respect to commercial and financial implications.

Methods: A multi-centre cross-sectional survey study was performed. Consecutive patients attending four out-patient clinics were asked to complete paper-based questionnaires. An electronic version of the same questionnaire was created on Survey Monkey with a link made public on a social media website for a period of 24 hours. Data was analysed using SPSS.

Results: 351 questionnaires were completed (99 paper, 252 electronic). The majority of respondents were female (n=288, 82%), and highly educated, with 244 (70%) attending college/university. Most participants supported genetic research (267, 76%), more frequently for common diseases (274, 78%) than rare disorders (204, 58%, $p<0.001$, x2). 103 (29%) had participated in scientific research, and 57(16%) had donated material to a bio-bank. The majority (n=213, 61%) would not support research with potential financial/commercial gain. 106(30%) would decline to participate in research if researchers would benefit financially, compared to 49(14%) if the research was supported by a pharmaceutical company, ($p<0.001$, x2). Respondents would provide buccal samples (258, 74%) more readily than tissue (225, 64%) or blood (222, 63%).

Conclusion: A high level of support for genetic research exists among the Irish population, but active participation is dependent upon a number of factors, notably, type of biological material required, frequency of the disease in question, and commercial interest of the researchers.

P08. Pedigree Drawing in the Department of Clinical Genetics: An Audit of Adherence to International Recommendations

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A pedigree is the symbolic language of clinical genetic services and a visual representation of a family's medical history and genetic relationships. It assists diagnosis, identification of relatives at risk, and is a crucial tool in identifying inheritance patterns of genetic disorders. We aimed to examine adherence of clinical genetics professionals of the Department of Clinical Genetics (DCG) to international guidelines for pedigree drawing.

A retrospective chart review of pedigrees drawn in 102 consecutive outpatient appointments in October 2014 was undertaken. Each pedigree was scored using a standardised proforma adapted from international guidelines. Data was recorded with respect to referral type, legibility and pedigree complexity.

Pedigrees were completed in 98(96%) charts. The median score obtained was 10/20(2-16). Pedigree identifier was recorded in 30(31%). Sixty-one (62%) pedigrees were signed, and 57(58%) dated. The proband was identified in 34(35%), with date of birth (DOB) recorded in 32(32%). First degree relatives (FDRs) DOBs were stated for 24(25%), and age only in 31 (32%). Ethnicity was recorded in 13(13%). Presence/absence of consanguinity was noted in 24 (24%). The majority of pedigrees included ≥3 generations 94 (96%), including a median of 22 (3-66) individuals.

Although the majority of pedigrees contained large volumes of data on multiple individuals across multiple generations, deficiencies were identified in specific areas. While pedigree drawing should be a standard competency for all healthcare professionals, genetic professionals' standards should be exemplary. Results were presented at a Departmental Clinical Meeting, impediments to adherence with guidelines identified and recommendations for improvement discussed. Re-audit is currently ongoing.

P09. Beware of the genome

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Exome and genome sequencing are being hailed as important tools in diagnostics and personalised medicine. This technology has already integrated into some aspects of mainstream medicine in Ireland. But are we overlooking the scale of the challenges and pitfalls that these tests present? Here, we discuss a number of issues that we have encountered during our research studies.

Incidentals and VOUS: The European Society of Human Genetics advocates for stringent filtering of data to minimise the risk of incidental findings. However, our research shows that incidental findings can still occur, despite using stringent filters. Counselling can be difficult even in cases where the incidentals are of proven pathogenicity. Furthermore, a large proportion of incidentals are variants of unknown significance (VOUS), making interpretation and reporting very challenging. Should we act on VOUS? And at what cost to the healthcare system?

Misclassified variants: Our understanding of how genetic variants impact our health is still in progress. It is not surprising that recent studies are showing that variants originally reported as pathogenic are actually benign. As new information emerges, it is possible that variant classification will change. What are the implications for patient counselling?

Filtering: There are numerous tools and databases available for data filtering. It is now becoming evident that different analysis tools

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give different results. The lack of standardisation could pose a significant problem, particularly in a clinical setting?

Whilst exome/genome sequencing has significant potential to improve diagnostic yield, it is important that all stakeholders are aware of the potential pitfalls and challenges to ensure safe implementation of this new technology.

P10. YouTube, animation and genetic education

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We have developed a number of short videos, some animated, to help develop integrated online genetic education. Our vision is to develop core videos on topics such as pedigree drawing, genetic cascade and predictive testing, exome/genome sequencing, incidental findings and ethics, relevant to practises in Ireland. Outside of the core, we have specialist topic videos relevant to genetics, created by colleagues from diverse disciplines. Our target audience are health care professionals from all aspects of mainstream medicine.

Much of our content, such as our six animated videos, are freely available on YouTube. These videos already have ~30,000 views. Families can view them prior to an appointment.

We found that short videos (~5 minutes) are more popular; the viewer stays with the video through its entirety in contrast to long videos. As viewers post thumbs up and thumbs down as well as comments, this is a useful way of gaining prompt feedback. Our two recent chromosome translocation videos have already had >18,000 views and links to the ESHG website have been provided. We are translating these videos into ten languages to increase applicability. http://bit.ly/RecipTranslocation & http://bit.ly/RobsTranslocation

Feedback includes: "Wow this video was more helpful than any other genetic video on YouTube" and "Now I understand it thanks".

Whilst YouTube is used by the public to access genetic information, much of the educational content is aimed as researchers. There is a market for simple genetic information to be developed for the public.

Grants: UCD; Temple Street children's fund for Health; Shire Pharmaceuticals

P11. A Case of Metaphyseal Chondromatosis with D-2 Hydroxyglutaric Aciduria

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A developmentally appropriate thirteen month old girl, born to non-consanguineous Irish parents, presented with asymmetry or an extra crease in the midshaft of her right arm and relative short stature (occipitofrontal circumference - 91st centile, weight - 50th-75th centile, Length - 0.4th-2nd centile). A radiograph of the arm followed by a skeletal survey revealed bilateral symmetrical irregularities of the metaphyses of the humeri (proximal), femora (proximal and distal), and tibiae (proximal and distal) with less marked changes in the fibulae, feet and phalanges. Irregular chondral dysplastic changes in the left iliac blade were also noted. The epiphyses were spared, the skull, vertebrae, ribs, clavicles were unremarkable and bone age was normal. Urinary D2-Hydroxyglutarate was approximately 55 times the normal level confirming a diagnosis of metaphyseal chondromatosis with D-2 hydroxyglutaric aciduria. This is likely due to somatic mutations in the isocitrate dehydrogenase gene which is currently under analysis. The prognosis is guarded and the recurrence risk is considered to be <1%. This case highlights 1: an unusual combination of characteristic skeletal and metabolic abnormalities which has rarely been reported and 2: the importance of performing urine organic acid in patients who present with generalized enchondromatosis.

P12. Segmental overgrowth syndromes caused by somatic mosaic mutations in PIK3CA

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Patient Age and Sex	Part of Body Affected with Overgrowth	Learning Disability	Other findings	Gene Mutation
2 year old boy	Left Leg (particularly 4th and 5th toes)	No	No	PIK3CA (H1047L) Left leg (10-20 % cells) Right leg (0% cells)
16 year old girl	Generally Overgrown, Right hemihypertrophy	Mild	Capillary Malformation	PIK3CA (E418K) Right arm (50% cells) Left arm (25% cells)
6 week old girl	Right Foot	No	Displaced bones in foot	Result awaited
13 month old girl	Macrocephaly	No	Polymicrogyria	Result awaited
16 year old boy	Generally overgrown, left side larger than right below neck, opposite above neck	Mild	Capillary Malformation	Result awaited
3 year old boy	Hemimegalencaphaly	Mild/Moderate	Naevus flammeus	Result awaited
11 month old girl	Right leg	No	Right Hydronephrosis	Result awaited

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Segmental overgrowth syndromes are rare, poorly classified disorders which carry a significant burden of morbidity and mortality that pose diagnostic, prognostic and management challenges. Recently, somatic mutations in the phosphatidylinositol-3-kinase/AKT/mTOR [PROS] cellular signalling pathway have been shown to underline many overgrowth disorders. We present 7 cases of segmental overgrowth presenting with wide phenotypic variation (see Table). Pathogenic somatic mutations in PIK3CA were identified in two cases to date. Genetic analysis is awaited on the other four cases. Such cases are reclassifying segmental overgrowth disorders and helping the development of targeted therapies such as mTOR inhibitors. A collaboration with Cambridge University is facilitating a further 35 cases of segmental overgrowth to be enrolled for investigation and possibly inclusion in a treatment clinical trial.

P13. Microdeletion/microduplication of the proximal 15q11.2 (BP1-BP3) region: an emerging susceptibility locus

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The proximal long arm of chromosome 15 contains clusters of LCRs located at five common breakpoint sites, referred to as BP1-BP5. This region is susceptible to rearrangements mediated by non-allelic homologous recombination which results in various deletions and duplications. Two common classes of deletions are described in individuals with Prader-Willi /Angelman syndrome (PWS/AS). PWS/AS deletion is flanked by either proximal BP1 or BP2 and the more distal BP3. Individuals with PWS/AS with Type I deletions (BP1-BP3) have been reported with more severe phenotype than individuals with Type II deletions (BP2-BP3). The BP1-BP2 region spans approximately 500kb and contains four highly conserved genes, TUBGCP5, NIPA1, NIPA2 and CYFIP1; TUBGCP5 is expressed in subthalamic nuclei while the latter three genes are widely expressed in the central nervous system. Recent studies have suggested an association between BP1-BP2 deletions/duplications with an abnormal clinical phenotype including dysmorphisms, speech and motor delay, autism, behavioural problems and seizures. However, imbalances in this region have also been seen in the normal population and in mildly affected carriers suggesting that the region contains genetic material associated with incomplete penetrance. We identified 27 patients with imbalances within the proximal 15q11.2 (BP1-BP2) region, all presenting with various degrees of developmental delay. Analysis was conducted using a high resolution microarray-based comparative genomic hybridization (aCGH). Parental studies were carried out where possible. The results presented here indicate that 15q11.2 BP1-BP2 copy number changes may increase susceptibility to neurodevelopmental problems.

P14. Orphanet Ireland : Mapping Ireland's Rare Disease Activity

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Orphanet is an international information portal for rare disease (RD) activity. 39 countries participate in rare diseases data collection, with over 41,000 daily site hits to www.orpha.net from over 200 countries. Disease summaries are written by experts and link to more detailed information. Data collected includes clinical expert centres, medical laboratories, patient organizations, research projects, registries, clinical trials and biobanks; as well as reports on RD prevalence and orphan drugs.

Orphanet Ireland is funded by the EC 3rd Joint action on RD and the HSE, and located at the National Rare Diseases Office. Our short term goal is to ensure the accuracy of the existing Irish data, then to create a comprehensive rare disease resource database within the next 2 years.

Data on all RD activity can be self-declared by clinicians, researchers and patient organizations but is verified and validated by the Orphanet Ireland to ensure it meets inclusion criteria. Data will also be collected from departmental and professional websites, regulatory and funding bodies, as well as direct contact with professionals.

The aim of centralizing Irish rare disease information is 1: to provide a resource to clinicians and patients looking for or with a new RD diagnosis, and 2: to promote links between professionals and the patients concerned, within and between countries. Orphanet Ireland will serve as the unifying platform for RD activity for designation of centres of expertise (ongoing) and of laboratories and researchers participating in Reference Networks (from 2016) to fulfil Ireland's European and Cross Border Directive requirements.

P15. miR-24 regulates p27 expression in prostate cancer

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MicroRNAs (miRNAs) are small, non-coding RNA molecules with an important role in cancer. In prostate cancer, several miRNAs are expressed abnormally suggesting they may be useful markers for diagnosis, prognosis, and potential therapeutic intervention in this disease. In this study we used PCR to investigate the expression of miR-24 in a panel of prostate cancer cell-lines and in a series of clinical prostate biopsy specimens. The biological significance of miR-24 expression in prostate cancer cells was assessed by a series of in vitro bioassays and the effect on proposed targets p27 (CDKN1B) and p16 (CDK2NA) was investigated. We showed that miR-24 expression was significantly lower in prostate cancer cell lines compared to a normal prostate epithelial cell line. Decreased expression of miR-24 was also more frequently observed in both needle core and prostatectomy tumour tissue relative to matched normal tissue. Low miR-24 expression correlated with high PSA serum levels and other markers of increased prostate cancer progression. Importantly, over-expression of miR-24 inhibited cell cycle, proliferation, migration and clonogenic potential of prostate cancer cells, as well as inducing apoptosis. p27 and p16

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were confirmed as targets of miR-24 in prostate cancer cells and a significant inverse correlation between miR-24 and p27 was revealed in clinical prostatectomy specimens. These findings provide evidence that miR-24 has a tumour suppressor role in prostate cancer and also targets p27 and p16 in prostate cancer cells. We propose that it may be a useful progression biomarker or focus of therapeutic intervention for this disease.

P16. Cognitive analysis of schizophrenia risk genes: focus on genes with epigenetic function

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Schizophrenia is a psychiatric disorder characterised by positive and negative symptoms as well as cognitive impairment. Disrupted epigenetic processes are observed in complex and single gene brain disorders that exhibit cognitive deficits, and have been recently studied as potential targets of pharmaceutical intervention for the treatment of cognitive deficits.

Genome wide association studies (GWAS) have identified 108 chromosomal regions associated with risk of schizophrenia, implicating 350 genes. The aim of this study was to identify risk genes for schizophrenia with epigenetic functions and test these genes for association with cognitive deficits in schizophrenia. Cross-referencing 535 epigenetic genes with 350 GWAS genes identified 5 candidate genes: RERE, SATB2, EPC2, EP300 and KDM3B. The effect of risk single nucleotide polymorphisms (SNPs) in these genes on cognition was examined using a dataset of psychosis cases (n = 905) and controls (n = 330) who had completed tests in 5 areas of cognition: IQ, working & episodic memory, attention and social cognition. Regression was carried out using a linear model. For RERE, there was association between the schizophrenia risk allele and attention ($p = 0.03$). For SATB2, there was association with social cognition ($p = 0.003$). For EPC2, an association was found with full scale IQ ($p = 0.004$) and performance IQ ($p = 0.001$). An association was found between the schizophrenia risk allele for KDM3B and verbal IQ ($p = 0.038$). This initial analysis provides support for our hypothesis that risk genes with epigenetic functions contribute to cognitive deficits in schizophrenia.

P17. Do Irish periodic paralysis patients have a common genetic origin?

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Periodic Paralyses (PPs) are rare autosomal dominantly inherited skeletal muscle channelopathies characterised by episodic weakness secondary to abnormal muscle excitability. PPs are broadly classified into hyperkalaemic (HyperPP) or hypokalaemic (HypoPP) based on serum potassium (K^+) levels. HypoPP is caused by mutations in CACNA1S and SCN4A awhile the less frequent HyperPP is generally caused by SCN4A gene mutations.

We have recruited a growing cohort of Irish PP patients for which comprehensive clinical and genetic data has been gathered. We believe that this group of PP patients are phenotypically and genetically distinct. Firstly, contrary to publications, we have detected more HyperPP than HypoPP. Secondly, we have detected only one of the common SCN4A gene mutations and finally each of the patients is unusual clinically with attacks of longer duration and increased severity.

The aim of this project is to investigate this group of Irish periodic paralysis patients in which the same gene defect has been described to determine whether there is a common genetic background.

We will use haplotype analysis of polymorphic microsatellite markers in the SCN4A gene region to determine if there is a shared genomic region.

We will present the results of this study and discuss the implications for the diagnosis and management of these patients.

P18. PCR-RFLP assay for the detection of LHON Mutations

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Leber hereditary optic neuropathy (LHON) is one of the most common inherited optic neuropathies with an incidence of up to 1 in 31,000 worldwide and results in significant visual morbidity among young adults. The disorder is the result of mitochondrial dysfunction and results from primary mitochondrial DNA mutations affecting complex I subunits of the respiratory chain. Approximately 95% of LHON patients will have one of 3 mitochondrial mutations, G3460A (13%), G11778A (69%) and T14484C (14%) in NADH Dehydrogenase subunits 1, 4 and 6 respectively with other rare mutations accounting for the final 5%. Visual recovery can occur in some LHON patients but the extent of the visual recovery is influenced by the mutation involved, highlighting the need for a simple robust and cost effective mutation detection strategy.

The 3 common mutations are typically identified by individual end-point PCR-RFLP, ARMS PCR or PCR followed by Sanger / Pyrosequencing. This study developed a multiplex PCR-RFLP assay to detect the 3 common LHON causing mutations in a single tube format.

Primers, based on the reference sequence NC_012920.1, were designed to incorporate a MaeIII restriction site in the presence of the 3460A, 11778A and 14484C mutations and the multiplex assay reliably detected the 3 mutations in LHON patient DNA and in synthetic LHON controls harbouring the 3 common mutations cloned into plasmids.

In conclusion, we developed a simple cost effective assay to detect 95% of LHON causing mutations and developed a set of cloned controls providing an unlimited patient free resource for LHON testing.

P19. Targeting hypoxia in prostate cancer cells to increase treatment efficacy

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Androgen deprivation therapy e.g. bicalutamide (BCA) is widely used to treat advanced prostate cancer; however, within 1.5-3 years most tumours have progressed to androgen independence (Abate-Shen C; Genes Dev 14, 2410-2434; 2000). Previously we showed that daily BCA causes an initial profound hypoxia (<0.1%) in LNCaP tumours that recovered after ~17 days. This was accompanied by progression to a more malignant phenotype indicating hypoxia-driven treatment failure (Ming L. *Int J Cancer* 2013;**132:**1323-1332). Combination with AQ4N, a unidirectional hypoxia activated pro-drug (uHAP), blocked this progression. We have now characterised gene expression changes during treatment and have investigated the effect of a novel uHAP (OCT1002) in blocking these effects. LNCaP prostospheres were treated with vehicle, BCA, OCT1002 and combination therapy. Prostosphere size was measured pre and post treatment. Clonogenic assays and flow cytometry was carried out on treated prostospheres to measure changes in invasive potential and apoptosis, respectively. Furthermore, LNCaP-Luciferase expressing cells ($4x10^6$) were implanted into SCID mice, treatment (as above) commenced when tumours reached ~$150mm^3$. Tumours were measured every 2 days using calipers. Bioluminescence in the lung was calculated at the experimental endpoint. In vitro and in vivo data reveal the potential of OCT1002 when used in combination with BCA. Combination treated prostospheres had stunned growth rate, higher apoptosis and reduced colony formation compared to control groups. In vivo data shows that combination therapy results in a significant tumour growth delay and reduced lung metastases by approximately 40%.

P20. Schizophrenia-associated SNPs proximal to neurotransmission genes impact cognitive performance in patients and controls

D Cosgrove[1], D Morris[1,2], D Harold[2], M Gill[2], A Corvin[2], G Donohoe[1,2]

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Schizophrenia (SZ) is characterised by positive, negative and cognitive symptoms. As SZ is highly heritable, recent research has focused on GWAS, the most recent of which identified 83 new regions of interest associated with SZ. The link between these and specific functions in SZ is currently unknown. To take these results forward, these need to be identified, be that at the level of protein, neural pathway or phenotype.

To characterise the effect of SNPs on cognitive function, first a selection was carried out based on the following classifications 1: proximity of SNP to gene, 2: unique association of this gene to SNP, and 3: gene involvement in neurotransmission, which is disrupted in SZ. This resulted in a selection of eleven SNPs in close proximity to ten genes: four involved in glutamatergic neurotransmission (GRM3, GRIN2A, SRR, CLCN3), five signalling (CACNA1C, CACNB2, HCN1, RIMS1) and two receptor genes (DRD2, CHRN). Neuropsychological measures of social cognition (Reading the Mind in the Eyes, Hinting Task, Internal, Personal, Situational and Attributional Questionnaire) were analysed to assess the impact of each SNP on social cognitive function.

Analyses indicated a significant effect on measures of cognition in patients and controls. SNPs in the regions of CACNB2 (r^2=0.032, p=0.001) and RIMS1 (r^2=0.007, p=0.032) show a significant effect on scores on the Hinting Task and Reading the Mind in the Eyes, respectively. These findings implicate risk SNP effects on the generalised neurotransmission process as opposed to any one specific neurotransmitter.

P21. Impaired cognition in schizophrenia: Genetic risk factors related to MHC loci

J Holland[1], D Morris[2], D Cosgrove[3], D Harold[4], O Mothershill[5], A Corvin[6], G Donohoe

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Introduction: Although the etiology of schizophrenia (SZ) is largely unknown, it is increasingly clear that genetic and environmental interactions contribute to cognitive deficits associated with this disorder. Recent Genome wide association studies (GWAS) have indicated a link between SZ and immune dysregulation, especially genetic mutations related to the major histocompatibility complex (MHC). Cognitive deficits are core features of Schizophrenia and related disorders, which relate to genetic risk. This study aims to explore the relationship between MHC risk variants for SZ and cognitive deficits, while also relating findings to brain activity.

Methods: To test if MHC risk variants impair cognition, ANCOVA analysis is performed on genetics data previously collected in a GWAS. Cognition measures are compared in groups with and without MHC genetic risk, in a population of SZ sufferers and healthy controls. Functional MRI imaging will also be performed to test if genetic risk relates to altered neural activity.

Results: Preliminary analyses suggest that MHC risk variants contribute to impairments in cognition in domains of social cognition, IQ and attention. Further analysis will be performed to test for environmental mediators of this relationship, looking at cannabis use and urbanicity. BOLD fMRI will also be used to test for a relationship between MHC risk and altered neural activity, using MATLAB SPM.

Conclusions: The MHC genetic variant may serve as a significant risk marker for schizophrenia, and further elucidate etiology of this neurodevelopmental disorder. Future studies on neurobiology of social cognition, and greater knowledge of genetic risk may establish targets for interventions.

P22. In vivo gene silencing by siRNA delivery to the corneal epithelium in a keratin-12- bioluminescence mouse model

SD Atkinson[1], EH Allen[2,3], JE Moore[4], DG Courtney[2], E Maurizi[2], MA Nesbit[2], WHI McLean[3], DM Leslie Pedrioli[3], CBT Moore[2]

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Aim: To create a bioluminescence mouse model which expresses firefly luciferase in the corneal epithelium to assess gene editing and gene silencing for the cornea.

Methods: A gene targeting vector was generated where the Krt12 coding sequence in and the splice donor site of exon 1 were replaced with a transgene cassette containing a luc2-Multiple Targeting Cassette (MTC) gene fusion. The vector was transfected by electroporation into the Taconic Artemis C57BL/6N Tac ES cell line. Homologous recombinant clones were isolated and validated, and the mice bred with luc2-positive/ PuroR-negative offspring used for colony establishment.

To visualise the expression of luc2 within the corneal epithelium, luciferin substrate diluted in viscotears was applied to the front of the eye and then luciferase expression was imaged and assessed using a Xenogen IVIS Lumina Imager and LivingImage 3.2 software.

Intrastromal injection of siGlo siRNA was used to determine the localisation of siRNA within the corneal epithelium and then the established mouse model was treated with either native or Accell "self-delivery" siRNA.

Results: The Accell "self-delivery" siRNA induced potent sustained allele specific silencing for 7 days, while native versions of siRNA resulted in significant knock-down for 1 day only ($p<0.05$).

We have created and validated a bioluminescence mouse model and have utilised it to assess siRNA in vivo. This mouse model coupled with the Lumina imager will allow us to assess topical delivery of gene therapies to the ocular surface allowing validation for future translation to clinical use.

P23. Mutant allele-specific gene silencing in autosomal dominantly inherited Fuchs' corneal dystrophy using CRISPR Cas9 nuclease

E Maurizi[1], D Courtney[1], SD Atkinson[1], JE Moore[1], MA Nesbit[1], CBT Moore[1]

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Dominant-negative or gain-of-function disease-causing mutations are not suitable for gene supplementation therapies. The CRISPR Cas9 system has emerged as a powerful in vivo and in vitro RNA-guided sequence specific nuclease. Critical for target site recognition by the Cas9 nuclease, a 3bp protospacer-adjacent motif (PAM) is located adjacent to its 3'end. A review of known point mutations that cause corneal dystrophy showed that over 30% result in the formation of a novel PAM site. To investigate whether these mutations could be specifically targeted by CRISPR/ Cas9 we focused our attention on the Fuchs' endothelial corneal dystrophy (FECD), where the L450W mutation in the alpha2 chain of Collagen VIII (COL8A2) gene creates a new PAM site absent in the wild-type allele.

In vitro assays were designed to determine the efficiency and specificity of Cas9 cleavage. Wild-type and mutant COL8A2 genes, cloned into a Luciferase reporter vector, together with single guide RNA (sgRNA) Cas9 constructs, were used to transfect AD293 cells. The sgRNA targeting Cas9 to a site adjacent to the L450W mutation showed a significant ($50\% \pm 3.9\%$, $p<0.01$) knockdown of mutant allele expression, without effect on wild type.

AD293 cells were co-transfected with equimolar quantities of wild-type and mutant COL8A2 constructs and sgRNA/Cas9 constructs and allele specificity was confirmed at the mRNA level by pyrosequencing and qPCR.

Thus, the L450W PAM-specific sgRNA was revealed to be an efficient genome editing tool, with the potential for developing a targeted therapy for FECD that will be applicable to other diseases caused by dominant-negative or gain-of-function mutations.

P24. Genetic insights into the population structure of the Sherpa and neighbouring Nepalese populations

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Nepal, located on the southern-slope of the Himalayan arc, has a complex demographic history and is home to 125 recognised ethnic groups. The Sherpa, who reside in the mountainous eastern region of Nepal, are believed to have migrated from Tibet 400-600 years ago. We set out to shed light on the population structure of eastern Nepal, in particular the Sherpa.

We established a cohort of 118 Sherpa from multiple high-altitude villages in the Khumbu region of eastern Nepal. We identified seven ethnic groups of interest from the Nepalese census that represent approximately 50 % of the total Nepalese population; Chettri, Rai, Magar, Tamang, Newar, Nepali and Aryan. We included 82 individuals from these ethnic groups, who were resident in regions in close proximity to the Sherpa.

We also included genotype-data to represent the greater Himalayan region which included individuals from the Pamir mountain-range, India, Pakistan and China. Via the analysis of dense genotype data, we investigated genetic distance, admixture and levels of homozygosity within and between populations.

Our results suggest the Nepalese are highly-admixed population with ancestry primarily from north of the Himalaya but with some geneflow from the south. We confirmed the presence of an ancestral component that appears specific to high-altitude populations of the Himalaya. This is enriched in the Sherpa, particularly in individuals from the Thame village in Khumbu. Patterns of homozygosity observed in the Sherpa and Nepalese are consistent with consanguinity and are likely to be a result of population isolation.

P25. The development and testing of a custom gene panel to aid clinical diagnosis in an adult epilepsy clinic

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Around 40,000 people in Ireland are living with epilepsy and

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approximately 30% of patients are refractory to treatment. A clear understanding of the underlying cause offers the potential to improve treatment for refractory epilepsy. Further, a fast, accurate diagnosis reduces the diagnostic odyssey and associated expensive testing.

Next-generation sequencing can give complete ascertainment of genetic variation across the genome, or focused ascertainment within the coding regions of a subset of genes. This enables clinicians to identify known pathogenic mutations or novel candidate mutations that may cause a patient's epilepsy. Recent studies have illustrated the relatively high diagnostic yields for gene-panel and exome sequencing in epileptic encephalopathies, with yields in the region of 20-30%. In this study we set out to develop a gene panel for epilepsy, and test the diagnostic yield in a refractory, adult patient cohort.

We used Agilent SureDesign to design a custom gene panel containing over 400 genes linked to epilepsy and epileptic encephalopathies from published literature and a review of similar commercially available panels. We selected for sequencing a subgroup of patients (n=30) with a suspected genetic cause to their epilepsy. DNA samples were be enriched using the SureSelect QXT protocol before sequencing on an Illumina MiSeq. Alignment and variant calling was performed using Burrows-Wheel Aligner and SureCall software. We utilized databases such as OMIM, ClinVar and available literature to arrive at a set of candidate variants.

Results from this study will inform on the effective integration of next-generation sequencing to adult epilepsy clinics in Ireland.

P26. 5-Hydroxymethylation marks a class of neuronal gene regulated by intragenic methylcytosine levels

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We recently identified a class of neuronal gene inheriting high levels of intragenic methylation from the mother and maintaining this through later development. We show here that these genes are implicated in basic neuronal functions such as post-synaptic signalling, rather than neuronal development and inherit high levels of 5mC, but not 5hmC, from the mother. 5mC is distributed across the gene body and appears to facilitate transcription, as transcription is reduced in DNA methyltransferase I (Dnmt1) knockout embryonic stem cells as well as in fibroblasts treated with a methyltransferase inhibitor. However in adult brain, transcription is more closely associated with a gain in 5hmC, which occurs without a measurable loss of 5mC. These findings add to growing evidence that there may be a role for 5mC in promoting transcription as well as its classical role in gene silencing. Further interrogation of the mechanisms behind the persistence of gametic marks could potentially lead to insights into neurological disorders.

P27. The MTHFR A667C polymorphism and its association with reduced fertility

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The MTHFR gene located at 1p36.3, encodes the folate dependent enzyme 5,10-methylenetetrahydrofolate reductase, necessary for homocysteine metabolism and paramount in the creation of active vitamin B9. Defects in the gene have been associated with a plethora of pathological states such asCVD, congenital defects, reduced pregnancy and cancer.

The C677T polymorphism has been associated with various anencephalies, chiefly neural tube defects. During embryology NTD's are a known risk factor for late stage spontaneous abortion leading to reduced fertility. To assess the risk of MTHFR derived infertility we assessed 466 women attending a fertility clinic for the MTHFR polymorphism using ARMS PCR.

We found 248 (61%) of patients carried the C677T polymorphism while 181 (39%) did not carry the mutation. Of the 248 which were found to carry the polymorphism 203 were heterozygous for the mutation while 45 were homozygous. This data highlights the necessity for MTHF genetic testing. As described above, variations in the MTHFR gene may increase the risk of neural tube defects by changing the ability of methylenetetrahydrofolate reductase to process folate. Once MTHFR status is known doctors can then supplement folate more reliably.

P28. Differential responses of clinically important gene classes to transient loss of DNA methylation in human differentiated cells

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Background: Methylation of DNA sequences at promoters, CpG islands and other elements plays a vital role in regulating gene activity. In human, loss of methylation is known to play a causative role in imprinting disorders and in inappropriate germline gene expression in cancers. While in mouse, loss of function mutants have given great insight into the targets of methylation, functional studies in human have been largely limited to cancer cells and more recently stem cells, not normal adult cells. Methods: Stable knockdowns of the maintenance methyltransferase DNMT1 were generated in normosomic hTERT-immortalised adult fibroblasts. Genome-wide methylation levels were assayed using the Illumina 450K bead array. Results were analysed using RnBeads and Galaxy. Locus-specific methylation was verified using pyrosequencing and clonal analysis. Validation was achieved using transient siRNA. Results: Loss of function was poorly tolerated and all clonally-expanded cell lines had spontaneously restored DNMT1 levels by silencing of the shRNA. Evidence for a genome-wide methylation erasure event followed by a wave of remethylation could be clearly traced. Gene bodies and the shores of CpG islands showed the clearest loss of methylation overall. While most CpG islands are normally unmethylated and so unaffected, both imprints and germline genes fall into the rarer category of normally methylated islands: of these two, lasting loss of methylation was much more common among imprints than germline genes. Conclusions: 1: transient loss of methylation is poorly tolerated; 2: a robust mechanism for remethylation exists even in adult cells; 3: aberrant remethylation is frequent on recovery and 4: Imprints are particularly sensitive.

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P29. Whole exome sequence analysis in a multigeneration Northern Irish family with pterygium

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Pterygium is a wing-shaped fibrovascular lesion of the ocular surface that leads to blindness in severe cases; it is reported as a premalignant condition with the potential to progress to ocular surface squamous neoplasia. Epidemiological studies show a correlation between pterygium and prolonged and intense exposure to ultraviolet (UV) light. In certain families however a much higher susceptibility to development of pterygium has been observed, suggesting a genetic cause.

Whole exome sequencing (WES) was performed to determine a causative mutation in five affected individuals and one unaffected sibling from a Northern Irish family (6 affected and 18 unaffected) with pterygium in multiple generations, in whom UV-B exposure was documented to be much lower than at equatorial latitudes.

Variant alleles identified by WES were screened with an assumption of autosomal dominant inheritance. The number of candidates genes were reduced, using different filters (confidence, common variants, predicted deleterious and genetic screening), to five, and then to one biologically plausible candidate through literature analysis. Cosegregation of the variant allele with pterygium in the family was confirmed by PCR and restriction enzyme analysis.

Expression of this gene in pterygium tissue samples, from both low UV-exposure (Northern European) and high UV-exposure (South American) populations was assessed. In vitro functional MTT and scratch assays demonstrated increased proliferation in cells transfected with the mutant compared to wild-type gene.

This study shed lights on the possible genetic mechanisms underlying pterygium formation, suggesting a role for the identified candidate gene in the general mechanism of UV-induced pterygium.

P30. Investigating the role of polymorphism rs2910164 in mir146a in cancer predisposition

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Micro(mi)RNAs are non-coding RNA molecules that bind with cis-regulatory regions in target messenger(m)RNA to exert post-transcriptional effects on gene expression, influencing a host of physiological and pathological processes. Polymorphisms in genes encoding miRNAs, or in miRNA-mRNA binding sites have been associated with cancer risk. MiR146a has a role in inflammation and is postulated to be a tumor suppressor miRNA.

The aim of this study was to investigate the frequency and impact of polymorphism rs2910164 in HSA-pre-mir146a in a cohort of patients with breast and thyroid cancer compared to cancer free controls.

The study group comprised Irish patients with breast cancer and French and Irish patients with non-medullary differentiated thyroid cancer (DTC), as well as cancer free controls. DNA from study participants was genotyped using a Taqman-based platform. Data was analysed using SPSS v22 and the Online Encyclopedia for Genetic Epidemiology studies.

The study group included 1250 patients, including 637 controls, 524 breast and 179 DTC cases. The variant was detected with a minor allele frequency (MAF) of 0.18 in controls, 0.21 in breast, and 0.28 in DTC cases. The variant conferred per allele odds ratio of 1.22(1-1.5, p=0.05, X^2) for breast, and 1.7 (1.31-2.25, p<0.0001) for DTC. An allele dosage effect was observed for both cancers, with rare homozygous genotype conferring greater risk than heterozygous for both cancer types.

A common variant in pre-mir146a is associated with breast and thyroid cancer predisposition. Further work is required to fully elucidate how this finding can be made clinically useful.

P31. The Dihydrofolate reductase 19bp polymorphism is not associated with biomarkers of folate status in healthy young adults, irrespective of folic acid intake

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Background: Dihydrofolate reductase (DHFR) is essential for the conversion of folic acid to active folate needed for one-carbon metabolism. Common genetic variation within DHFR is restricted to the noncoding regions and previous studies have focused on a 19 bp deletion/insertion polymorphism (rs70991108) within intron 1. Reports of an association between this polymorphism and blood folate biomarker concentrations are conflicting.

Objective: We aimed to evaluate whether the DHFR 19bp deletion/insertion polymorphism affects circulating folate biomarkers in the largest cohort to address this question to date.

Methods: Young healthy Irish individuals (n= 2,507) between 19 to 36 years old were recruited between February 2003 and 2004. Folic acid intake from supplements and fortified foods was assessed using a customized food intake questionnaire. Concentrations of serum folate and vitamin B-12, red blood cell (RBC) folate and plasma total homocysteine (tHcy) concentration were measured. Data were analysed using linear regression models.

Results: Folic acid intake was positively associated with serum (P <0.0001) and RBC folate concentration (P = 0.0005) and was inversely associated with plasma tHcy (P = 0.001) as expected. The DHFR 19 bp polymorphism was not significantly associated with either serum (P = 0.82) or RBC folate (P = 0.21), or plasma tHcy (P = 0.20), even in those within the highest quintile of folic acid intake (>326μg folic acid/day; P = 0.96). A non-significant trend

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towards lower RBC folate by genotype (P = 0.09) was observed in the lowest folic acid intake quintile (0 – 51 μg/day).

Conclusion: In this cohort of young healthy individuals the DHFR 19bp deletion allele does not significantly affect circulating folate status, irrespective of folic acid intake. Our data rule out a strong functional effect of this polymorphism on blood folate concentrations.

P32. Mapping Human Ancestry On The New York Subway System

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In recent years the concept of analysing large amounts of data as part of the development of 'Smart Cities' has emerged. In the Pathomap project, led by Dr. Christopher Mason from Weill Cornell Medical College and with UCD ACoRD participation, DNA was sequenced from thousands of samples taken from surfaces in the New York City Subway System. The purpose being to catalogue the microbiome of the subway for the first time and monitor changes to better understand the spread of pathogens.

Human DNA was also sequenced; using the ancestry analysis software AncestryMapper and Admixture, we examined how the genetic profile of stations matched that of the ethnic and racial demographics of the area as per the 2010 census.

Hispanic and African American populations being highly admixed presented interesting challenges. Since the samples were derived from multiple individuals, the results presented many interpretations; for example, did the result indicate an area that was 20% black and 80% white or 100% Puerto Rican. Should one assume an average of ~14% European ancestry for African Americans? Is that nationally-average number appropriate for New York? We found areas with high levels of consistency, particularly ones with homogeneous populations and others where the method did not seem to match the area, few were completely against the local demographics.

In the course of this we built an automated pipeline to work through the hundreds of samples, uploading this to Curoverse, a web infrastruture that hosts open-source bioinformatic and genomic software as part of the Arvados project.

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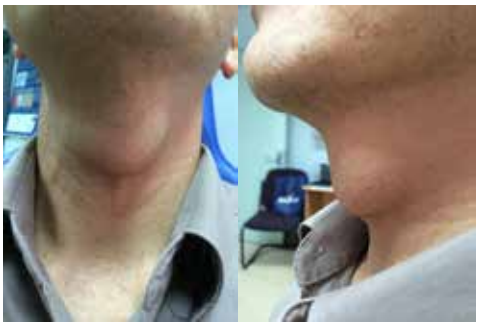
Curiositas

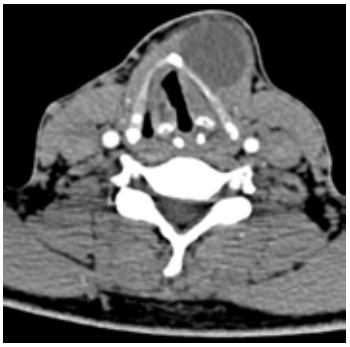
GENERAL PRACTICE QUIZ

A 39 year old man presents with a swelling in his neck that has been progressively enlarging over the last few months.



1. What clinical tests would you perform to assess him?
2. The swelling moves upwards when the tongue is protruded. What is the likely cause, and how common is this condition?
3. Describe the embryological origin of the thyroid and its significance in this case.

A representative image from his CT scan is shown below.



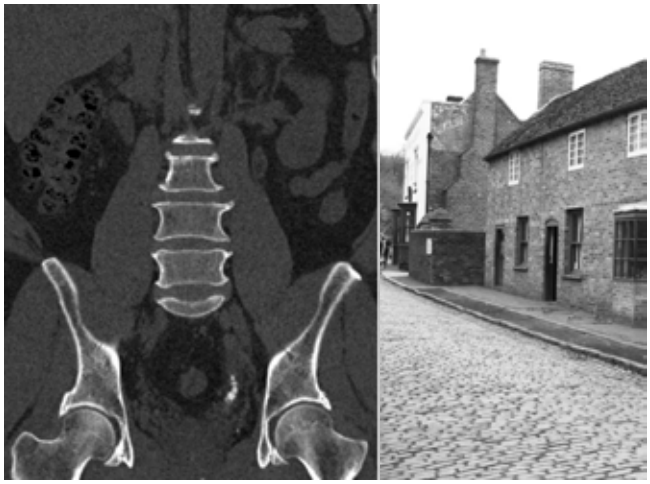
Glenn Ritchie (Medical Student, Queen's University Belfast) and Dr Ian Bickle (Consultant Radiologist, Raja Isteri Penigran Anak Saleha Hospital, Bandar seri Begawan, Brunei Darussalam)

MEDICAL STUDENT QUIZ

1. With regard to skin cancer, what does this image represent?
2. What is the clinical significance of this region?
3. Explain Mohs' micrographic surgery

Claire Lagan (Biomedical Scientist, Queen's University Belfast) and Dr Joe Houghton, Clinical Senior Lecturer (Queen's University Belfast)

POSTGRADUATE QUIZ



1. What abnormality is shown on the CT image above?
2. What procedure can this be a complication of?
3. What is the German term that links this radiological sign with the photograph on the right?

Michael Corr (Medical Student, Queen's University Belfast) and Dr Ian Bickle (Consultant Radiologist, Raja Isteri Penigran Anak Saleha Hospital, Bandar seri Begawan, Brunei Darussalam)

AND FINALLY...

A patient with chronic lymphocytic leukaemia attends for routine clinical review. Venous blood is sent for analysis and the laboratory phone urgently with the results shown in panel A. A further blood sample is collected using an alternative blood bottle, and the results in panel B are returned.

	A (Clotted)	B (Heparin)	C (Clotted)	D (Heparin)
NA	137	132	136	136
K	6.7	7.3	4.4	4.6
CL	103	103	102	102
CO2	25	22	23	23
UREA	6.8	6.8	7.0	6.7
CRE	112	121	126	123

The patient is not on potassium supplements or drugs linked with hyperkalaemia. An ECG is normal. He is not given any treatment, but two further blood samples are sent to the laboratory urgently and the results in panel C and D are returned.

1. How would you explain the change in the potassium result?
2. What conditions predispose to this phenomenon?
3. How should an accurate potassium concentration be obtained in these circumstances?

Dr Paul Hamilton (Specialty Registrar, Chemical Pathology, Belfast Health and Social Care Trust)

ANSWERS See overleaf

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

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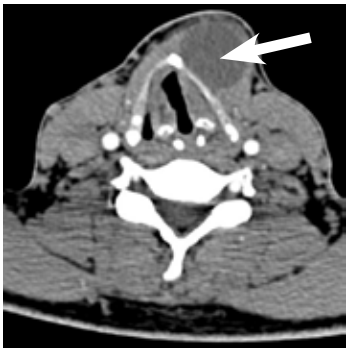
Curiositas: Answers

GENERAL PRACTICE QUIZ

1. Abnormalities of the thyroid gland or thyroglossal duct can cause swelling in this midline location. Thyroid swellings move on swallowing, while thyroglossal cysts tend to move when the tongue is protruded.
2. A thyroglossal cyst is a common painless midline neck swelling. Approximately 7% of people have remnants of the thyroglossal duct[1]. It is the commonest cause of midline neck swellings in children, accounting for 70% of congenital neck abnormalities; 76% of cases present before the age of 6 years[1].



3. Derived from endoderm, the thyroid primordium descends in the midline of the neck from the base of the tongue and courses anterior to the hyoid bone to an infrahyoid position anterior to the thyrohyoid membrane, thyroid cartilage, and trachea[2]. The inferior portion of the thyroglossal duct differentiates into the pyramidal lobe of the thyroid gland[2]. As such, thyroglossal duct cysts are found below the hyoid bone in 85% of cases, but can lie anywhere between the foramen caecum and the suprasternal notch[1]. Due to its attachment to the tongue, protrusion of the tongue will raise a thyroglossal cyst superiorly. This classical sign is virtually pathognomonic of thyroglossal duct cysts.

1) Karmakar S et al. Thyroglossal Cyst: An Unusual Presentation. Indian J Otolaryngol Head Neck Surg. 2012; 65(S1):185–7.

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Glenn Ritchie (Medical Student, Queen's University Belfast) and Dr Ian Bickle (Consultant Radiologist, Raja Isteri Penigran Anak Saleha Hospital, Bandar seri Begawan, Brunei Darussalam). *Thank you to the patient who kindly gave written consent for these images to be published.*

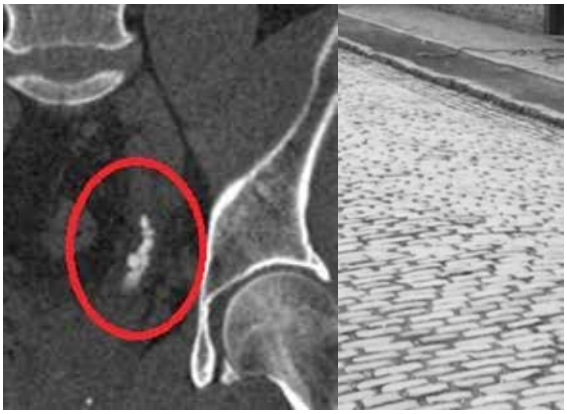
MEDICAL STUDENT QUIZ

1. The image depicts the H-zone which is an anatomical region of the face that includes the temple, ear, eyelids, nose and lips.
2. The H-zone is considered a high-risk site for basal cell carcinoma, the commonest human cancer. Tumours that arise in this region often have a greater extent of invasion than is initially appreciated by clinicians, and therefore attempts at routine primary excision are less likely to be successful. These regions also tend to be cosmetically sensitive.
3. Mohs' micrographic surgery is a technique that is used to treat high-risk cutaneous basal cell carcinoma. The method was developed by Frederic Edward Mohs in 1938 at the University of Wisconsin. The technique involves initially removing the tumour with a minimal amount of surrounding healthy tissue. Detailed microscopic examination (by a histopathologist or suitably trained clinician) of the surgical margins of the carefully orientated excised specimen is then carried out whilst the patient is still at clinic. If the margins are clear then surgery is complete. If the margins are positive then small amounts of further tissue are removed in the relevant area(s) until clear margins are finally obtained. Recurrence rates are lower using this technique compared with standard excision, and a better cosmetic result is more likely. However, this technique is labour intensive and is therefore quite costly.

Claire Lagan (Biomedical Scientist, Queen's University Belfast) and Dr Joe Houghton, Clinical Senior Lecturer (Queen's University Belfast)

POSTGRADUATE QUIZ

1. A stack of radio-opaque stones is visible in the distal left ureter.
2. This can be a complication of Electronic Shock Wave Lithotripsy (ESWL), a common treatment for renal calculi. ESWL is a non-invasive method that utilises auditory waves to break up a calculus with minimal collateral damage. Steinstrasse may also occur spontaneously due to multiple ureteric stones.
3. This sign is known as "Steinstrasse", a term derived from the German for "stone street." Steinstrasse is a common complication of ESWL, with a reported incidence of as high as 8%. The risk is related to the size of the original stone and its anatomical site. It is caused when fragments of a broken calculus become lodged in the ureter causing obstruction and hydronephrosis. Patients normally present with pain and discomfort, or in more severe cases, obstructive pyelonephritis and urosepsis. Treatment can be either conservative, further ESWL or surgical (with procedures such as percutaneous nephrolithotomy, ureteroscopy or open surgery), depending on severity and anatomical position. In order to minimise the risk of developing Steinstrasse after ESWL, patients are encouraged to increase fluid intake and be physically active. Adequate follow-up post-ESWL allows Steinstrasse to be identified and treated early.



Michael Corr (Medical Student, Queen's University Belfast) and Dr Ian Bickle (Consultant Radiologist, Raja Isteri Penigran Anak Saleha Hospital, Bandar seri Begawan, Brunei Darussalam). *Curiositas would like to thank Mr Roger Bickle for his image of the cobbled street.*

AND FINALLY...

1. This is a case of pseudohyperkalaemia, i.e. the true serum potassium concentration is normal despite an apparently elevated level reported by the laboratory. In this case, the man's fragile leukaemic cells have released potassium in those samples delivered to the laboratory using the pneumatic tube system (samples A and B), presumably due to vibration and pressure changes. For samples delivered to the laboratory by the hospital porters (C and D), the potassium concentration is normal.
2. Pseudohyperkalaemia can occur with: haemolysis, delayed processing of blood, very high white cell or platelet counts, potassium contamination and abnormal red blood cells. In leukaemia, the disease sub-type, degree of leucocytosis, type of blood tube and manner of transport to the laboratory may all be factors[1].
3. If pseudohyperkalaemia is suspected, blood should be collected carefully into both clotted and lithium heparin tubes, and transported to the laboratory manually as soon as possible. Alternatively, a point of care device might be available (e.g. a blood gas analyser with a potassium facility).

1) Dastych M and Čermáková Z. Pseudohyperkalaemia in leukaemic patients: the effect of test tube type and form of transport to the laboratory. Ann Clin Biochem. 2013. 51(1) 110-113.

Dr Paul Hamilton (Specialty Registrar, Chemical Pathology, Belfast Health and Social Care Trust)

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Book Case

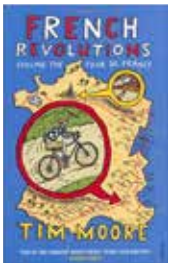
Dr Gerry Hanna considers 6 books along the theme of medicine, cycling and people.

MARIE

Gordon Wilson
and Alf McCreary
(Collins – Marshal Pickering 1990).

Many of us will always remember the distressing scenes from various incidents during the troubles. I have vivid memories of looking after the victims of the Omagh bomb during my second week as JHO in the Royal Victoria Hospital in 1998. In the weeks following the Omagh bomb I re-read Marie by Gordon Wilson and it brought me to tears again. Gordon will always be remembered for forgiving those who planted the Enniskillen bombing and who killed his daughter Marie in 1987. His immediate response ""I bear no ill will. I bear no grudge" was reported worldwide and Gordon became a Peace Campaigner. This simple book tells the story of Marie and the events around the Enniskillen bomb and Gordon's hope for peace. Evocatively, towards the end of the Book Gordon recalls Marie's last words, "Daddy, I love you very much."

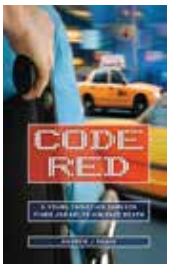
FRENCH REVOLUTIONS: CYCLING THE TOUR DE FRANCE



Tim Moore (Yellow Jersey Press 2012, first published 2001).

Cycling has always been my favourite form of relaxation and exercise from and I have been fortunate to have been involved in a number of iconic cycles with colleagues such Dr Seamus McAleer and Dr David Stewart. This book brings back memories of my first such cycle along the Camino in 2006. Tim Moore, with little preparation (this I can relate to…) cycles the entire route of the Tour De France shortly before the real race takes place. He recounts encounters with French dogs, cars, hotels and how he copes by over-indulging in red wine over lunch. This is a hilarious read which any cyclist will enjoy and relate to.

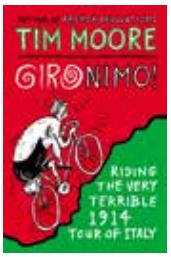
CODE RED



Andrew Drain
(Christian Medical Fellowship 2010)

I was privileged to have been in Andy's year at Medical School Year at QUB. He was such a wonderful person, he was bright (came top of our year), witty and, above all, was so genuine. As he was completing his final fellowship in Cardiothoracic Surgery in Memorial Sloan Kettering, New York, Andrew was diagnosed with acute lymphoblastic leukaemia. This book recounts his experiences as doctor and young father facing serious illness and ultimately death. Published after Andrew's death, in the book he provides key advice on how to communicate to patients with serious illness. But more profoundly, by following the story of Job, he explains how with the help of faith, he comes accept his own illness and subsequent death.

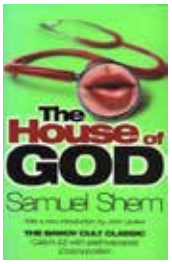
GIRONIMO!



Tim Moore (Yellow Jersey Press 2012)

I just had to include another cycling book by Tim Moore. This book was launched in Belfast to coincide with the Start of the Giro d'Italia in 2014 and recounts Moore's journey following the route of the terrible Giro d'Italia of 1914, in which only 8 out of a field of 81 cyclists competed. To my mind this is his best book to date. The combination of the story of his ride, interspersed with flash-backs to the original 1914 tour along with colourful and often humorous descriptions of the various regions of Italy is a real joy to read.

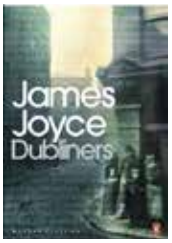
THE HOUSE OF GOD



Samuel Shem (Black Swan 1998, first published in 1978)

This book should be mandatory reading for all Foundation Year Doctors, during the foundation years. It recounts the experiences of an intern in the 'Best Medical School' in Boston in 1978 as he attempts to put medical theory into action and encounters unforeseen consequences. The book is a reflective and at times hilarious read of life as a hard working intern. In the book, Shem defines the rules of the House of God, which although are ironic, are still applicable nearly 40 years on. My favourite is rule 12: "If the radiology resident and the medical student both see a lesion on the chest x-ray, there can be no lesion there."

DUBLINERS



James Joyce (Penguin Classics 2000, first published in 1914).

After a lot of frivolity I thought I had better finish on my favourite classics. Joyce's Dubliners, originally written in 1905, was not published until 1914 owing to initial rejection and disputes with his publishers (academics take solace!). The book is a collection of short stories of life in Dublin after the turn of the century. Joyce's vivid accounts from childhood to death cover a range of social predicaments, but the abiding theme is the constant strain and anxiety of the Dubliners to conform to or to evade the societal constraints of that era and to some extent the utter futility of their effort.

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Game Changers

TRANSANAL ENDOSCOPIC MICROSURGERY – CHANGING THE MANAGEMENT OF EARLY RECTAL CANCER

Mr Robert A. J. Spence, Ms Paula M. Loughlin, Mr Roger E. Lawther

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Rectal cancer is the fifth most common cancer in adults. While the management of rectal cancer has become increasingly multimodal, surgical excision in the form of anterior resection, or abdomino-perineal excision, remains the primary intervention. There is debate about the optimum surgical approach to early stage rectal cancer (T1,N0), and endoscopically unresectable rectal polyps.

Transanal endoscopic microsurgery (TEM) has emerged as a less invasive alternative to traditional surgery. It is the intraluminal excision of a rectal lesion, with a clear, magnified view, using an operating rectoscope, allowing for organ-preserving surgery. TEM has a number of advantages over radical surgery, including avoidance of stoma, decreased pain, faster recovery, and much shorter hospital stay, typically 24 hours. Importantly, several studies comparing TEM to radical abdominal surgery show no significant difference in recurrence (4-8%), or survival. A recent meta-analysis comparing TEM with standard trans-anal surgery demonstrated a lower rate of margin involvement, decreased tumour recurrence, and reduced specimen fragmentation with TEM.

Careful patient selection is essential. TEM is now an accepted treatment for large benign polyps and early low risk rectal cancers (T1), which have no adverse pathological features. High-risk T1 tumours with poor differentiation and lymphatic involvement are better served with conventional resection. The use of TEM in node negative T2 and T3 tumours is unclear and requires further study. There is a role for TEM in the palliation of those with advanced rectal cancers, that due to co-morbidity, or metastatic disease, are unfit for major resection. As the use of this technique becomes more widespread, there are implications for service planning and training.

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ENDOVASCULAR THERAPY FOR ACUTE ISCHAEMIC STROKE

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Stroke secondary to proximal vascular occlusion has a poor natural history unless rapid recanalization can be achieved. Unfortunately intravenous thrombolysis has modest efficacy at achieving this in the setting of a large clot burden[1]. Endovascular therapy (mechanical thrombectomy) via utilizing a retrievable stent has shown promise to effect the rapid recanalization required.

The Royal Victoria Hospital, Belfast Trust was recently the sole UK recruiting centre for the ESCAPE trial[1], which compared outcome in anterior circulation stroke patients treated with endovascular therapy plus standard care versus standard care alone. Patients were selected into the study based on advanced CT imaging criteria, which had to demonstrate a small core infarct, proximal vascular occlusion and salvageable brain (that is ischemic, but not yet irreversibly infarcted). For patients randomized into the endovascular arm, emphasis was put on procedural speed, with a target CT to groin puncture of <60 minutes and groin puncture to procedure completion of <30 minutes.

The study demonstrated that the rate of functional independence at 90 days from stroke onset increased from 29.3% to 53.0% in the endovascular group and there was a decrease in mortality from 19.0% to 10.4%.

The American Heart Association/American Stroke Association in their updated guidelines has now endorsed endovascular therapy for selected stroke patients[2]. As this therapy becomes standard of care, the challenge for us in Northern Ireland is to fully implement a 24/7 service and to ensure that patients eligible for this treatment are transferred as quickly as possible to benefit from it.

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A NEW DAWN FOR THE TREATMENT OF CYSTIC FIBROSIS

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Cystic Fibrosis (CF) is an inherited, life limiting, multisystem disease characterized by viscid secretions in multiple organ systems. Progressive respiratory failure remains the most common cause of morbidity and mortality with a current median survival of 41 years. The disease affects over 10,000 people in the United Kingdom. The mainstay of therapy is the treatment and reduction of respiratory infections and optimizing nutritional status.

Cystic fibrosis is caused by a defect in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene causing altered chloride and water transport. Over 2,000 different mutations of this gene have been described although not all cause CF. Approximately 50% of patients are homozygous for the ΔF508 mutation.

Ivacaftor (Kalydeco) is the first in a new class of transformative medications known as CFTR Modulators. It improves the transport of chloride across the cell membrane resulting in a significant increase in lung function and a reduction in respiratory infections.[1] It is licensed for use in patients with the G551D and other similar mutations (5-10% of patients).

More recently two positive phase III trials have been completed to assess the efficacy of Ivacaftor along with another CFTR Modulator, Lumacaftor, in patients homozygous for the ΔF508 mutation.[2] This combination therapy (Orkambi) is currently licensed in the US with a European Medicine Agency review expected later in 2015. However, these drugs are expensive and the cost per quality adjusted life year (QALY) for Ivacaftor is between £285,000 and £1,077,000.[3] There are several new CFTR modulators undergoing clinical trials at present.

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Ulster Med J 2015;**84(3):**220-221

So you want to be a **Medical Volunteer**

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Medical Volunteer with Physicians for Human Rights, Occupied Palestinian Territories

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Accepted: 19th April 2015
Provenance: Invited article.

INTRODUCTION

When you ask colleagues why they entered medicine many say it was to help people however evidence suggests that job satisfaction is decreasing.[1] Perhaps you are becoming tired and are looking for a new challenge. Well why not use your skills and become a medical volunteer.

BENEFITS

Many volunteer programmes overseas take place in difficult clinical surroundings. Resources are scarce. Comprehensive history taking and thorough clinical examinations are vital to provide a diagnosis. This in turn increases proficiency, not simply in terms of technique, but in enhancing clinical judgement and decision making, particularly when considering how to prioritise patients based on clinical need. Medical volunteering allows for the expansion of clinical knowledge by providing unique opportunities to experience disease entities and clinical signs not common or prevalent within the UK. Furthermore, opportunities to advance personal knowledge in other medical specialities arises, a luxury rarely afforded outside of the foundation programme.

Perhaps most crucially, medical volunteering is a key means of gaining experience in global health. The world has changed fundamentally in recent years, with accessible air travel resulting in the continuous movement of people and subsequently disease.[2] We, as doctors, are increasingly exposed to pandemic and communicable diseases within the NHS. Medical volunteering overseas permits first hand exposure to, and training in management of these conditions. Moreover, it provides greater understanding of the impact which non-communicable diseases have worldwide, thus providing an opportunity to examine alternative treatment approaches adopted in other healthcare systems. This acquisition of knowledge and ideas can in turn be transferred to the NHS and used to generate innovative solutions for UK patients.[3]

Interpersonal skills are enhanced through engagement in overseas volunteering. Competence in areas such as problem solving develop rapidly. Reflecting on my own experience in the West Bank, I often find myself challenged when treating patients due to lack of clinical equipment or medication. I have had to adapt and learn using dose conversions to provide patients with a similar drug when their medication has not been available, and have learnt to adapt to a scarcity of resources, regularly using lemon juice as an antibacterial handwash between patients. A further issue to consider is that of communication. When volunteering overseas, communication can be troublesome due to language barriers, thus necessitating an interpreter. Whilst frequent use of an interpreter can advance certain verbal skills, including the use of simplistic language to explain elaborate concepts, it can hinder the ability to form a meaningful relationship with a patient. Therefore, the development of strong non-verbal communication skills, including; eye contact, hand touching, etc., assume even greater importance when establishing a relationship with the patient. Unquestionably, these skills are enhanced through volunteering. In further espousing the benefits of overseas volunteering schemes, Lord Crisp, in his 2007 report entitled, *Improving health at home and abroad*, cited leadership development as one of the most important gains for volunteers and noted that those returning to the UK were seen as having a greater understanding of how to enact change, communicate across professional cultures and work as part of a team.[2] Finally, volunteering has been linked to many positive health benefits for those who choose to take this unconventional step. Increased confidence, self esteem and lower rates of depression have been noted amongst those who have taken time to work abroad.[4]

CHALLENGES

Getting established as a medical volunteer abroad can be demanding. Companies have been created to facilitate those wishing to engage with medical volunteering however they may not provide schemes in a desired location or medical speciality. Agencies such as MSF (Medicine Sans Frontiers) have strict entrance requirements and typically seek volunteers for 'disaster' relief. As such responsibility to arrange contact with a volunteer programme tends to be an independent process, placing great onus on the interpersonal skills of the erstwhile volunteer.

It is important to have realistic expectations of what is achievable when choosing to volunteer overseas. It can be challenging to see so many individuals in need and to have to turn people away due to a lack of resources. It is thus necessary to be aware that the assistance you provide is appreciated, however it will not help amend all the short fallings in the local healthcare system. This can have a significant impact on you as an individual and when coupled with being far from your support networks can be a challenge that needs to be carefully considered. More often than not, being paid for your work abroad is a luxury. Some organisations attempt to offset costs by providing food or housing for the volunteer but setting aside the ethical and moral dilemmas that being remunerated in developing or 'conflict' areas can raise, one should be aware of the fact that volunteering abroad will require significant financial reserves.

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Finally, if the volunteer post is for a protracted duration, it can be problematic obtaining the appropriate demonstrative information for appraisal and revalidation for re-entrance into the home setting. To date, the GMC does not have specific appraisal guidelines for volunteer medical doctors and therefore standard guidelines apply. This is an unsatisfactory situation that will require clarification moving forward. Information for appraisal must be procured by alternative means but can be achieved through the diligent work of the volunteer. With access to online BMJ webinars and continued personal development (CPD) modules available worldwide, demonstration of advancement of personal knowledge can be produced.

CONCLUSION

Medical volunteering overseas whilst challenging is an enjoyable and rewarding process. It has the dual benefit of allowing a recommitment to helping the most vulnerable whilst providing an opportunity to develop both personally and professionally. Whilst appreciating the benefits, it should also be noted that, medical volunteering overseas is not achievable, nor desirable for everyone. However, engaging in short term volunteer projects, either at an international, national or even local level, should be more readily encouraged. Volunteering can be as big or as small as you can offer, from clinical assistance, education or mentoring to equipment donation and fundraising, thus reaffirming our commitment as doctors to truly succeed in our goal of 'helping people'.

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

A Consultant or GP Principal (or equivalent) is required to act as guarantor of the manuscript (usually as a co-author) in case of any issues that may arise after publication.

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- *Example:* Devlin LA, Price JH, Morrison PJ. Hereditary non-polyposis colon cancer. *Ulster Med J* 2005;**74(1)**: 14-21.
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Front cover: A Journey to Kitovu: Dr Sandra McNeill in Africa.