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Guest Editorial

Fantastic Data and Where to Find It.

When I was a Junior House Officer in the old RVH back in the mid-1990s I thought digital technology was on the cusp of completely revolutionising healthcare. I wrote a program for my Psion organiser called "WardRound" that allowed me and some of my colleagues to track our patients and their results and to electronically manage handovers, tasks and theatre lists. It was effectively an electronic health record system in our white coat pocket alongside our Oxford Handbook - and we did make some preliminary explorations with the publisher into trying to digitise that too...

Over two decades later, IT has led to some considerable improvements in how we deliver care, but we've unleashed a magical menagerie of systems that, while they work well within their narrow area, are often difficult to get to play nicely together. The data within these systems largely stays locked away, out of reach of other systems and divorced from the patient. When we've created interfaces, integration engines and messaging standards, those workarounds have tended to be partial, costly to set up and maintain and prone to error and miscommunication.

It's ironic that in a modern healthcare system, where many of our treatments and diagnostic modalities are at the technological cutting edge, we're still massively reliant on paper charts, Post-It notes, corridor conversations and custom-and-practice to provide the glue that binds it all together. And then there are the IT systems and procurement processes that don't work well, and arguably get in the way of patient care.

The Expert Panel chaired by Prof Rafael Bengoa[1] recognised that in order for our Health & Social Care System to survive, we need to transform how we deliver services. The "Quadruple Aim" of healthcare calls for: improving patient experience of care, improving the health of the population, achieving better value by reducing the per capita cost of health care, and improving staff experience. This means substantial process redesign, and digitising the patient record is an inescapable component of that. Professionals need better information. Patients need to be better enabled to manage their own health.

For this to work we need to break down the barriers between our multitudinous silos of data, so that the data can follow the patient across the traditional boundaries between care domains in the system.

In some ways, the digitisation of healthcare is already underway. The Northern Ireland Electronic Care Record (NIECR) is the jewel in the crown of our health IT ecosystem. From the outset it was, and remains, a clinically-led, IT-supported programme to address real patient-facing issues. There is no doubt that it has delivered major benefits in making patient data accessible, but, behind the scenes, the effort of maintaining all the interfaces to multiple systems is impeding new developments.

Globally, the story of digitising healthcare is not one of unalloyed success, and the example of the costly National Programme for IT (NPfIT) fiasco in NHS England is salutary. Our positive experience with NIECR is something of a rarity - the rule seems to be that large-scale IT deployments in healthcare create more problems than they solve. In his frank and enlightening book "The Digital Doctor"[2], Dr Bob Wachter explains some of the perils and process problems involved in implementing Electronic Health and Care Records (EHCRs), as well as the human factors that wreak can havoc. Issues around security and governance are hugely important. And when problems arise in clinical processes, they very frequently turn into clinical risks that may result in harm to our patients. However, as NIECR shows, it can sometimes turn out right.

We need to understand where the risks lie. If we don't address the problems caused by disjointed data systems, vendor lock-in, paper records and disempowered patients, we will continue to haplessly chase our data around a system that will collapse. Costs will continue to rise, inequalities will build, the economy will suffer and we'll lose opportunities to make a difference. Most of all, patients will be exposed to avoidable harm.

It might seem attractive to purchase an all-singing all-dancing EHCR that will do everything - assuming that we even *know* what we want. There is a slight problem - such a fantastic beast does not exist. While some current "megasuites" promise a great deal, they can't cover the full needs of a regional health economy, so there will always be the need to integrate other systems. Furthermore, many of the specialist bits that they can do aren't as good as the "best of breed" software solutions that have been specifically designed for those use-cases. There are also serious issues about access and sharing of data in vendor-specific data repositories, as well as providing quality analytics to healthcare planners.

Part of the solution is to insist on interoperability from the outset. "Interoperability" is a tricky word that can mean different things in different contexts. My own view is that it must encapsulate the principle that data is collected once, then shared seamlessly across multiple care scenarios in order to absolutely minimise time spent at the computer and maximise time spent with the patient. For example, a patient's blood pressure and heart rate, recorded at home, should be available

in the diabetic clinic, cardiology clinic or GP surgery, without the care professionals having to hunt for them or transcribe them from one piece of paper to another. Such free and easy data flow absolutely requires adherence to agreed open standards of data recording and interchange. Fortunately, such beasts are emerging, and it is encouraging to see the health IT industry moving in this direction.

In his report to the English Department of Health[3], Bob Wachter identified a serious need that applies as much to Northern Ireland as to anywhere else. Our clinicians must be trained in informatics and process design if we are to create health service transformation. We've made a start with the appointments of Chief Clinical Information Officers (CCIOs) in each Trust, and the NI CCIO Network links them with colleagues in the Health & Social Care Board, the Public Health Agency, and Primary Care. Work is underway to establish Clinical Digital Councils in the Trusts, linking a diverse range of professionals - medical, nursing, AHP, IT, administrative and others - to generate innovative thinking around how we apply digital technology to healthcare. But this is only the beginning. We have a long way to go.

The time has come to embark on a clinically-led, IT-supported, patient-centred, outcome-focused journey towards a regional Electronic Record-in-Common for NI (#ERiC4NI), which will unite and liberate our patients' data, in support of the Quadruple Aim. The Minister[4] and the Expert Panel have given us the mandate to proceed. For tomorrow's patient and tomorrow's clinician, let's get our geek on.

Shane McKee, Guest Editor

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Review

Cardiotoxicity Following Cancer Treatment

Walls GM[1], Lyon AR[2,3,] Harbinson MT[4], Hanna GG[5]

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ABSTRACT

More than half of those born after 1960 will develop cancer during their lifetime. Fortunately, owing to improved diagnosis and treatment, cure rates have risen steadily over the last three decades. With an increased survivorship, more will experience adverse effects of cancer therapeutics on the heart. As the oncologist's focus begins to encompass the issues of cancer survivorship, awareness of the management of cardiac toxicity would be prudent for all physicians looking after patients with cancer.

INTRODUCTION

Cancer and heart disease are the two most common causes of death in Northern Ireland. As cancer survivorship increases, understanding of the links between cancer treatments and cardiovascular disease becomes crucial for all medical practitioners. As cure rates improve, increasing priority can be given to optimising quality of life rather than focusing on prevention of cancer recurrence. Patients may view the adverse effects of cancer treatment in equal concern with the diagnosis of cancer itself, and with the development of new anti-cancer therapies, physicians must be vigilant for the symptoms and signs of emerging cardiovascular problems.

The last decade has seen an exponential growth in the numbers of anti-cancer treatments available, especially systemic anti-cancer treatment (SACT) and radiotherapy. It is these two anti-cancer therapies that are implicated in the emerging field of cardio-oncology, whether the aim of cancer treatment is curative or palliative (Table 1). This article explores the relationship of these treatments to cardiotoxicity, the indicative signs and symptoms and the management options available.

OVERVIEW OF ANTI-CANCER THERAPIES

Radiotherapy delivers energy via ionising radiation to neoplastic cell DNA in such a way that the resultant damage induces cell death preferentially in malignant tissue. Approximately 40% of patients diagnosed with cancer receive radiotherapy[1]. Radiotherapy may be delivered using external beam radiotherapy (EBRT) (Figure 1), sealed internal sources, for example gold seeds for prostate cancer, brachytherapy and unsealed internal sources, for example, radioactive iodine for thyroid cancer. The key principle of minimising normal tissue irradiation whilst providing the optimum dose to the cancer target dictates that factors such as tumour histology, dimensions and position are used in determining the choice of irradiation method. Since the 1960s, treatment of lung and breast cancer and lymphoma with thoracic radiotherapy has increased cardiovascular morbidity via radiation toxicity[2]. In general radiotherapy techniques which do not deliver radiation to the heart do not cause cardiotoxicity.

TABLE 1:

Commonly used cardiotoxic anti-cancer treatments

Cancer Treatment	Examples
Cytotoxic chemotherapy	doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, cisplatin, paclitaxel
Targeted therapies	trastuzumab, sunitinib, pazopanib
Hormonal therapies	tamoxifen, anastrazole, letrozole, goserelin, enzalutamide, abiraterone
Radiotherapy	breast, lung, mediastinal lymphoma and oesophageal radiotherapy

The mechanism of action of each of SACT agent depends on the family and the era that they originate from, with newer agents having quite different targets than more established treatments. Cytotoxic chemotherapy is the nomenclature used to describe drugs such as the anthracyclines (eg. doxorubicin) and antimetabolites (eg. 5-fluorouracil) which are generally non-specific and which cause apoptosis and cause cell death by altering key components of cellular metabolism or by directly damaging DNA.

Hormonal therapies, molecular targeting agents and immunotherapies are more specific in their mode of action. Their cardiotoxicity risk can occur via a number of mechanisms:

1. Direct 'on-target toxicity' if the molecular target in the

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cancer also serves an important role in cardiovascular biology (e.g. trastuzumab.)

2. Indirect 'on-target toxicity' if the molecular target in the cancer is also a modifier of cardiovascular risk leading to the accelerated progression of a second disease (e.g. GnRH agonists for prostate cancer which increase LDL and diabetes risk leading to atherosclerosis and increased risk of myocardial infarction.)

3. 'Off target toxicity' where the drug appears to inhibit a range of molecular targets, not only the principle target molecule in the cancer, and inhibition or activation these additional pathways imparts cardiovascular risk (e.g. sunitinib displays both on-target and off-target toxicity.)

Fig 1. A linear accelerator for EBRT

EXAMPLES OF CARDIOTOXIC TREATMENTS

External beam radiotherapy

Lung cancer

Curative intent radiotherapy is offered to patients diagnosed with stage I - III non-small cell lung cancer or limited stage small cell lung cancer who have a good Performance Status[3]. EBRT is often the treatment of choice for patients who decline, or are unsuitable for surgery. Recent progress in radiation technology has the potential to revolutionise lung cancer treatment, with advances such as stereotactic ablative radiotherapy reported to have comparable results with surgical resection[4]. Radiotherapy also has a role in the control of incurable lung cancer, which affected two thirds of the 1143 total cases diagnosed in Northern Ireland in 2012[5].

As observed in the general population, patients who are male, older age, African-Caribbean background, have pre-existing cardiac disease or have other co-morbidities experience a greater risk of cardiovascular morbidity following thoracic irradiation[6]. It is difficult to precisely determine the direct impact of radiotherapy from other risk factors for cardiovascular disease in patients with lung cancer owing to the sizeable impact of smoking. Ischaemic heart disease is more common in patients with tumours of the left lung compared with the right, after radiation treatment[6]. Recently developed alternative methods of delivery of thoracic radiotherapy have achieved increased survival rates and reduced treatment durations for patients without increasing long-term toxicity[7].

Breast cancer

Given the very high local control rates seen in patients with early breast cancer, an increased emphasis on avoidance of toxicity is given. Breast cancer radiotherapy constitutes 30% of a radiotherapy unit's caseload[8]. Adjuvant radiotherapy is offered to patients diagnosed with early and locally advanced breast cancer (over a third of patients with breast cancer receive radiotherapy[9]). However, in previous large overviews of breast cancer using data collected over 40 years, the reduced breast cancer mortality attributable to adjuvant radiotherapy did not always translate into an overall survival gain, probably due to an increased cardiac mortality in patients receiving treatment to the left breast[10,11].

Major coronary events after left-sided breast irradiation have a bimodal peak incidence, with many patients affected in the 4 years post-treatment, and others >20 years post-treatment[10]. It has been shown that unintended cardiac irradiation during left breast treatment occurs in almost one half of patients despite CT-based treatment plans excluding this area[12]. As seen with lung cancer, cardiotoxicity in breast radiotherapy is dependent upon laterality, with a cardiovascular mortality ratio of 1.33 (left breast versus right) for treatment delivered in the 1970s[13]. Women aged < 35 years are at greatest risk of radiation toxicity, with a 6.5 x lifetime risk of cardiovascular death compared with the general population[14]. Recent evidence suggests that for selected older patients, with low risk breast cancer, the cardiovascular risks of radiotherapy may outweigh the potential benefits[15]. The burden of cardiotoxicity in patients with breast neoplasms has decreased as a consequence of improvements in radiation technology and some investigators have found the effect of tumour laterality has been negligible since 1993[16,17].

Other thoracic radiotherapy

Mantle radiotherapy describes the extended pattern of radiation fields used to target supra-diaphragmatic lymph node groups, often encompassing the mediastinal and hilar lymphatics. Hodgkin's disease patients, for whom mantle radiotherapy was primarily used in the past have a higher risk of developing calcific valvular disorders (both stenosis and/or regurgitation)[18], myocardial infarction, cardiomyopathy and pericardial disease[19]. As a result, the relative risk of patients in this group developing heart failure is 4.9[19]. This group of patients are also at risk of symptomatic (usually syncope) and asymptomatic conduction abnormalities[20].

A recent review of the limited data on oesophageal cancer found a crude rate of radiation cardiotoxicity in these patients of 10.8%[21]. Adverse effects in order of increasing incidence were pericardial effusion, ischaemic events and heart failure. A recent review of pacemaker and implantable cardiac defibrillator safety in radiotherapy has acknowledged that

certain energies of radiotherapy pose a risk of malfunction and clinical oncologists are awaiting an update in the relevant guidelines[22].

Systemic anti-cancer therapy

Anthracyclines

Drugs such as doxorubicin and epirubicin form disruptive cross-links between paired DNA strands. They have an important role in the chemotherapy regime for many cancers including breast, gastrointestinal and blood. Cardiotoxicity due to an anthracycline is seen in 5.4% of breast cancer patients, and has been viewed as dose-dependent and related to the cumulative dose given over time[23]. The increased cardiac event rate is usually observed many years after treatment and is related to a patient's pre-existing cardiovascular risk factors[24]. Under the age of 70, anthracycline cardiotoxicity most often manifests as heart failure in breast cancer treatment[25]. Alternative preparations of the drug can be used to reduce the risk. Liposomal infusions may be less harmful than boluses and cardioprotective agents may be co-administered to further reduce the effect (e.g. angiotensin converting enzyme (ACE) inhibitors, beta blockers, dexrazozane) have been used[26,27]. Another anthracycline, epirubicin has been associated with mild rises in troponin levels unrelated to ischaemic events in the month following infusion[28].

Trastuzumab

Trastuzumab is a monoclonal antibody directed towards the HER2 epidermal growth factor receptor and is licensed for use in metastatic breast cancer patients with over-expression of this receptor[29]. The associated type of cardiac dysfunction differs from that seen with classic cytotoxic drugs in that it is observed early (i.e. within weeks of commencing treatment), in a range of severities, independent of dose and it has a mainly reversible pattern without any ultrastructure changes[30]. In a study of 179 breast cancer patients, 44% of patients developed a cardiac event (defined as New York Heart Association (NYHA) III or IV heart failure or a reduction in ejection fraction) during the year of treatment, and almost a tenth had a second[31]. A total of 7% patients in this study had their trastuzumab discontinued, though discontinuing treatment did not affect the rates of a second cardiac event occurring. Prior or concomitant radiation therapy doesn't influence trastuzumab cardiotoxicity[32], but anthracycline therapy does[33].

Other SACTs

Intercalating agents such as cyclophosphamide employ a similar mechanism of action to anthracyclines (disruption of DNA 'unzipping' in replicating cancer cells) and are associated with early heart failure (one week post-treatment) and haemorrhagic myocarditis[34].

Antimetabolite drugs such as 5-fluorouracil (5-FU), have a number of mechanism of actions, but exert their main effect by triggering apoptosis in malignant cells by a process called a thymineless death[35]. These drugs may cause acute chest pain during or shortly after administration which occurs through the mechanism of coronary artery vasospasm[36]. Recognition of this is important for patients on capecitabine and infusional 5-FU as on-ongoing administration of those agents must be stopped until the symptoms have settled and cardiac investigations are completed.

TABLE 2:

Commonly used cardiotoxic SACT and their adverse cardiovascular effects

Drug / Family of Drugs	**Cardiotoxicities**
Anthracyclines	Heart failure (late and irreversible)
Trastuzumab	Heart failure (early and reversible)
Cyclophosphamide	Heart failure (early), haemorrhagic myocarditis
Antimetabolites	Coronary vasopasm, acute coronary syndromes
Platinum	Acute coronary syndromes
Taxanes	Heart block, bradycardia, tachyarrhythmia
Bevacizumab	Hypertension, thromboembolism
Sunitinib, sorafenib, pazopanib	Hypertension, heart failure, myocardial infarction

Platinum-based intercalating agents may also cause this symptom. Unlike the pattern seen in antimetabolites, the risk continues for many years, and cisplatin can be detected in the serum at 20 years[37].

Taxane drugs such as paclitaxel and docetaxel disturb the microtubules needed to separate original and fresh copies of DNA in the dividing cell. These are commonly used in ovarian and breast cancer treatment and have been linked to heart block, bradycardia and tachyarrhythmias with a cumulative incidence of 0.5%[38].

Hormonal treatments have not been consistently shown to increase the risk of cardiac events despite interfering with lipid metabolism[23].

Bevacizumab, an agent targeting vascular endothelial growth factor receptors used in colorectal cancer, has been linked to cardiotoxicity via hypertension and thromboembolism[39]. Sunitinib targets this receptor in renal cell carcinoma and was strongly associated with cardiotoxicity in one large study[40]. Over a tenth of patients experienced cardiovascular events including myocardial infarction and heart failure, over a quarter had an asymptomatic decrease in ejection fraction of 10% or more and almost one half of patients were diagnosed with hypertension following drug administration.

DIAGNOSIS OF HEART FAILURE

Whilst oncological treatments may cause a range of adverse

cardiovascular conditions, the commonest is heart failure. Heart failure is a complex syndrome in which the ability of the heart to maintain the circulation of blood is impaired[41]. Approximately half of patients die within 4 years[42] however mortality rates are improving[43].

Biomarkers of cardiac injury (e.g. cardiac troponin I concentration) have been shown to identify patients at risk for anthracycline cardiotoxicity and predict a poor response to cardiac therapy[44,45]. The finding of a significantly raised B-type natriuretic peptide level (BNP or its precursor fragment NT-proBNP) provides evidence of heart failure with high sensitivity[46]. Whilst not useful in an unselected cohort of patients receiving SACT, NT-proBNP trends can identify at-risk patients treated with anthracyclines[47].

Echocardiography is an excellent tool for identifying the patient with heart failure. A reduction in left ventricular ejection fraction (LVEF) is a late finding and may occur only after a significant amount of myocardial damage has occurred. Advanced echocardiographic techniques such as global longitudinal strain measurement may detect left ventricular impairment earlier than conventional LVEF[48]. Deteriorations of 13.7% or more from baseline warrant continued increased clinical vigilance with fair sensitivity (88%) and specificity (71%)[49].

TEXT BOX 1:

Application of natriuretic peptides to CTRCD

- raised natriuretic peptide level is evidence of heart failure (highly sensitive)
- elevated NT-proBNP after an anthracycline identifies patients at risk of CTRCD
- CTRCD is not limited to high-dose regimes
- persistent elevations after 72 hrs predict progressive decline in left ventricular failure
- raised levels are associated with a greater risk of developing trastuzumab CTRCD

CANCER THERAPEUTICS-RELATED CARDIAC DYSFUNCTION

Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD) is defined by the European Society of Cardiology (ESC) as a decrease in LVEF of 10% or more, to a value less than the normal range[50]. CTRCD can further be divided into those who develop symptoms of overt heart failure and those who have an asymptomatic decline in systolic function. The ESC also sub-classifies systolic dysfunction by the degree of reversibility following clinical intervention:

- Reversible (returns to within 5% of baseline)
- Partly reversible (>10% improvement, >5% below baseline)
- Irreversible (<10% improvement, >5% below baseline).

It is felt that the most important factor is demonstration of reversibility.

All patients should be treated with an ACE inhibitor/ angiotensin II receptor blocker (ARB) and a beta blocker licensed for heart failure. Some of these drugs have been assessed specifically in CTRCD patients, and may be preferable to others in the same drug class, as not all agents seem to be beneficial[51].

In patients with early evidence of left ventricular impairment during cancer treatment, introduction of ACE inhibitors and possibly beta blockers may be helpful to recover cardiac function, and offer cardioprotection against further cancer treatment if required - particularly those with a history of cardiac disease. Different strategies are currently employed in various specialist centres with Cardio-Oncology services, including surveillance with echocardiography and cardiac biomarkers, early detection and cardioprotection during chemotherapy or cardiotoxic targeted molecular therapies. Involvement of the Heart Failure Specialist Team is essential.

TRASTUZUMAB

It is important to appreciate that the majority of the 44% patients developing cardiotoxicity after trastuzumab had mild

TEXT BOX 2:

Recommended actions for patients undergoing cardiotoxic anticancer therapy

BEFORE COMPLETING TREATMENT	AFTER COMPLETING TREATMENT
Be aware of the cardiotoxic potential of patients' anti-cancer treatment plan Investigate new or changing cardiovascular symptoms	
Ensure patients are aware of the potential for heart problems during/after cancer treatment Monitor weight, lipid profile, glycaemic control during hormonal therapies Update the Oncologist early with relevant investigation results and medication changes	Regular and relevant cardiac function testing no later than 6 months following high-risk treatments and if normal/ asymptomatic Approach metastatic and non-metastatic patients with identical monitoring Liaise with a cardiologist if there is a suspicion of cardiotoxicity

or no symptoms[31]. The implication of previous or concurrent anthracycline is also worth recognising - this triples the risk[31]. Whilst no study has been designed to test this link specifically, a recent very large population-based study indicates that sequential therapy (anthracycline followed by trastuzumab) is more dangerous (4 x hazard ratio) than concomitant treatment (2 x hazard ratio)[52]. It is postulated that the cumulative oxidative damage from an anthracycline is negatively modulated in the vulnerable by trastuzumab via its direct mechanism of action on the HER2 pathway and some data suggests that a delay in initiating trastuzumab allows the myocytes to recover before a "second hit"[44].

New elevations in cardiac troponin I were commonly seen after the first cycle, resolved within 3 months with patients developing cardiovascular symptoms by 8 months. In the same study, baseline troponin elevation patterns (following cytotoxic chemotherapy and prior to trastuzumab) were consistent with the hypothesis that the conventional time to commence trastuzumab may be during a period of myocyte vulnerability[52]. Therefore abnormal troponin values should prompt clinicians to follow up symptoms actively whilst a Cardio-oncology opinion is awaited. There is less data about using BNP for diagnosis and prediction of CTRCD with trastuzumab, compared with anthracyclines. Exploratory analyses have established that NT-BNP can be raised in absence of impaired LVEF on echocardiogram [53], suggesting LVEF is not sensitive enough to detect subclinical damage from SACT. The Australian CATS (Cardiotoxicity of Adjuvant Trastuzumab) study should address this need when it is reported [54].

Protocols for managing trastuzumab cardiotoxicity have been developed[55,56]. In the event of a severe drop in LVEF or the development of clinical heart failure, cessation of trastuzumab is clearly indicated. For cases with mild subclinical dysfunction, continuation of therapy with careful LVEF monitoring and protective medical therapy may be appropriate. Figure 2 is the traffic light triage approach suggested by the National Cancer Research Institute[55]. The traffic light system guides clinicians when to increase monitoring, when to refer to Cardiology and when to continue/discontinue trastuzumab and ACE inhibitors.

The clinical outcome of trastuzumab cardiotoxicity is more favourable than anthracyclines and in many cases, re-challenge may be safely carried out[44]. In the PRADA study, patients randomised to cardioprotection with candesartan or metoprolol suffered less cardiotoxicity from trastuzumab with candesartan (no benefit from metoprolol observed)[50]. Future studies should seek to clarify the need for cardioprotection as trastuzumab becomes increasingly prescribed not only for breast but other tumour types.

CONCLUSIONS

Cardiovascular disease and cancer are very common treatable conditions. Survival rates for cancer have increased significantly over the last three decades. Increased survivorship increases the chances of developing treatment related complications such as cardiovascular disease. Both oncologists and non-oncologists need to be aware of the clinical syndromes and the potential treatments available for cardiovascular disease related to cancer treatment. The development of new specialist Cardio-Oncology services can help oncologists, haematologists and primary care access specialist care for cancer patients before, during and after treatment with cardiotoxic therapy.

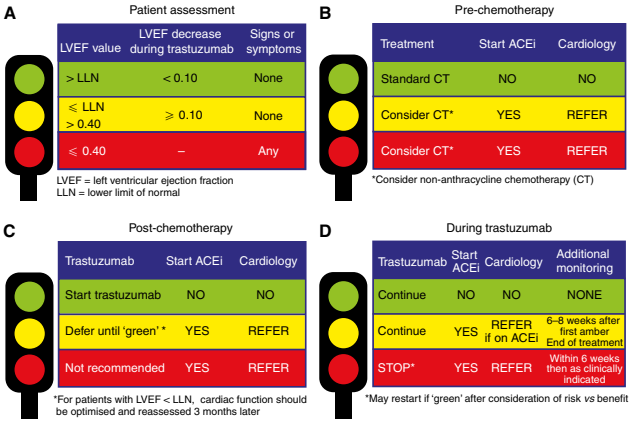

Fig 2. NCRI Traffic Light System

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Clinical Paper

An Assessment of Fetal Cerebral and Hepatic Perfusion in Normal Pregnancy and Pre-Eclampsia Using Three-Dimensional Ultrasound

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ABSTRACT

Background: Pre-eclampsia and placental causes of intrauterine growth restriction (IUGR) are part of the same spectrum of disorders. In IUGR, there is preferential shunting of blood to the fetal brain at the expense of other organs. We wanted to demonstrate that this also occurs in pre-eclampsia using three dimensional (3D) ultrasound. The 3D indices of perfusion are: flow index (FI), vascular index (VI) and vascularisation flow index (VFI) which reflect tissue vascularity and flow intensity.

Methods: Fourteen normal pregnant women and 14 with diagnosed pre-eclampsia were recruited. Scanning was conducted by 2 observers using a Voluson E8 machine. Perfusion was measured at a pre-defined position within the fetal brain and fetal liver. The power Doppler signals were quantified using the 'histogram facility' to generate 3 indices of vascularity: FI, VI and VFI. The unpaired t-test was used to compare differences between groups. The hypothesis was that fetal brain FI, VI and VFI would be similar between women with normal pregnancy and women with pre-eclampsia, but measurements would be reduced in the fetal liver in women with pre-eclampsia.

Results: Maternal characteristics of age, body mass index and gestation were not different between groups. The depth of insonnation did not differ between groups.

Fetal cerebral perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia. The mean (SD) for FI was 22.4 (5.7) vs. 21.1 (4.3) respectively (p=0.49). For VI, the mean (SD) was as 64.7 (40.4) vs. 79.1 (27.4) respectively (p=0.28). For VFI, the mean (SD) was 14.8 (10.3) vs. 16.1 (5.5) respectively (p = 0.66).

Fetal hepatic perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia. The mean (SD) for FI was 34.4 (19.9) vs. 27.8 (11.0) respectively (p = 0.28). For VI, mean (SD) was 67.6 (36.0) vs. 87.3 (25.8) respectively (p=0.11). For VFI, the mean (SD) was 19.6 (11.6) vs. 23.1 (10.6) respectively (p=0.42).

Conclusion: Using 3D ultrasound, we were not able to demonstrate preferential shunting of blood to the fetal brain at the expense of the fetal liver. Due to the high variability of our data, no definite conclusions can be derived from this work. A larger study may be required.

Key words: Pre-eclampsia, 3D ultrasound, perfusion.

INTRODUCTION

The patho-physiology of pre-eclampsia is believed to be placental in origin, with inadequate trophoblastic invasion of spiral arteries compromising placental blood flow[1]. The disease of pre-eclampsia overlaps with placental causes of intrauterine growth restriction (IUGR), where 20% of women with pre-eclampsia will have a growth restricted baby below the 10th centile[2]. Previous research studying IUGR has demonstrated preferential vascular shunting to the fetal brain as a compensatory measure for poor placental perfusion[3].

The current study aims to investigate whether this 'brain-sparing' effect is also demonstrable in pre-eclampsia. In other words, is there preferential shunting to the fetal brain at the expense of vascular flow to other major organs, such as the fetal liver?

With the advent of three dimensional (3D) ultrasound, physicians have been able to obtain in-vivo indices of perfusion [4,5]. These indices are flow index (FI), vascular index (VI) and vascularisation flow index (VFI) which are believed to reflect vascularity and flow intensity.

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In order to demonstrate preferential vascular shunting to the fetal brain in pre-eclampsia, we hypothesise the following:

1. Fetal cerebral perfusion is similar in pre-elampsia compared to normal pregnancy using the indices of FI, VI and VFI. .
2. Fetal hepatic perfusion is reduced in pre-eclampsia compared to normal pregnancy using the indices of FI, VI and VFI.

MATERIALS AND METHODS

Full research ethical and governance approvals were granted for this study (Research ethics no: 11/NI/0082; Research governance no: IRAS 57428). 14 normal pregnant patients and 14 with pre-eclampsia were recruited, and informed consent obtained. Normal pregnancy was defined as women with no pre-existing maternal co-morbidities, on no medication and no antenatal complications or concerns regarding fetal growth. Pre-eclamptic patients met the criteria of confirmed hypertension (BP >140/90mmHg on two consecutive occasions four hours apart); and significant proteinuria (>2+ on urinalysis; or >0.5g/24h on urine collection). Exclusion criteria included gestation less than 20 weeks; multiple pregnancy; and pregnancy with an abnormal fetus.

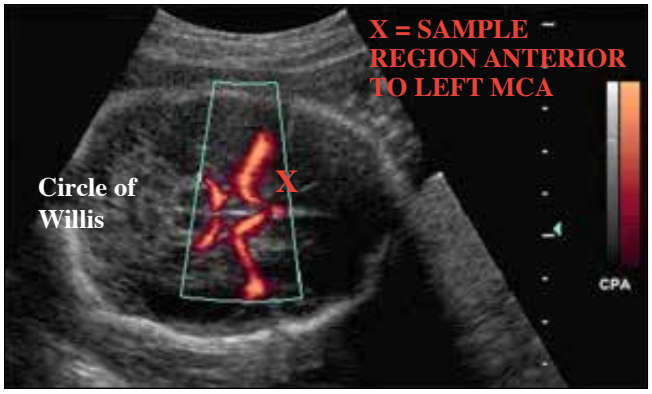

Fig 1. Fetal Cerebral Perfusion

Ultrasound scanning was conducted by one of two observers who had received identical training in the technique. A Voluson E8 machine with a 6 MHz trans-abdominal probe was used. The Voluson default settings were kept constant at: frequency 'mid'; dynamic 'set 3'; balance '>150'; smooth '4/5'; ensemble '11'; line density '8'; power Doppler map '4'; artefact suppression 'off'; power Doppler line filter 'off'; and, quality 'high'. Gain, signal power, pulse repetition frequency and speed of acquisition were controlled for. When measuring an area of perfusion, colour flow and 3D power Doppler angiography (3D-PDA) were applied to a pre-defined anatomical location, and the depth of insonnation also recorded. From within the area measured, a constant spherical sample volume was chosen. The power Doppler signals were then semi-quantified utilising the 'histogram facility', generating the three indices of vascularity: FI, VI and VFI.

Identifying fetal cerebral blood flow and measuring perfusion

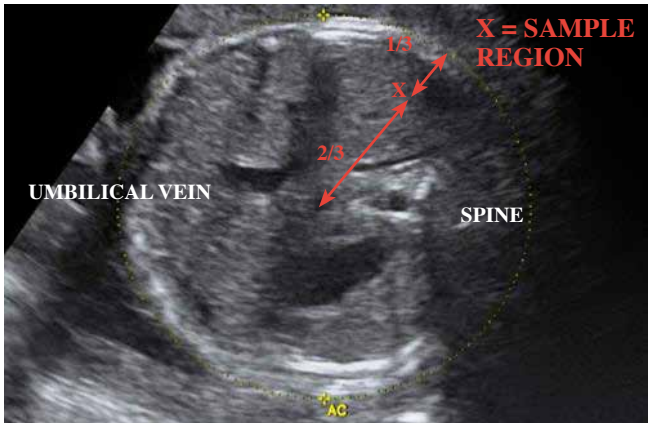

Fig 2. Fetal Hepatic Perfusion

Colour flow Doppler was used to identify the fetal Circle of Willis in the standard biparietal diameter view. The left middle cerebral artery (MCA) was visualised and the half way point of this vessel was identified. The region of vascularity sampled was arbitrarily fixed as 1cm anterior to this half way point of the left MCA (Figure 1). 3D-PDA was applied to this region.

Identifying fetal hepatic blood flow and measuring perfusion

The standard view used in measuring abdominal circumference was obtained. An imaginary line was drawn from the centre of the abdomen to the periphery, and 3D-PDA was applied to the hepatic region 2/3 of the distance from the centre along this line (Figure 2).

RESULTS

There was no statistically significant difference in age, body mass index or gestation between women with a normal

TABLE I:

Patient Demographics

	Normal n=14 mean (SD)	**Pre-eclampsia n=14 mean (SD)**	**t test P value**
Age (years)	29.5 (7.0)	28.4(6.0)	0.67
Body Mass Index (kg/m2)	23.6 (4.9)	26.2 (5.9)	0.22
Mean Arterial Pressure (mmHg)	89.2(6.5)	118.2 (5.1)	< 0.01
Gestation at scanning (weeks)	35+4	34+0	0.40
Depth of insonnation (cm) – Cerebral cortex	6.1 (1.7)	5.7 (1.3)	0.47
Depth of insonnation (cm) – Fetal liver	6.6 (1.6)	7.1 (2.2)	0.49

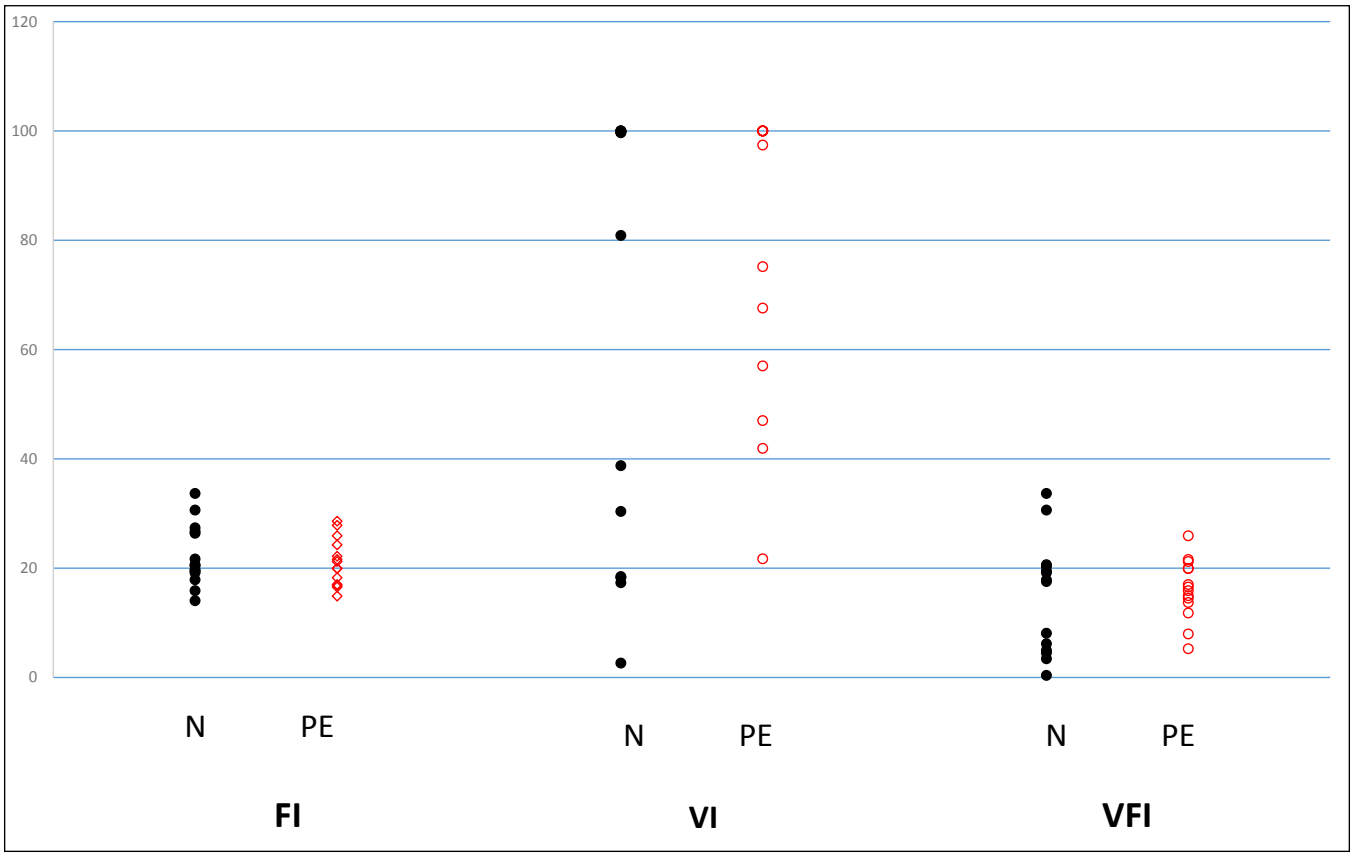

Fig 3. Data distribution of fetalcerebral perfusion indices

TABLE II:

Fetal Cerebral Perfusion

	Normal (n=14) Mean (SD)	**Pre-eclampsia (n=14) Mean (SD)**	**t test p-value**
FI	22.4 (5.7)	21.1 (4.3)	0.49
VI	64.7 (40.4)	79.1 (27.4)	0.28
VFI	14.8 (10.3)	16.1 (5.5)	0.66

TABLE III:

Fetal Hepatic Perfusion

	Normal (n=14) Mean (SD)	**Pre-eclampsia (n=14) Mean (SD)**	**t test p-value**
FI	34.4 (19.9)	27.8 (11.0)	0.28
VI	67.6 (36.0)	87.3 (25.8)	0.11
VFI	19.6 (11.6)	23.1 (10.6)	0.42

pregnancy and women with pre-eclampsia (Table 1). Women with pre-eclampsia had a higher mean arterial pressure (MAP). Depth of insonnation was not different between groups for either cerebral or hepatic perfusion measurements.

For women with pre-eclampsia, 5 of 14 delivered a baby that was growth restricted as defined by plotting birthweight on a customized growth chart.

Indices of fetal cerebral perfusion were not different between women with a normal pregnancy in comparison to women with pre-eclampsia (Table 2). The mean (SD) for FI, VI and VFI was not different between groups. For FI, the mean (SD) was 22.4 (5.7) vs. 21.1 (4.3) for normal vs pre-eclampsia groups respectively (p=0.49). For VI, the mean (SD) was 64.7 (40.4) vs. 79.1 (27.4) respectively; p = 0.28. For VFI, the mean (SD) was 14.8 (10.3) vs. 16.1 (5.5) respectively; p= 0.66. The overall distribution of this data is shown in Figure 3.

Fetal hepatic perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia (Table 3). The mean (SD) for FI was 34.4 (19.9) vs. 27.8 (11.0) between the normal and pre-eclampsia groups (p = 0.28). For VI, mean (SD) was 67.6 (36.0) vs. 87.3 (25.8) respectively (p=0.11). For VFI, mean (SD) was 19.6 (11.6) vs. 23.1 (10.6) respectively (p=0.42). The overall distribution of this data is shown in Figure 4.

DISCUSSION

The main findings were that three-dimensional indices of perfusion were not different in the fetal brain or fetal liver in women with pre-eclampsia compared to normal pregnancy. Hence the concept of a 'brain sparing effect' has not been demonstrated in this sample population.

The strengths of this study are that the 3D ultrasound technique was robustly standardized and the two groups of patients were matched for general characteristics.

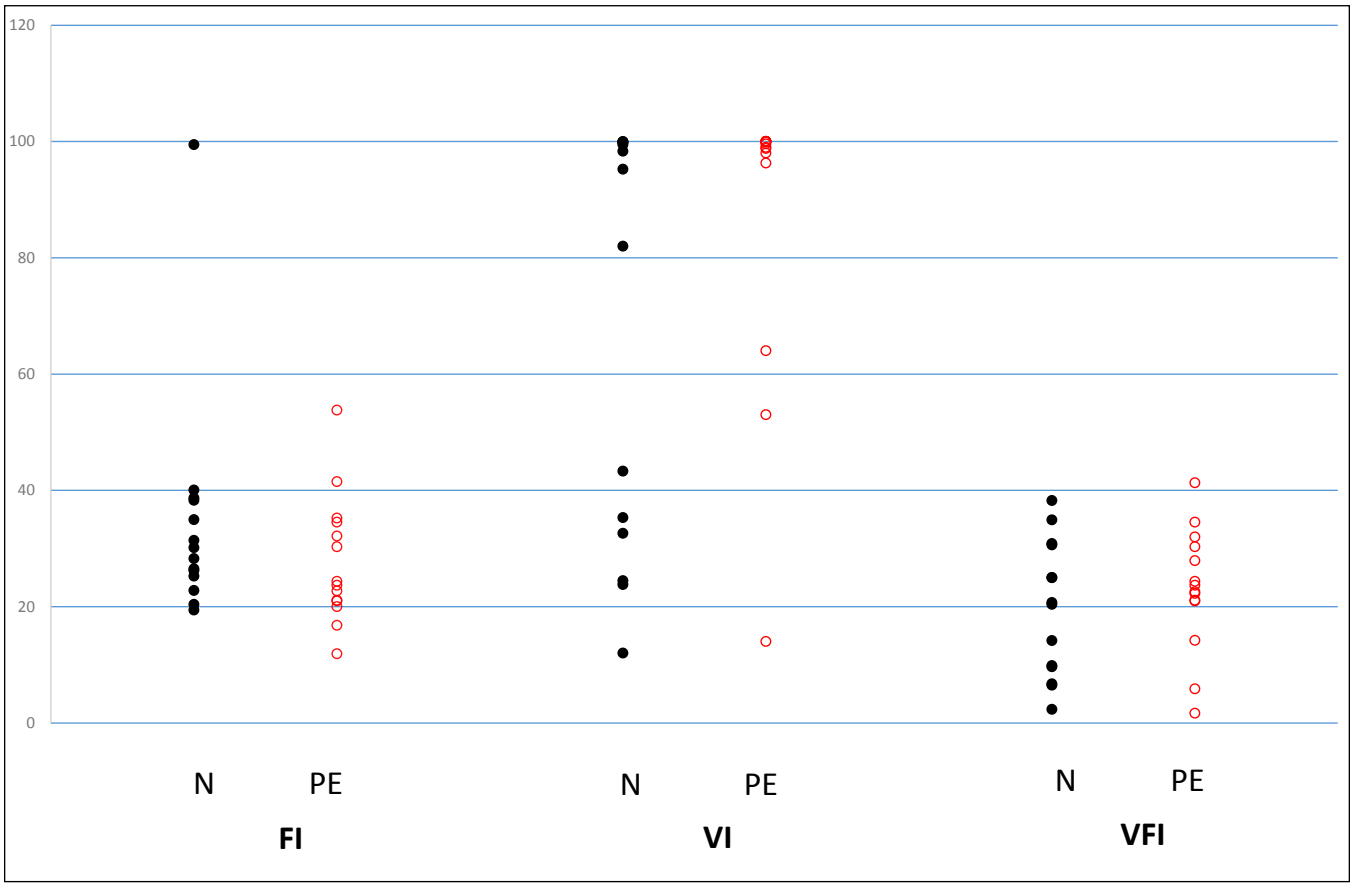

Fig 4. Data distribution of liver perfusion indices

A weakness of this study was the small sample size. Patients were also scanned by two different operators although every effort was made to ensure consistency in scanning techniques.

There are several possible explanations why no differences between groups were found. The first explanation is that there is truly no difference between these two populations in terms of fetal cerebral perfusion and fetal liver perfusion.

The second explanation is that the women selected who had pre-eclampsia had mild disease and therefore any differences would have been more difficult to detect, especially given the small number of patients. It would have been difficult to recruit women with severe pre-eclampsia to this study without compromising the safety of these women.

The third explanation is that the method used to assess perfusion is poor. In the current study, the variability of the data in both the normal population and the population with pre-eclampsia is wide. The methods of FI, VI and VFI have been criticized in a previous study as the measurements, particularly for VI and VFI, had wide variability[6]. Previous work from our unit concur with this assertion[7,8].

Despite our skepticism of 3D ultrasound as a method of assessing perfusion, we undertook this study as currently there are no other non-invasive methods of assessing perfusion in a fetus.

Taken together, we suggest that no clinical conclusion can be derived from our current study.

Previous work from our unit demonstrated a statistical difference in certain regions of the placenta in pre-eclampsia compared to normal pregnancy despite wide variability in measurements obtained[8]. The apparent poor performance of the test in the current study has prompted us to perform a sample size calculation using our current data. We chose to perform a sample size calculation using FI as this is believed to be most stable[6]. A sample size calculation for FI using an alpha or 0.05 and a Power of 80%, suggests a requirement of 302 women in each group to demonstrate a statistical difference. It may therefore be appropriate to consider performing a larger study.

DECLARATION OF INTEREST

No conflict of interest declared.

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Clinical Paper

Outcome of primary rhegmatogenous retinal detachment surgery in a tertiary referral centre in Northern Ireland – A regional study

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Provenance: externally peer-reviewed

Abstract

Purpose: To report the primary and final success, functional outcome and complication rates of patients with primary rhegmatogenous retinal detachment (RRD) who underwent retinal detachment surgery in a tertiary referral centre in Northern Ireland.

Venue: Vitreoretinal service, Royal Victoria Hospital, Belfast, Northern Ireland.

Methods: This is a retrospective case series of all patients who underwent primary RRD repair between 1st of January 2013 and 31st of December 2013. Charts were reviewed. Patients' demographics, overall primary and final success, functional outcome, complication rates were identified and recorded. Subgroup analysis according to lens status and foveal attachment was also performed.

Results: A total of 212 cases of primary RRD were included. Mean age at time of surgery was 56.6 years (range 9-90 years); 175(82.5%) had pars plana vitrectomy (PPV), 27 (12.5%), scleral buckle (SB) repair and 10 (5%) pneumatic retinopexy (PR). Overall primary and final success rate were 86% and 95.6% respectively. Overall mean visual acuity improved from 1.1 to 0.4 LogMAR postoperatively after a mean follow-up of 9 months. There was no significant difference in the primary success rate in relation to the baseline lens status ($\chi^2 = 3.4$, $P = 0.2$) and to the baseline macular status ($\chi^2 = 0.6$, $P = 0.7$). Presence of proliferative vitreoretinopathy (PVR) negatively affected the primary success rate ($\chi^2=7.2$, $P = 0.03$). Poor prognostic factors for success were PVR at presentation, inferior breaks and increasing number of detached quadrants.

Conclusions: This study demonstrates a success rate comparable with other centres with a low rate of final failure. Despite sub-specialism and the great advances in VR surgery, the biology of RRD dictates a failure rate. New therapies may improve results in the future.

INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is the separation of the neurosensory retina from the retinal pigment epithelium (RPE) resulting from a tear or a hole in the retina.[1] Its incidence is about 1 in 10,000 per year[1] and more than 50% of RRDs occur spontaneously with no history of surgical or non-surgical trauma.[2]

Techniques for the management of RRD include scleral buckling, pars plana vitrectomy, pneumatic retinopexy, alone or in combination. Each of these techniques has its own profile of advantages and disadvantages. Retinal reattachment with a single procedure is recognized to be associated with better visual outcome.[3] Rates for primary reattachment are reported between 85% - 90% in uncomplicated cases[4-6] and 60% - 70%[7] in high-risk eyes; approximately 5% of eyes have permanent anatomical and functional failure.[8]

A decade ago, the national audit of the outcome of primary RRD[9] and other audits from vitreoretinal (VR) units in the UK showed that there has been an increase in the primary success rate with increased subspecialisation.[10-11] Since then, there is a paucity of published outcome data from VR units in the UK.

All VR surgeries in Northern Ireland (population 1.8 million) are carried out by the VR service of Royal Victoria Hospital in Belfast consisting of 6 retinal specialists who perform an average of 780 VR surgeries yearly of which RRD surgery comprises 30% of the workload.

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We conducted this study to provide contemporary data about retinal detachment surgery in a UK based unit and to determine if the primary success rate has changed over the last decade because of advances in retinal surgery. We also report the final visual outcome, complication rate and analysis of failure.

METHODS:

This is a retrospective case series of the outcome of primary RRD repair. A total of 212 eyes of 211 patients who underwent surgery for primary RRD from 1st of January 2013 to 31st of December 2013 were identified and included in this study. Data were retrieved from pre-designed VR audit sheets and patients' case notes.

The authors confirm that data collection conformed to all local policy at Belfast Health and Social Care Trust and this study was registered with the audit department (number 4588).

The main outcome measures were: 1) primary success defined as retinal reattachment with single operation and no residual intravitreal tamponade after 2 months, 2) final success defined as retinal reattachment with more than one operation and no residual silicone oil tamponade, 3) failure defined as persistent retinal detachment anywhere or retinal reattachment with long-term silicone oil tamponade and 4) final visual acuity after a minimum of 6 weeks of follow-up.

Cases of other types of retinal detachment or cases with previous history of vitreo-retinal procedures were excluded.

STATISTICAL ANALYSIS:

Data were analysed using the statistical packages for social sciences SPSS (version 22.0; SPSS, Inc., Chicago, IL). Descriptive statistics were generated for continuous variables and categorical variables. For statistical purposes, Best Corrected Visual Acuity (BCVA) was converted to the logarithm of the minimum angle of resolution (LogMAR). Cross tabulation with Pearson's chi square test was used to investigate the relation between the primary success rate with lens status at baseline, surgical procedure, baseline macular status and presence of PVR. Independent sample T-test was used to assess the difference in mean final BCVA by baseline status of macula, lens status, surgical procedure and presence of PVR. The chosen level of statistical significance was $P < 0.05$.

RESULTS:

Patient Demographics, Macular Status and Presenting Visual Acuity

Of the 212 eyes included, the mean age was 56.6 years (range, 9-90 years) with 66% male subjects and 51.5% right eyes. One patient presented with simultaneous bilateral retinal detachment. Table 1 shows a summary of pre-existing ocular history for RRD in our series. Table 2 summarises the characteristics of RRD at presentation.

The presenting BCVA was recorded in all cases with a mean LogMAR of 1.1. The mean BCVA for the macula-on group was 0.2 compared to 1.6 in the macula-off group including 45 eyes with CF vision, 36 eyes with HM vision, 9 eyes with PL vision.

Table 1:

A summary of pre-existing ocular risk factors in retinal Detachment

Condition	(n) %
Previous Cataract Surgery	(51) 24.6%
Contralateral retinal detachment	(11) 5.19%
Myopia	(16) 7.5%
Laser refractive surgery	(7) 3.3%
Previous retinopexy (laser/cryopexy)	(4) 1.98%
Previous trauma	(5) 2.36%
Complicated cataract surgery	(2) 0.94%
Others	
• **Stickler syndrome**	(1) 0.47%
• **Sickle cell retinopathy**	(1) 0.47%
• **Ocular albinism**	(1) 0.47%

Surgical Technique

All cases were operated on by 6 consultant vitreo-retinal surgeons and 3 vitreo-retinal fellows under direct supervision. Overall, 82.5% (175) of the cases had pars plana vitrectomy (PPV), 12.5% (27) had scleral buckle (SB) and 5% (10) had pneumatic retinopexy (PR) as a primary procedure. Of those who had PPV as a primary procedure, 67% were operated by classic 20-gauge PPV and the remainder by 23-gauge trans-conjunctival sutureless technique. Two patients had combined cataract and PPV. Scleral buckles were circumferential in 55%, segmental in 38% and radial in 7%; 28% had subretinal fluid (SRF) drainage with buckling. PR as a primary procedure was only used in uncomplicated phakic detachments.

Phakic and pseudophakic eyes with retinal detachment were analysed separately. In the phakic group (161 eyes), 78% (126), 16 % (25) and 6% (10) had PPV, SB and PR respectively. In the pseudophakic group (51 eyes), 96% (49) had PPV and 4% (2) had SB.

Primary and Final Success Rate

The overall primary success rate of retinal reattachment was 86% with a follow-up of 2 – 18 months. 31 patients (14%) required more than one procedure to reattach the retina. The average number of operations was 1.1 (range 1-4). There was no significant difference in the primary success rate between the 3 different surgical procedures with success rate of 86%, 85% and 80% for PPV, SB and PR ($\chi^2 = 0.6$, $P = 0.9$). There was no difference in the primary success between 20 and 23 gauge PPV. Patients with retinal dialysis (7) achieved 100% re-attachment rate with scleral buckling. Patients presenting

TABLE 2:

The characteristics of retinal detachment at presentation.

Characteristics	% Of cases
Phakic	75%
Macula attached	38%
Number of breaks • **1-3 breaks** • **4-6 breaks** • **>7 breaks**	 58% 34% 8%
Types of retinal breaks • **Giant retinal tear** • **Dialysis** • **Inferior breaks** • **Combined Schisis detachment** • **Myopic macular hole**	 1.4% 3.3% 12.3% 0.4% 0.4%
Proliferative vitreo-retinopathy (grade C and above)	20%
Total (4 quadrants) RRD	3.77%

with giant retinal tears (3) had 100% success rate with a planned 2-stage procedure using perfluorocarbon liquid (PFCL) as a short term postoperative tamponade, with PFCL removal and replacement by gas or silicone oil after 7 days.[15]

Lens status was analysed as a possible factor affecting success. In the phakic group, the overall primary success rate was 87% compared to 78.4% in the pseudophakic group and this was not statistically significant ($\chi^2 = 3.4$, $P = 0.2$).

There was no significant difference in the success rate in relation to the macular status ($\chi^2 = 0.6$, $P = 0.7$); primary success was higher for macula-on RRDs with 91.4% reattachment compared to 82.4% in macula-off group. Final success rate of 100% was attainable in the macula-on group compared to 92% for the macula-off group

TABLE 3:

Comparison of preoperative and postoperative BCVA in relation to the status of the macula at presentation.

BCVA: best corrected visual acuity. Postoperative BCVA has been measured at the last follow-up.

Macular Status		Preop BCVA (LogMAR)	Postop BCVA (LogMAR)
Macula ON	Mean	0.2	0.2
	N	81	81
	Std. Deviation	0.3	0.3
Macula OFF	Mean	1.6	0.6
	N	131	131
	Std. Deviation	0.9	0.6
Total	Mean	1.1	0.4
	N	212	212
	Std. Deviation	09.	0.5

The overall final success rate of retinal reattachment was 95.8% without silicone oil; an additional 3.7% (8 eyes) were reattached with silicone oil. Less than 1% (2 eyes) remained detached, 1 eye deemed inoperable and 1 eye for which re-operation was refused by the patient.

Eyes with a complicating factor (PVR grade C, inferior breaks and total retinal detachment) were analysed as a subgroup; primary success rate was 76%, 81%, 75% in the PVR, inferior breaks and total RRD groups respectively. Final success rate increased to 85.7% and 88.4% in the PVR and inferior breaks groups respectively but remained at 75% for the total RRD group. Hypotony and choroidal detachment at presentation (2 eyes) were also associated with poor outcome with long-term silicone oil in the eye and multiple surgeries. We found that the presence of PVR negatively affected the primary success rate ($\chi^2=7.2$, $P = 0.03$).

14% (31 eyes) were primary failures requiring further surgery. Reasons for failure were: missed or new break (16 eyes), PVR (11 eyes), inadequate retinopexy leading to re-opening of the primary break (7 eyes) and in 3 eyes the reason for re-detachment could not be identified.

POSTOPERATIVE VISUAL ACUITY:

Postoperative vision was recorded at the final follow-up visit. The overall mean improved from presenting BCVA of 1.1 to 0.4 at final review. In 131 eyes with macula-off RRD, the VA improved from a mean 1.6 to 0.6 including 5 eyes with CF, 2 eyes with HM vision, 2 eyes with LP and 1 eye with NPL vision. For eyes with a macula on RRD, VA remained at a mean of 0.2 postoperatively. In 27 eyes undergoing a SB, the VA improved from a mean of 0.7 at presentation to 0.4 at final review. For the 175 eyes with primary PPV, the mean presenting VA 1.2 improved to 0.5.

Tables 3 and 4 compare the pre- and post-operative vision in relation to the macular status and the surgical procedure. Table 5 summarises VA at final visit by baseline status of macula, lens status, surgical procedure and presence of PVR. Macular status at baseline and PVR presence at baseline were significantly related to final BCVA ($P = 0.04$ and $P = 0.03$, respectively).

COMPLICATIONS OF RETINAL DETACHMENT SURGERY:

There was no endophthalmitis or other major postoperative complication. One scleral buckle patient undergoing drainage sustained a localised subretinal haemorrhage which did not affect the macula. Of the vitrectomy subset, 18.3% (39) of eyes underwent cataract surgery during the follow-up period. 4.7% (10) eyes had temporary raised intra-ocular pressure (IOP) and 1.98% (4) patients continued to have persistent raised IOP with optic nerve damage requiring long-term glaucoma medications. Epiretinal membrane formation was

found in 1.98% (4) of patients.

DISCUSSION:

This study provides contemporary data about retinal detachment surgery in a tertiary referral centre in the UK a decade after the last UK national audit. The reoperation rate for primary RRD in our centre was 14% with single surgery. Primary and final success rates of retinal re-attachment were 86% and 95.5% in line with current standard of practice.

TABLE 4:

Comparison of preoperative and postoperative BCVA in relation to the surgical procedure.

BCVA: best corrected visual acuity. Postoperative BCVA has been measured at the last follow-up.

Procedure		Preop BCVA (LogMAR)	Postop BCVA (LogMAR)
Vitrectomy	Mean	1.2	0.5
	N	175	175
	Std. Deviation	1.0	0.6
Scleral buckle	Mean	0.7	0.4
	N	27	27
	Std. Deviation	0.6	0.3
Pneumatic Retinopexy	Mean	0.3	0.3
	N	10	10
	Std. Deviation	0.4	0.3
Total	Mean	1.1	0.5
	N	212	212
	Std. Deviation	0.9	0.5

The trend in RRD surgery in the UK has changed over the last two decades. In the national audit of RRD surgery[9], the vast majority of cases (83%) underwent SB procedure and only 17% had PPV. The same findings were reported in a three cycles audit done by Johnson et al[11] over a 10-year period where the percentage of patients had PPV increased from 1% to 48%. Since these reports,[9,11] the use of PPV in RRD surgery has been increasing as reflected in our series with 82% undergoing PPV. Sutureless small gauge vitrectomy (23G and 25G) has become progressively more popular despite some controversy about its use.[17] At the time of this study, 33% of PPVs had undergone 23G sutureless PPV and there was no difference in the success rate between the classic 20G and 23G PPV. Neither of these UK-based audits[9,11] reported using PR as a primary procedure for RRD which reflects the practice pattern of RRD in the UK. In our experience, PR is a useful technique with an 80% primary success rate in simple uncomplicated RRD i.e. phakic eye with either a single break or closely located breaks in the superior fundus with no PVR.

There is a wide agreement about the best approach for some types of RRD, but for most cases there is lack of an evidence base to make a well-advised choice of technique. For example, there is a clear evidence for PPV in complex retinal detachment i.e. cases complicated with PVR, trauma, GRT.[12] On the other hand, SB has a very high success rate in cases of round hole RRD and cases with anterior small breaks without much PVR.[16] Controversy arises in the management of medium complexity RRD such as cases with multiple breaks, excessive vitreous traction and break size of over 1-2 clock hours, which are common. Advocates of vitrectomy argue that it can directly eliminate vitreous traction and media opacities particularly with the advances in surgical instrumentation and wide-angle viewing system. It also avoids SB-related complications, such as drainage problems, diplopia and infection of the implant; however, PPV carries its own risks and complications including high rate of cataract formation, iatrogenic breaks, postoperative positioning requirements and high cost of surgical instrumentation.

The Scleral Buckling Versus Primary Vitrectomy in RRD study (SPR study)[13] has made a significant contribution to

TABLE 5:

Final BCVA at final review by baseline status of macula, lens status, surgical procedure and presence of PVR.

	Final BCVA (±SD)	Significance (P value)	95% Confidence Interval
Macula on (n=81)	0.2±0.3	reference	
Macula off (n=131)	0.6±0.6	0.04	-0.5 to 0.2
Phakic (n=161)	0.5±0.5	reference	
Pseudophakic (n=51)	0.5±0.6	0.3	-0.2 to 0.1
Vitrectomy (n=175)	0.5±0.5	reference	
Scleral buckle (n=27)	0.3±0.2	0.08	-0.07 to 0.2
Pneumatic retinopexy (n=10)	0.3±0.3	0.3	-0.04 to 0.4
PVR absent (n=144)	0.4±0.4	reference	
PVR present (n=42)	0.7±0.6	0.03	0.1 to 0.4

the evidence base in RRD surgery . It was the first large prospective randomised clinical trial to compare outcomes of SB versus PPV in medium complexity cases. It concluded that there was a better improvement of VA with scleral buckling in phakic eyes and a high primary success rate using vitrectomy in pseudophakic eyes. Our results confirm their conclusion, though without statistical significance. We support the use of PPV for pseudophakic detachment with or without supplementary SB. Pseudophakic eyes having PPV had a primary success 78.4% and had a higher chance of needing final silicone oil fill. We attribute this to a tendency for late presentation of RRDs when the macula is already detached; in our series 63% of pseudophakic eyes presented with macula-off RRD and 13% presented with inferior breaks RRD, which may explain the late presentation and the tendency to have PVR. Pseudophakic eyes tend to have small breaks in the periphery and the view to the peripheral retina is often suboptimal because of capsular opacities and optical aberrations from the implant.

Our failure rate is consistent with the EVRS study report[12] and was associated with pre-operative risk factors including choroidal detachment, hypotony, PVR and total detachment, which are generally accepted as poor prognostic indicators for reattachment.[14] Choroidal detachment and hypotony were found in 2 eyes of our series with poor final visual acuity of no perception of light and counting fingers.

A strength of this UK based study is that the results represent real world clinical data and it should help draft a contemporaneous benchmark for VR surgery for RRD especially within an era of revalidation and change in UK medical regulatory. This study has limitations because of its retrospective nature. We acknowledge a possible bias in this study which may have an effect on calculating re-operation rate; some cases of failed attachment occurring after 2013 may have not been included. However, we believe that this number is likely to be small as literature suggests that failure usually occurs within 3 months of primary surgery.[15]Also, as the waiting time for surgery was not recorded in many cases, we could not conclude whether this had an impact on the anatomical and visual outcomes. However, in our centre, macula-on cases are operated on within 24-48 hours and macula-off cases operated on within a week.

To conclude, this study demonstrates comparable success rates to other centres where there is a specialist-led VR service. It reflects the current trend in RRD surgery for increasing usage of PPV. Despite sub-specialism and the great advances in VR surgery, the biology of RRD dictates a failure rate. New therapies may improve results in the future.

Authors have no financial interest to declare.

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Clinical Paper

Outcomes of Sacral Nerve Stimulation For Faecal Incontinence in Northern Ireland

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Abstract

Background: Sacral nerve root stimulation (SNS) is an effective and developing therapy for faecal incontinence, a debilitating condition that can result in social and personal incapacitation.

Objectives: The objectives of this study are to assess the morbidity of the procedure, improvement in the incontinence scores and Quality of Life (QoL) following SNS.

Materials and methods: Patients were identified from the Northern Ireland regional SNS service from 2006 to 2012. Numbers of patients who had temporary placement and permanent placement were collated. Pre and postoperative assessment of severity of incontinence and QoL was performed using Cleveland Clinic Incontinence Score (CCIS) and Short Form-36 (SF-36) respectively. Statistical analysis was undertaken using Wilcoxon signed rank test. Morbidity was assessed by retrospective review of patient records.

Results: Seventy-five patients were considered for trial of a temporary SNS. Sixty-one proceeded to insertion of a temporary SNS and, of these, 40 elected to have a permanent SNS. There was a significant reduction in the pre-SNS and post-SNS Cleveland Clinic Incontinence Scores from median of 14 to 9 respectively (p=0.008). There was a significant improvement in Role Physical (p=0.017), General Health (p=0.02), Vitality (p=0.043), Social Functioning (p=0.004), Role Emotional (p=0.007), Mental Health (p=0.013) and Mental Health Summary (p=0.003). However, this is not reflected in the bodily pain and physical functional domains.

Conclusion: Permanent sacral nerve stimulation is effective and results in significant improvement of faecal incontinence scores and quality of life.

Keywords: Faecal incontinence, Sacral nerve stimulation, Quality of life

INTRODUCTION

Up to 1.4 percent of the population, aged over 40 years, in the United Kingdom is affected by major faecal incontinence,[1] a debilitating condition associated with a high level of physical and social disability. Prevalence increases with age and incontinence is reported in 7% of otherwise healthy adults over 65 years of age.[2] The aetiology of faecal incontinence is multifactorial with obstetric trauma one of the commonest causes. Other causes include sphincter damage secondary to perineal surgery for perianal fistulas and haemorrhoidectomy, idiopathic degeneration of the sphincter muscles, neurological conditions like pudendal nerve neuropathy, multiple sclerosis, diabetes mellitus, traumatic spinal cord injuries and congenital anorectal malformations.

The symptoms of faecal incontinence can be helped by changes in lifestyle and dietary habits. In particular, use of bulking and anti-diarrhoeal agents and biofeedback, can help in improving symptoms in a significant proportion of patients. When conservative measures fail to bring about improvement however, surgical options can be considered. Sphincter repair, graciloplasty, artificial anal sphincter, conventional and dynamic gluteoplasty, antegrade continence enema procedures and colonic conduit formation are well investigated surgical alternatives but the long term results are not promising. Failure of these treatment options often result in patients considering a permanent colostomy.

Sacral Nerve root Stimulation (SNS), was first developed in 1979 and used as a treatment for faecal incontinence in 1995. It is now established as a safe procedure that offers a unique opportunity to select appropriate patients through a temporary trial prior to permanent implant placement, and is an effective alternative therapeutic option in addition to the

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conventional procedures outlined.[3-5] In this study, we report the Northern Ireland experience with SNS in the management of patients with faecal incontinence and assess incontinence scores and QoL following permanent implant placement. The complications encountered as a consequence of the procedure are also reported.

PATIENTS AND METHODS:

All the patients aged 18-75 years who presented to clinic with one or more episodes of faecal incontinence per week and having failed conservative treatment were selected for temporary external stimulator placement. Endo-anal ultrasound, ano-rectal manometry and pudendal nerve terminal motor latencies were performed preoperatively with manometry repeated postoperatively. Patients with 50% reduction of incontinence score at 2 weeks follow-up were selected for permanent implant placement. Data were collected retrospectively from patient records.

Cleveland Clinic Incontinence Score (CCIS) was used to quantify the severity of incontinence and was assessed at 6 weeks and 12 months post-operative follow up. SF-36 questionnaires were completed retrospectively to compare the preoperative quality of life (QoL) with that at 6 weeks following surgery. Statistical analysis was undertaken using Wilcoxon signed rank test. Post-procedure morbidity was assessed by retrospective review of patient records.

Temporary and permanent procedures were carried out with the patient in a prone jack-knife position under general anaesthesia. The temporary wire was placed in the S3 and S4 foramen and the one that gave the maximum perianal spasm and toe flexion when the temporary wire was stimulated was used for the two weeks of the test. Electrodes for the permanent implant were placed in the same foramina to duplicate the response achieved during the test period. A Medtronic (Model No. 3023) [Pulse width: 210µs, Frequency: 14 Hz] stimulator was inserted in a subcutaneous pocket created above the iliac bone. One dose of prophylactic antibiotic was administered at induction of anaesthesia.

Before discharge, patients were counselled by the senior author and the stimulator programmed to the amplitude just below the threshold for individual patient sensation. Patients were reviewed at the clinic at 6 weeks, 3 months and one year following the procedure by the senior author. Severity of incontinence and QoL were assessed using CCIS and SF36v2 forms respectively. Patients were sent postal questionnaires with a postal and telephone reminder at 4 weeks.

RESULTS:

75 patients presenting to the colorectal clinic between 2006 and 2012 were identified as having been assessed as suitable for consideration of a sacral nerve stimulator. 70 (93.3%) of these patients were female. The major indication for assessment was faecal incontinence (72 patients, 96%). This was mostly urge incontinence or urge and passive incontinence (49.3%).

Preoperative Assessment

61 of the 75 patients were selected as appropriate for trial with temporary implant placement, 14 either declining the procedure, not having true faecal incontinence, or not having tried all conservative measures. Of these, 60 were female of whom 70% had at least one previous pregnancy. 64.2% had required perineal intervention during delivery, which included perineal tear, forceps delivery or episiotomy. 57.3% of the initial 75 patients considered for temporary placement of SNS had previously undergone perianal surgery, ranging from anal sphincter repair, haemorrhoidectomy and anal pull through (Table 1). The median age of patients was 42 years (range: 22-76 years). Patients were discharged on the same day following temporary wire placement and the following morning after placement of the permanent implant.

Table 1:

Number of patients with previous perianal surgery

Previous Perianal Surgery	Number of Patients
Anterior Sphincter Repair	18
Second Degree Tear Repair	1
Third Degree Tear Repair	12
Fourth Degree Tear Repair	1
Haemorrhoidectomy	4
Anal pull-through	2
Perineal Burn	1
Ano-vaginal Fistula	1
Reconstruction following Trauma	3

All the patients had either Ultrasound Scan (USS) or Magnetic Resonance Imaging (MRI) assessment of their anal canal. 61.7% of the patients who proceeded to a temporary wire had either a defect, scar or thinning of their anal sphincter, with the rest having no abnormality on imaging. Thirty-nine patients had a pudendal nerve assessment prior to temporary SNS assessment. This demonstrated bilateral delay in 33.3% of patients, right-sided delay in 12.8% of patients, left-sided delay in 5.1% of patients and 48.7% of patients' pudendal nerve assessments were reported as normal.

Temporary SNS

A temporary SNS was placed in 61 patients. Of these, 40 patients (65.6%) reported an improvement in their Cleveland Clinic Incontinence Score of greater than 50% and all of these patients proceeded to permanent SNS implant placement. There was no morbidity from the procedure itself, however, there were some technical failures reported with two patients having wire failure due to wire dislodgement and one patient suffering battery failure, giving a total complication rate of 4.9%.

Permanent SNS

Cleveland Clinic Incontinence Scores:

In the patients who proceeded to permanent implant placement there was a significant reduction in the pre-SNS and post-SNS Cleveland Clinic Incontinence Scores from median of 14 to 9 respectively (p: 0.008). There was no difference in improvement at 6 weeks or 12 month follow up and at their most recent follow up 78% of patients reported continued improvement from their baseline symptoms prior to placement of the SNS (Table 2).

Quality of Life:

When assessed by SF36 Questionnaire patients reported a significant improvement in Role Physical (p=0.017), General Health (p=0.02), Vitality (p=0.043), Social Functioning (p=0.004), Role Emotional (p=0.007), Mental Health (p=0.013) and Mental Health Summary (p=0.003) (Table 3). However, these improvements were not shared in the bodily pain and physical functional domains.

Manometry:

There was no significant improvement in the pre and post-operative median resting (26.2 mm Hg vs. 28.3 mm Hg) and squeeze (49.6 mm Hg vs. 57.2 mm Hg) pressures. Median follow up period was 39 months (range: 4-108 months).

Morbidity:

In 6 patients there was an initial suspicion of infection. Five of these patients were given antibiotics for erythema around the wound and 1 of these patients had wound breakdown. A further patient was found to have a sterile abscess. Ten patients (25%) initially reported pain at the site of permanent implant, however in 6 of these cases it resolved with reprogramming or spontaneously and 4 had persistent pain requiring analgesics for more than six weeks.

Technical issues & Follow up:

The device required reprogramming in 62.5% of cases, however, this was usually performed at an outpatient appointment. Reprogramming by a Medtronic representative was required in 10% of cases. Repositioning of the SNS was required in three patients including one case where the stimulator had to be replaced due to infection following wound breakdown. There was one episode of wire failure in this cohort and one episode of battery failure after the device had been in place for over five years.

DISCUSSION

Faecal incontinence is a debilitating condition associated with significant stigmatisation and embarrassment. Difficulty in travelling, working and maintaining interpersonal relationships frequently results in the patient suffering from social isolation, depression and a reduced quality of life. This has substantial economic implications on individuals, family members and the healthcare system.[2] Community costs in the Netherlands were measured at €2169 in 2005 and $4110 per year in the US in 2012.[6 7]

Conservative treatment is effective in more than half of patients but more intensive treatment is required in a proportion of them.[8] Various studies have reported short term success rates, varying from 33 to 100% [9], with sphincter repair procedures, such as post anal repair, perineal reefing and overlapping sphincteroplasty, although the results worsened with increasing length of follow-up. Total pelvic floor repair, which combines anterior sphincter plication with levatorplasty, and post anal repair is reported to be a viable option when compared to post anal repair or levatorplasty for idiopathic incontinence.[10]

Other procedures, such as neo-sphincter procedures, graciloplasty (stimulated or non-simulated) and artificial bowel sphincter insertion, are technically demanding with high initial costs.[8] Dynamic graciloplasty is associated with morbidity and mortality rates of 0 to 13% and 0.14 to 2.08% respectively.[11] Artificial bowel sphincter insertion has success rates of 70-88% with morbidity rates as high as 33% [12] and explantation rates of up to 40%.[13] Stoma formation has the associated costs of hospitalisation and maintenance.

SNS continues to develop as therapy for faecal incontinence.[14] It was initially used for the treatment of urinary urge

TABLE 2:

Cleveland Clinic Incontinence Score

Type of incontinence	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

Never 0; rarely < 1/month; sometimes <1/week and >1/month; usually <1/day and >1/week; always >1/day[28]

Jorge J, Wexner S. Etiology and management of fecal incontinence. Dis Colon Rectum 1993;36:77-97. Reprinted with permission of Cleveland Clinic Florida.

incontinence and non-obstructive urinary retention.[15] These patients observed a simultaneous improvement in bowel symptoms and its use was consequently investigated extensively in the treatment of faecal incontinence and constipation. Matzel et al were the first to report its use in faecal incontinence in 1995.[5]

The mode of action of SNS remains unknown. The clinical effect may be due to voluntary somatic, afferent sensory and efferent autonomic motor stimulation achieved by sacral nerve root stimulation.[16] In addition, the pelvic part of the sympathetic chain and large myelinated alpha motor neurones that innervate the external anal sphincter and levator ani muscles are also stimulated. The resulting neuromodulation probably results in a change in sphincter function, hindgut function or a combination of these leading to improved continence.[17] There is no evidence as yet to suggest why some patients do not gain sufficient benefit to warrant permanent implantation.

TABLE 3:

Short form 36 quality of life assessment.

Subscale	Median pre op	Median post op✷	p-value
PF	39.2	47.5	0.059
RP	28.7	42.2	0.017
BP	41.4	43.75	0.051
GH	28.6	40.55	0.020
VT	39.6	45.8	0.043
SF	24.1	40.5	0.004
RE	20.9	32.6	0.007
MH	28.9	35.9	0.013

✷ at 6 weeks post operative follow up

In our series, 40 of the 61 patients (65.6%) had marked improvement in incontinence scores with temporary wire placement and went on to permanent implant placement. Three of these remaining patients in our series opted for permanent colostomy.

Jarrett MED (2004) in a systematic review of published literature found that 56% of 266 patients proceeded to permanent implant.[17] Uludag et al, Jarrett et al, Rosen et al and Leroi et al had permanent implantation rates of 77, 78, 80 and 55% respectively.[17-20] This shows that our rate was within the previously reported range and the differences of conversion may reflect variation in selection of patients and willingness to offer something to people with a very debilitating condition.

Various authors report improved continence scores and quality of life but using different scales of measurement (Wexner score, Cleveland clinic incontinence scores; SF-36, American Society of Colon and Rectal Surgeons questionnaire and Royal London Hospital questionnaire) perhaps due to the unavailability of a single validated scoring system to assess faecal incontinence.[14 21 22] This can make direct comparison between studies quite difficult.

Our study showed that, overall, there was a significant reduction in Cleveland Clinic Incontinence score from median 14 to 9 (p=0.008). This compares favourably with other studies which show a similar reduction in CCIS from a range of 12-18 to a range of 1-10.[14] The number of patients in these studies is very variable, as is the length of time of follow up, which could be as short as 6 months, making valid comparison difficult.[14] It is noted that the extent of improvement in these studies varies considerably and it is unclear whether there is a bigger improvement when starting from a higher or lower baseline, however, they are all statistically significant.

In keeping with our results, several studies have shown significant improvement in quality of life with effective SNS and specifically a long-term sustained clinical benefit in 80% of patients at 7 years.[23 24] It was pleasing to see that there was very little tailing off in improvement amongst our cohort.

In our study, two patients had no change in the CCIS at 6 weeks follow up. One of them had associated proctitis of unknown aetiology that might have contributed to persistent symptoms. Incontinence score in this patient was 20 preoperatively and at 6 weeks follow up. This is reflected in the physical function, general health and vitality sub scores of SF-36 that remained the same post operatively. Another patient with a migrated electrode had no improvement in incontinence scores at 6 weeks. Interestingly, all the sub-scores of SF-36 remained the same post-operatively except for social function (35 vs. 29.6). However, the incontinence scores improved from 10 to 8 after the electrode was reprogrammed. Another patient had painful serous collection around the implant for which the implant was replaced on the opposite side.

Other reported adverse events in the literature include implant related pain due to the lead running subcutaneously over the iliac crest to the abdominally placed generator, pain over the generator when it was set as the anode, unspecified pain, infection of the implant and superficial wound dehiscence.[17] By placing the implant in the upper outer quadrant of the buttock on the patient's dominant side, the stimulator is not felt when sitting down and there is decreased lead associated pain. The tined lead electrodes, although more expensive, inhibit axial movement of the lead and probably reduce the migration rates.[25]

Nearly half of all patients experience loss of efficacy at some point. 62.5% patients required reprogramming at least on one occasion, with 10% requiring a Medtronic representative to assist with reprogramming for either symptom control or discomfort. Alternative stimulator settings at higher frequency would increase treatment efficacy in patients experiencing loss of efficacy if alternative settings are tested.[26] When the stimulators have been in place for some time battery failure is not uncommon and may require exchange of the pulse generator, seen in the original cohort at a rate of 89% at an average of 7.4 years.[27]

This study reports our early experience with sacral nerve stimulation. Limitations of this study include small patient population and a limited follow up period of 12 months. Although the success rates are good at 12 months, longer-term efficacy needs further evaluated. Furthermore, this procedure was subject to limitations by the purchasing commissioners in Northern Ireland. Following on from this review of SNS results it is planned to make it available more widely.

CONCLUSIONS:

This study has shown that the use of SNS for faecal incontinence results in significant improvement in incontinence and quality of life scores. Patient selection based on the improvement in continence with minimally invasive temporary wire stimulation is effective at predicting those who will benefit over the medium term. There are relatively low rates of morbidity associated with the procedure.

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Clinical Paper

Prevalence of Corneal Astigmatism in an NHS Cataract Surgery Practice in Northern Ireland

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ABSTRACT

PURPOSE: Post-operative corneal astigmatism following cataract surgery can leave the patient with visual impairment. Correcting it at the time of surgery with a toric intraocular lens (TIOL) can give patients a better final visual outcome. The purpose was to determine the prevalence of corneal astigmatism in a cataract population and assess the demand for TIOL.

METHODS: Keratometric data was collected and analyzed for all patients who attended for routine cataract surgery under the care of a single surgeon based in Altnagelvin Area Hospital, Northern Ireland (NI). All patients were included between January 2008 and December 2014. Data was collected retrospectively for this observational study.

RESULTS: There were 2080 consecutive eyes of 1788 patients. The mean corneal astigmatism was 1.09 ± 0.83. Corneal astigmatism was 1.50D or less in 1621 eyes (78%). It was more than 2.00 D in 242 eyes (11.6%), more than 2.50 D in 127 eyes (6.1%), more than 3.00D in 68 eyes (3.27%) and more than 3.50 D in 45 eyes (2.16%).

CONCLUSION: For routine cataract surgery, 41.3% of eyes had more than 1.00 D of corneal astigmatism and 11.6% had more and 2.00D. Females had more astigmatism than males. This shows the potential demand for the TIOL in this population.

Keywords: Astigmatism; Toric IOL; Cataract; Northern Ireland; NHS

INTRODUCTION

Corneal astigmatism can cause blurred or impaired unaided vision and post-operatively can reduce the final visual outcome after cataract surgery[1]. Correcting astigmatism at the time of cataract surgery can give spectacle independence for distance or near vision[2]. Calculation of pre-existing corneal astigmatism (CA) can be easily done by looking at the keratometric data pre-operatively. Various surgical techniques are available to correct small amounts of CA but can be unpredictable for correction of 1.5 dioptres or more of astigmatism[3]. Toric intraocular lens (TIOL) insertion is a predictable method of correcting astigmatism at the time of cataract surgery[4].

A small number of studies have attempted to ascertain the prevalence of corneal astigmatism (PCA) [2,5,6]. None have analysed first eyes or studied our Northern Ireland (NI) population. It would be useful to know the PCA to establish the demand for the TIOL and emphasise the need to consider the correction of pre-operative astigmatism.

MATERIALS AND METHODS

Data was collected retrospectively for consecutive patients who attended for elective cataract surgery between January 2008 and December 2014 under the care of a single surgeon in a public health service. The surgery was performed at

TABLE 1:

Characteristics of population

Age	Mean ± SD	75.20 ± 10.57
	Range	15 - 99
Patients (n)	1788	
Eyes (n)	2080	
Sex, n (%)	Male	805 (38)
	Female	1228 (59)
Corneal Astigmatism (Dioptres)	Mean ± SD	1.09 ± 0.83
	Range	0.00 - 7.47
K1 (Dioptres)	Mean ± SD	43.09 ± 1.61
	Range	33.90 - 48.01
K2 (Dioptres)	Mean ± SD	44.16 ± 1.62
	Range	38.14 - 51.37

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Altnagelvin Area Hospital, Londonderry or Tyrone County Hospital, Omagh. Experienced technicians measured keratometric data across the two sites, using either the IOLMaster (Carl Zeiss Meditec AG, Switzerland) or the Nidek hand held keratometer (NIDEK KM-500 Auto Keratometer, NIDEK Company Ltd, Japan). There were no exclusion criteria. The data was collected as part of a service improvement project and so did not require Institutional Review Board approval.

RESULTS

Data was compiled for 2080 consecutive eyes. The population was Caucasian and their characteristics are shown in Table 1. Results revealed a mean CA of 1.09 ± 0.83. CA was 0.50D or less in 521 eyes (25.0%), between 0.51 D and 1.00 D in 700 (33.7%) and between 1.01 and 1.50D in 400 eyes (19.2%). It was 1.50D or less in 1621 eyes (77.9%), more than 2.00 D in 242 eyes (11.6%), more than 2.50 D in 127 eyes (6.1%), more than 3.00D in 68 eyes (3.27%) and more than 3.50 D in 45 eyes (2.16%). This is illustrated in Figure 1. Females had a higher degree of corneal astigmatism with a mean CA of 1.12D as compared to males whose mean CA was 1.05D. Analysis of a sub-group of patients' first eyes from 2012 to 2014 showed a mean CA of 0.97 ± 0.68 dioptres (n=222) for male patients and 1.11 ± 0.85 dioptres (n=312) for female patients. This difference was statistically significant (p=0.03) confirming the trend noted in the total eye population. Table 2 outlines the distribution of CA by age showing a gradual increase in both the steep and flat meridians with age, except for the patients less than 30 years of age.

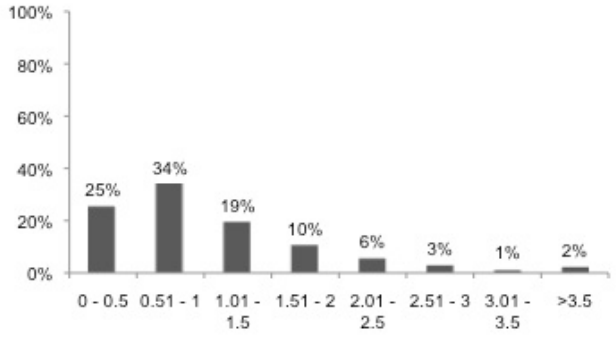

Fig 1. Distribution of Prevalence of Corneal Astigmatism

DISCUSSION

Our data on over 2000 eyes is presented. This showed the PCA in a cataract population and established the potential demand for the TIOL in patients with PCA of greater than 3 or 3.5 dioptres. The data highlighted the need for cataract surgeons to consider intraoperative correction of CA. As a real world sample our findings can be applied to similar populations in developed countries. We used two different keratometers over the duration of the study as technology changed over time. There is no gold standard instrument for keratometry and both give valid results.

Our mean CA of 1.09 ± 0.83 was higher than previously reported by Khan MI et. al (1.03 ± 0.728) on 1230 eyes in a British population and Ferrer-Blasco et. al (0.90 ± 0.93) on 4540 eyes in a Spanish population[2,6]. CA greater than 1.5 dioptres affects 15 – 20% of the general population[2,5,6]. Our results were similar for small to moderate degrees of CA showing 22% of patients with greater than 1.5 dioptres. Interestingly our population showed a higher prevalence of higher degrees of astigmatism, 11.6% having more than 2 dioptres and 2.16% having more than 3.5 dioptres[2,6]. Khan et al reported 9.69 % and 0.96% respectively. They had a similar number of eyes and mean age[6]. Unlike other populations[2,6,7]. our population had a gradual increase in both steep and flat values with age and a similar mean CA (Table 2). Females had a higher degree of mean CA compared to males and a higher prevalence of higher degrees of CA with 23% having more than 1.5 dioptres as compared to 18% of males.

TABLE 2:

Distribution of Corneal Astigmatism by each age group

Age Group	Average K1 (Dioptres)	Average K2 (Dioptres)	Mean Corneal Astigmatism (Dioptres)	*Number of Patients*
< 30 Years	43.65	44.82	1.17	*8 (0.38%)*
30-40 Years	42.21	43.45	1.24	*16 (0.77%)*
41-50 Years	42.50	43.73	1.23	*27 (1.30%)*
51-60 Years	42.87	44.05	1.18	*128 (6.15%)*
61-70 Years	43.04	44.05	1.01	*370 (18.0%)*
71-80 Years	43.13	44.16	1.03	*853 (41.0%)*
81-90 Years	43.08	44.20	1.12	*625 (30.0%)*
≥91 Years	43.75	44.92	1.17	*53 (2.55%)*

Post-operative CA following cataract surgery can cause blurred or impaired unaided vision with disappointment from patients increasingly expectant of spectacle independence. It can be corrected post-operatively with spectacle, contact lenses or further surgery (laser, secondary or Piggy-back IOL surgery). Identification of CA pre-operatively can however, allow correction at the time of cataract surgery (incisions along the steep axis of the cornea, limbal relaxing incisions, or the use of TIOL). Combining an on axis incision with a peripheral relaxing incision may overcome approximately 2.00 D of astigmatism[8] but has limitations with regard to wound positioning. Furthermore, there are risks associated with limbal relaxing incisions such as infection, wound gape and perforation. The outcome can also be variable[3]. The TIOL was first described in 1994. It corrects astigmatism in a single procedure and its use is becoming more frequent[9]. It allows the correction of 11 dioptres of astigmatism[10]. The TIOL outcome is more predictable[11] but correct axis placement in the eye is critical to effectiveness. Like Khan et al. we found that moderate CA (> 1.00 D) was prevalent in greater than 40% (41.3%) of patients, a group who may benefit from a TIOL[6].

The cost-effectiveness of TIOL versus the non-toric intraocular lens (NTIOL) is not yet established. The cost of a TIOL is up to £240 more expensive than the standard NTIOL. More clinic time is required to perform corneal topography

prior to selecting the TIOL. More theatre time is required to mark the axis on the eye and orientate the lens into position. The long-term costs of contact lens or spectacle correction are unknown and are often borne by the National Health Service through a spectacle voucher scheme. Correcting refractive error as a single procedure at the time of cataract surgery could be more cost-effective. Our data could inform a cost-effectiveness study.

CONCLUSION

We report the prevalence of CA in a UK cataract population of over 2000 eyes. The prevalence of CA within a Northern Ireland cataract population is a new finding. Of patients selected for elective cataract surgery, 41.3% of patients had more than 1.00 D of corneal astigmatism, 11.6% had more than 2.00D, 3.27% had more than 3.00D and 2.16% had more than 3.50D. Our study of 2080 consecutive eyes is likely to be representative of a public health service practice in the UK. It highlights a group of patients, particularly at the higher end of the spectrum with PCA of greater than 3 or 3.5 dioptres who may benefit from TIOL as a method of correcting their pre-existing corneal astigmatism at the time of cataract surgery. In particular, the procedure may be of benefit to Female patients.

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Four years of data were presented as a poster at ARVO 2013, Seattle, Washington, USA; 5th May 2013. It has not been published anywhere else

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Case Series

A rare characteristic neuroimaging pattern in hyperammonaemia.

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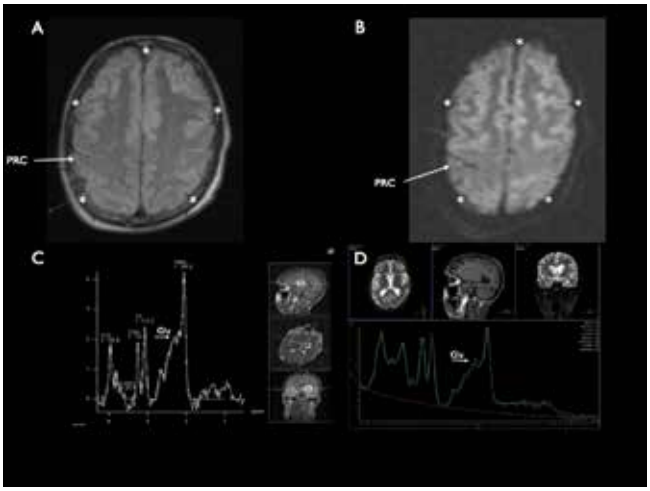
INTRODUCTION

Hyperammonaemia is a potentially life-threatening condition that is often neglected diagnostically. It presents with non-specific symptoms, such as encephalopathy. Delayed recognition leads to potentially irreversible neurological damage. We report 3 patients who on magnetic resonance imaging (MRI) of brain demonstrated a rare pattern of cortical signal change, which spared the perirolandic cortex. This characteristic radiological pattern should prompt immediate testing for raised serum ammonia, facilitating early treatment for this disorder.

CASE SERIES

Case 1:



Case 1. (A) Axial FLAIR and (B) Diffusion sequences (B1000) are presented showing the diffuse cortical abnormality indicated with * adjacent to the abnormal cortex. The perirolandic cortex is spared from this signal abnormality (PRC with white arrow). (C) Short TE baseline and (D) Short TE 2 months post presentation indicate dynamic changes in glutamine/glutamate peaks across time on spectroscopy (peaks indicated with white arrow and GLU).

A 40 year-old malnourished man with history of roux-en-Y-gastrojejunostomy for pyloric stenosis secondary to analgesia overuse, presented with septic shock and hepatic derangement. He developed refractory status epilepticus on day 2 of his hospital admission and received a loading dose of sodium valproate. Subsequently an ammonia level of 619 μmol/L was reported (normal in all 3 cases presented <52 μmol/L). Emergency dialysis normalized the ammonia level by the next day but he remained encephalopathic. An MRI brain was performed 5 days after presentation showing a diffuse increase in T2 and FLAIR signal within the cortex of both cerebral hemispheres (Figure A). There was sparing of the perirolandic cortex and occipital cortex bilaterally. This cortical high signal with sparing of the perirolandic cortex was also well visualised on B1000 images of diffusion weighted imaging (Figure B) with no associated low signal on the ADC (apparent diffusion coefficient) map . The initial short TE (35ms) magnetic resonance spectroscopy (Figure C) at presentation revealed a slightly elevated glutamine/glutamate peak with a slight decrease in choline and myoinositol peaks. These findings have been described in hepatic encephalopathy with elevated ammonia[1].

At the time of the MRI, the cause of the ongoing encephalopathy was thought to have been due to sepsis but the diagnosis of hyperammonemic encephalopathy was suggested after MRI was performed even though his ammonia level was at that stage normal. The possibility of the cortical signal change relating to status epilepticus or hypoxia was also considered but both were felt to be less likely particularly given the pattern of signal change and the previously very markedly elevated ammonia level.

Repeat short TE MR spectroscopy was performed two months later (Figure D). Whilst it is difficult to directly compare these spectra due to the differences in the y-axis, using creatine peak as a reference, there is a reduced level of N-acetylaspartate (NAA). NAA is a marker of normal neuronal activity and the reduction of NAA is consistent with significant brain atrophy which was noted on other MR sequences obtained at that

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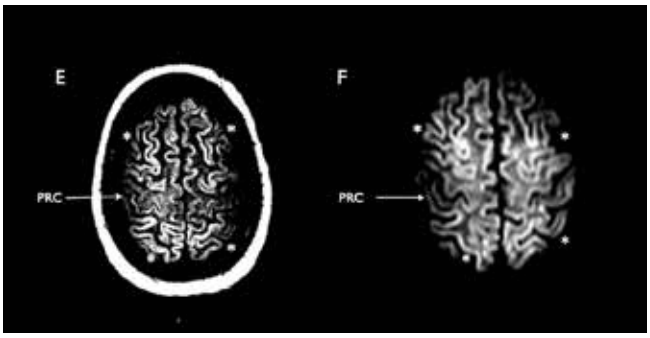
time and which can be seen on the planning images for MR spectroscopy (Figure D) . Although more equivocal, there was also a slight decrease in the glutamine/glutamate peak, which may reflect resolution of the hyperammonaemia.

A metabolic work up did not reveal any underlying urea cycle abnormality. His hyperammonaemia was attributed to a combination of malnutrition, acute sepsis, and poor hepatic reserve. Neurological recovery was poor at 6 months and he was quadriparetic and minimally responsive.



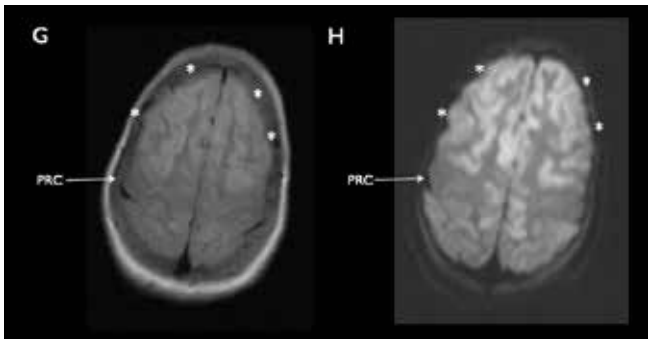
Case 2. (E) Axial FLAIR and (F) Diffusion sequence (B1000) imaging indicates the cortical abnormality with * and the spared perirolandic area of the cortex is indicated with PRC and a white arrow.

Case 2:

A 56 year-old man with a history of cirrhosis secondary to autoimmune hepatitis, presented with subacute lethargy, encephalopathy, and cortical blindness. Serum ammonia peaked at 133 µmol/L and remained elevated for 6 days prior to normalizing. It remained normal for three days before becoming elevated (ranging between 69-86 µmol/L) for 1 further week. MRI of brain was performed two days after the last recorded elevated ammonia (81 µmol/L). This demonstrated subtle cortical high signal change on the axial T2 and FLAIR imaging within the posterior frontal and parietal lobes bilaterally (Figure E). This pattern was best appreciated on B1000 images of diffusion weighted imaging, with striking sparing of the perirolandic cortex (Figure F). There was no associated low signal on the ADC map. The basal ganglia were not involved. Magnetic resonance angiography was normal. Early treatment of the hepatic encephalopathy resulted in a full visual recovery.

Case 3:

A 27 year-old woman with alcoholic liver disease and oesophageal varices presented with a major upper gastrointestinal bleed. She developed encephalopathy and required mechanical ventilation. Serum ammonia was elevated at 167 μmol/L. At this time MRI brain was undertaken, demonstrating abnormal cortical T2 and FLAIR high signal change (Figure G). The cortical FLAIR high signal change spared both the parietal and perirolandic cortex and was visible on B1000 images of diffusion weighted imaging (Figure H) without corresponding low signal on the ADC map. Medical complications supervened and she died.



Case 3. (G) Axial FLAIR and (H) Diffusion sequence (B1000) imaging indicates the cortical abnormality with * and the spared perirolandic area of the cortex is indicated with PRC and a white arrow.

DISCUSSION

The neuroimaging presented from these 3 patients with hyperammonaemia demonstrated cortical high signal on the diffusion weighted and FLAIR images without evidence of diffusion restriction. There was striking sparing of the perirolandic cortex in all 3 cases.

Eight other cases were identified in the literature describing this radiological pattern in patients with raised serum ammonia levels[2-3]. These imaging findings of diffuse cortical T2, and FLAIR hyperintensities with sparing of the perirolandic cortex - occurred in all but 1 of the reported cases. There was also involvement of subcortical sites, including the periventricular white matter, the thalami, and striatum. It is currently unknown why a diffuse cortical insult such as hyperammonaemia should cause selective sparing of the perirolandic cortex.

It is possible that differences in the cortical cytoarchitecture and receptor characteristics lead to a differential sensitivity to the toxic insult of elevated ammonia. It has been suggested that lower T2 prolongation in the perirolandic cortex may relate to reduced extracellular space water content. Another possibility is the protective effect from perineuronal nets (containing proteoglycans), which surround the neurons of the perirolandic and visual cortices in abundance[4].

The radiological differential diagnosis of cortical high T2 and FLAIR signals includes status epilepticus, hypoxic ischaemic injury, encephalitis and Creutzfeld Jakob disease. Clinically, it can be difficult sometimes to differentiate between these conditions in the encephalopathic patient in an intensive care unit, who may have a combination of such clinical features. These radiological findings may however be of value in suggesting hyperammonaemia as a possible cause (as illustrated in our first patient). Further corroboration in larger series is however required.

CONCLUSION

Awareness of this characteristic neuroimaging pattern among physicians and radiologists will help identify hyperammonaemic encephalopathy, which, if not treated quickly, carries a high morbidity and mortality.

ABBREVIATIONS:

TE - echo time. FLAIR - Fluid attenuated inversion recovery.

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Medical History

Robert Collis (1900-1975), early champion of paediatrics

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SUMMARY

Robert Collis, son of a solicitor and descendant of a prominent medical family, was born and spent his early years in Dublin. He received his secondary education and medical training in England, France and the USA, and played in Ireland's national rugby team. Whilst working in King's College Hospital in London he was inspired by Sir George Frederic Still to specialise in paediatrics and returned to Dublin to initiate substantial improvements in the provision of services for the health of children. He also became involved in campaigns to improve living conditions in the inner city and, at the end of the Second World War, he was among the first physicians to enter and work in the concentration camp in Belsen. Later, he played important roles in the creation and administration of medical schools in Nigeria as it became an independent state and finally returned to county Wicklow for his retirement. (Figure 1)

Fig 1. Portrait of Robert Collis. Reproduced by kind permission of the Royal College of Physicians of Ireland.

EARLY LIFE AND SCHOOL

William Robert Fitzgerald Collis, more usually known as Robert Collis, was born at Kilmore House on Killiney Hill in county Dublin on the 16th February 1900, a grandson of Maurice Henry Collis, Surgeon to the Meath Hospital, Dublin, and of John Barton, Surgeon to the Adelaide Hospital, Dublin, and President of the Royal College of Surgeons in Ireland. Acquiring a love of nature through play in the extensive gardens of Kilmore, throughout his life he would invariably be greatly distressed by the sight of a wounded animal. From the age of 9, he and his twin brother attended Aravon School in Bray, county Wicklow, travelling by train each day along the scenic coast of South Dublin but with little appreciation of the beauty of their surroundings until they went on to Rugby School where they were appalled by the contrasting ugliness of the English midlands. At Aravon they were drilled in arithmetic and spelling, were introduced to rugby football, and heard history lessons almost exclusively confined to events in mediaeval England, with only a brief mention of Ireland as represented by "the great Earl of Kildare and his battles". Then in January 1914 came the move to Rugby, where Robert immersed himself in developing his skills at rugby football on the games field, and his understanding of the Irish Question by daily reading of the newspapers in his private study. Back in Killiney for his first summer vacation, all political differences in Ireland now seemed to be obscured by the common causes of hatred of Germany and fears for Belgium, and for the autumn term he returned to a profoundly altered school, from which the older boys and many of the younger masters had departed for the Great War. School routine was disrupted, the standard of teaching declined, and all pupils were compulsorily recruited into the Officers' Training Corps (OTC). This did not suit Collis' temperament, but his rapidly-developing expertise in "rugger" earned him exceptional status and privileges in his school House and he came to enjoy the life so much that he had mixed feelings about going home at the end of term for Easter in 1916. [1-3]

Collis, his twin, and their two sisters picnicked in the Wicklow Hills on Easter Monday, knowing nothing of the

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Rising until their train journey home that evening was delayed and eventually curtailed. Passengers in a train travelling in the opposite direction brought news of great destruction and chaos in Dublin. Cycling into the city the following morning to see for himself, he was surprised to find few signs of disorder until he reached College Green, and then he heard rifle fire for the first time in his life as shots flew above him between opposing parties in Trinity College and Grattan's old Parliament Building. As he returned home, the city became strangely quiet and the streets were deserted, but fighting resumed on the following day and subsequently intensified. Collis acquired a Red Cross armband and assumed the role of first-aider in both the streets and the Meath hospital, using his OTC badge to enable him to pass through the British lines. Seeing a collie dog shot dead in the street distressed him more than anything else he had encountered during the fighting. Within a few days, peace and near-normal life returned quite suddenly, but afterwards Collis noticed a much more sombre mood among the citizens when news emerged of execution of some of the leading rebels.[3]

Back at Rugby again, Collis discovered he was now identified by the other boys as an Irishman, regarded as sharing some responsibility for what had happened. Before long, however, news from the Western Front came to progressively dominate their thoughts of the world outside, their House tutor leaving only to be killed a few days later, and frequent services commemorated the deaths of old friends and fellow pupils who had, as Collis put it, gone "out to fight on reaching the killable age". Conventional lessons at school had little appeal for him, rugby football assuming greater importance while fifteen hours a week of military training and helping the work on local farms occupied much of the time in his final year and a half. It was only in his last term, in the spring of 1918, that he started to find his lessons stimulating, and at the same time he was honoured to be appointed captain of the school rugger fifteen. Leaving Rugby, he had a brief holiday in Ireland before returning to England to train for six months for a commission in the Irish Guards, not quite completed when the armistice was signed.[3]

MEDICAL EDUCATION AND TRAINING

At that time, he had little desire to return to Ireland, and in 1919 entered Trinity College Cambridge to begin his study of medicine. His director of studies was Edgar Douglas (later Lord) Adrian (1889-1972) (who, with Sir Charles Scott Sherrington (1857-1952), would be the joint recipient of the Nobel Prize for Physiology or Medicine in 1932) and assisted another distinguished physiologist, the Newry-born Sir Joseph Barcroft (1872-1947) in his experiments to investigate prenatal life and hypoxaemia. Time was spared, of course, for membership of the Rugger Club, and he was soon playing regularly for Cambridge. In January 1920 he was picked to play for the South of Ireland against the North in Belfast and during the following season, despite having caught (undiagnosed) rheumatic fever and feeling weak, he was determined to travel over to Dublin and earn his second International Cap in the North versus South match. Returned to Cambridge, his fever continued and after ten days he developed erythema nodosum, with the fever continuing for nearly three weeks. After the rheumatic fever abated, Collis had a further three weeks' convalescence on the French Riviera, then travelled north to join some Cambridge friends at the Anatomy School in Paris, where they continued their dissection studies through the Easter vacation. Arrangements were made for Collis to spend the academic year 1921-1922 at Yale University on an exchange scholarship but, taking a few days off in New York City, he developed pleurisy, was then found to have tuberculosis and, after two months' rest in a friend's home in North Carolina, returned to Yale to collect his effects and took ship for Ireland.[3,4]

Fig 2. 26 Fitzwilliam Square, Dublin.

Arriving home as the civil war was getting under way, Collis concealed the knowledge of his tuberculosis, wishing to return to Cambridge for the summer term to take his final examinations rather than being sent to Switzerland. Before registering as a medical student in hospital, he regained strength during an extended vacation in Bavaria, Austria and the Dolomites as well as Ireland. His reputation as a 'Cambridge Blue' qualified him to be head-hunted for a scholarship at King's College Hospital, said to be the most modern in London at that time, and there he soon became captain of the rugby club while continuing to play for Ireland. Newly-qualified, his first six months as resident house physician in King's were followed by transfer to the new department of "Nerves and Children" where, on one side, he acquired the skills of neurological diagnosis and thought to

become a psychiatrist until, in the Children's Ward, exposure to the expertise and dedication of Sir George Frederic Still (1868-1941) changed his mind and prompted his desire to specialise in paediatrics. Moving to Bloomsbury, he became the last resident to work for Still before the latter's retirement at the Hospital for Sick Children in Great Ormond Street. He qualified MRCP, and then spent over a year on a Rockefeller research fellowship in the Paediatric Department at Johns Hopkins Hospital in Baltimore, Maryland. At that time, it was impossible to obtain the sort of post he wanted in Ireland, so he went back to Great Ormond Street to undertake research funded by the Medical Research Council and a philanthropic donation intended for investigation of the cause of rheumatic fever. The necessary experiments on animals distressed him as much as the suffering and deaths of his young patients; together they provided him with the material and insight for two outstanding papers. In those papers, published in 1932 and 1933, he resolved a current controversy about erythema nodosum by demonstrating it could accompany either streptococcal infection or tuberculosis and finding the latter to be the more frequent cause at that time in both London and Dublin. His investigations were, however, sometimes hindered by the reluctance of relatives to confirm the presence of tuberculosis in other members of a household.[3-6]

PROFESSIONAL LIFE IN IRELAND AND ABROAD

While the papers on erythema nodosum were being prepared, an unexpected letter arrived from Dublin's sole children's physician, Brian Crichton (1887-1950), announcing his impending retirement (to return to Sligo and manage the family seat) and offering to sell his house and practice in Fitzwilliam Square, an area where many prominent physicians and surgeons had their consulting rooms. (Figure 2) As well as paying for the house, Collis' father (who was Chairman of the Hospital Board) insisted he start work immediately at the Meath Hospital, where his duties in the Out-Patients frequently required refilling or maintenance of artificial pneumothoraces in numerous tuberculosis patients. At the same time, he applied to fill the vacancy in the nearby National Children's Hospital (Figure 3) where he was included in the trio of candidates short-listed for the post. The Board, "composed chiefly of ancient Anglo-Irish aristocrats", was unable to choose between them and all three were eventually appointed after lengthy discussion.[4]

Bethel Solomons (1885-1965), Master of the Rotunda Lying-in Hospital in Dublin from 1926 to 1933, who had also played for Ireland in international rugby matches, wanted Collis to organise a neonatal department in the Hospital. Brian Crichton had been the first paediatrician to be appointed to the Rotunda and during his time there (from 1927 to 1933) an infant ward was opened and the care provided successfully reduced the infant mortality rate.[7] Collis had briefly worked there before, when he had taken a month out to gain experience in midwifery while a student at King's College Hospital. Having resigned from the Meath (but retaining his appointment as a Visiting Physician in the National Children's Hospital), in his new role, he and Sister Maudie Moran soon developed a special incubator for premature babies. Such was the level of esteem in which he was held, a specialist neonatal unit was built in the hospital grounds. This gradually grew, and new techniques were developed in treatment and surgery for new-born children.[1,2,4]

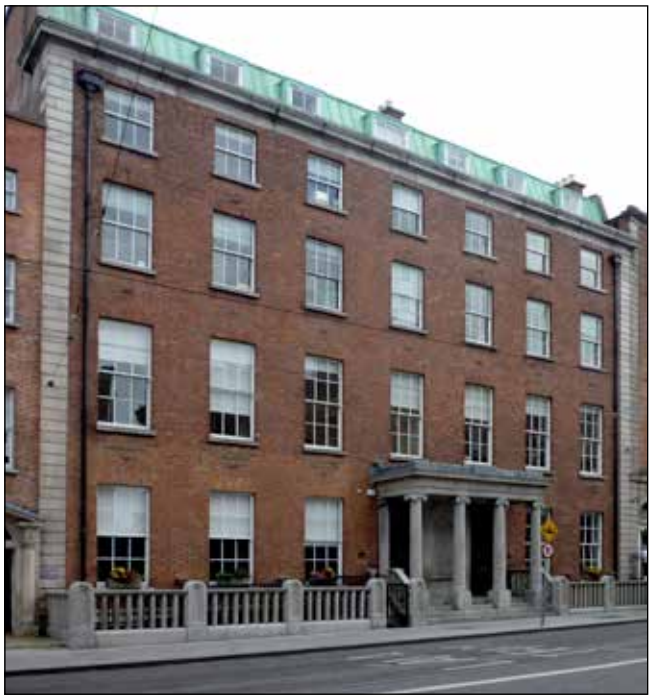

Fig 3. The National Children's Hospital (1887-1998), 87-91 Harcourt Street, Dublin.

In 1936 Collis started to write for a wider readership and published his autobiographical *The Silver Fleece* [3], which brought plaudits from literary Dublin and introductions to several of its leading members. In this wider social circle, he came to meet a Jesuit, Father Joseph Canavan (1886-1950), who asked him to help rouse public opinion about the living conditions in poorer areas of Dublin, first seen by Collis as a student. A committee named the Citizens' Housing Council, comprising prominent people from a variety of religious and political backgrounds, was formed to report and agitate about the state of the city's slums, and Collis wrote an influential letter to the Irish Press in 1936.[8] These activities in turn led Frank O'Connor (1903-1966) to ask Collis to write a play about the problem. *Marrowbone Lane* was declined by the Abbey Theatre but performed at the Gate Theatre in 1939 and again in 1941.[1,2,9] Its success stimulated the creation of a fund that contributed, inter alia, to the Fairy Hill home established in Howth, county Dublin for treatment of children with tuberculosis from Dublin's tenements, and to the formation of the National Association for Cerebral Palsy, known today as Enable Ireland.[4] In his Carmichael Prize essay "The State of Medicine in Ireland", published in 1943 [10], Collis placed special emphasis on the contemporary problems of tuberculosis and child health, both of particular concern to him. He also noted the disparity between city and rural areas in the ratio of patients to dispensary doctors, being 6220 in

Dublin and an average of 2300 in the remainder of the nation. At the time he returned to work as a paediatrician in Dublin the rate of infant mortality in the city was considerably greater than the average prevailing elsewhere in Ireland, and it did not start to fall substantially until the late 1940s onwards. He wrote in his essay:

> "*It has been said that the infant death-rate is the best measure of the child health in the community, or indeed the best single measure of the general standard of health of the community. Child health depends upon social conditions, combined with knowledge of the factors causing disease in childhood, together with a scientific attitude to their prevention and treatment. Hence when considering the wider aspects of social and preventive medicine it is necessary to give this subject very special consideration.*"

Comparing infant mortality in several different states on both sides of the Atlantic, he noted rates were much lower in those nations where paediatrics was formally included as a major subject in the undergraduate medical curriculum. In Ireland, the rates of both infant mortality and neonatal mortality have continually fallen since the essay was written (Figures 4 and 5).

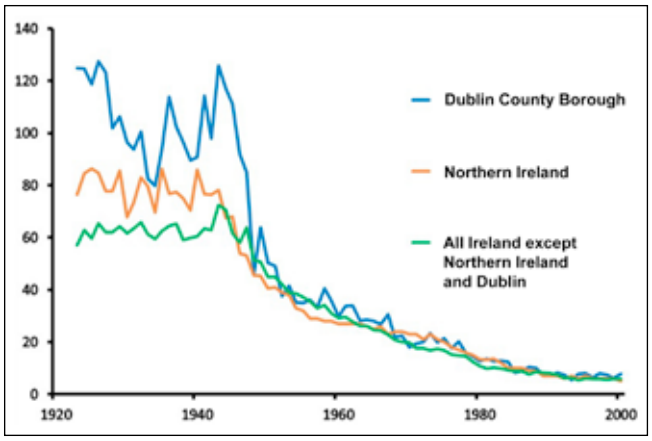

Fig 4. Infant mortality in Ireland from 1922 to 2000, expressed as numbers (under 1 year old) per 1000 live births (calculated from data in the Annual Reports of the Registrars-General for Northern Ireland, Saorstat Eireann and the Republic of Ireland).

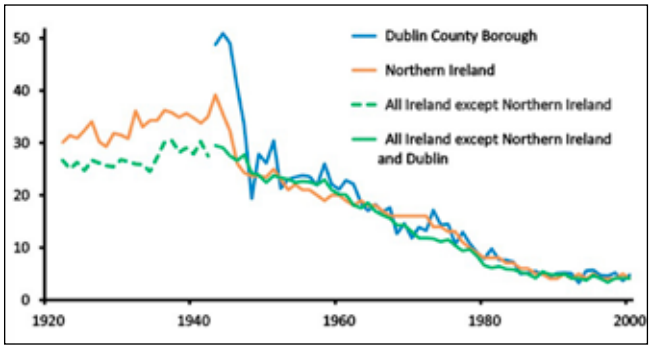

Fig 5. Neonatal mortality in Ireland from 1922 to 2000, expressed as numbers (under 4 weeks old) per 1000 live births (calculated from data in the Annual Reports of the Registrars-General for Northern Ireland, Saorstat Eireann and the Republic of Ireland).

During the Second World War, Collis contributed two articles about tuberculosis to The Bell magazine [9] and, as the war ended in Europe, he arranged to travel with other Irish doctors (including a surgeon at the Adelaide Hospital, Nigel Kinnear, and Patrick MacClancy, another paediatrician at the Rotunda who also used the Collis house in Fitzwilliam Square for his practice) to work for the organisation Civilian Relief assisting the British Red Cross in North Holland. Moving on to the Belsen concentration camp near Hanover, to be joined by a group of Dutch volunteers (which included a young lawyer and nurse, Han Hogerzeil (1920-2005)), they acted rapidly to save countless young lives and to restore them to normal family environments as soon as possible. As well as bringing some of the children from Belsen to convalesce at Fairy Hill, Collis brought Han back to Dublin and in 1947 they published a book about Belsen. [11] Parting from his wife Phyllis (née Heron) (1901-1993), he married Han and after she too had qualified in medicine at King's College Hospital they went to work in Nigeria in 1957, initially in a new medical school in Ibadan and subsequently in Lagos and at the Ahmadu Bello University. [12] He wrote two books about his experiences in Nigeria [13,14] and on his return to Ireland in 1971 he re-wrote and updated his autobiography, *To Be A Pilgrim*, but he died on the 27th May 1975 after a fall from his horse in county Wicklow, shortly before the book was published. [1,2,4] Robert, Phyllis and Han were all interred in the graveyard at Calary Church of Ireland in county Wicklow. [15] (Figure 6)

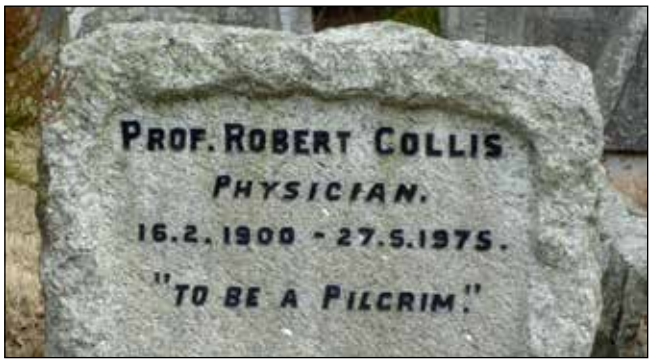

Fig 6. The grave of Robert Collis, Calary Church, county Wicklow.

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Medical Education

Enhancing Feedback On Case Reports To Third Year Medical Students On Clinical Attachment

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ABSTRACT

Preparation of case reports during student attachments has the attraction of reflecting real life clinical practice, but lacks standardisation when used in summative assessment. This study examined the occurrence and nature of feedback after the introduction of a new system of formative case reports in Third Year clinical attachments. Quantitative and qualitative methods were used to compare the new system to previous practice. Comparison of questionnaire responses demonstrated more and earlier feedback in the New Third Year, which was likely to be delivered at a meeting rather than as written comment. In the New Third Year, the quality of feedback was better and several markers of high quality feedback were rated more highly. There was no difference, however, in students' confidence in their ability to assess patients. The qualitative data from the New Third Year documented much excellent feedback but also examples of poor practice as well as inconsistency of advice. In conclusion, a relatively simple intervention effected radical changes to feedback practice and attitudes, although it is not known if the clinical skills of students improved.

INTRODUCTION

Preparation of case reports is well established at medical schools and involves skills and behaviours that are recognised attributes of established practitioners. Using case reports in assessment has been questioned on the grounds that grading does not correlate with overall assessment of clinical performance.[1,2] In recent years, assessment of clinical competence has shifted from summative assessment to formative learning events.[3,4] Formative assessment has been described as any assessment designed specifically to provide feedback[5] and has the potential to create more effective learners. Feedback can become a tool to encourage teaching and learning, and is positively correlated with achievement.[6]

This study focussed on the introduction of a new case report system in Third Year medicine at Queen's University Belfast requiring students to complete fewer cases but with greater emphasis on formative assessment and feedback. Unlike previous practice no summative mark was recorded.[7] We examined the effect of these changes on the nature and occurrence of feedback as well as the attitudes of students and teachers. Comparison was made with the previous system, which was used mainly to contribute to summative assessment.

METHODOLOGY

The comparison between the New Third Year case report system and the previous system was made using qualitative and quantitative methods involving both students and teachers.

SAMPLING

All Fourth Year medical students at Queen's University Belfast (Third Year during 2012-13, referred to as "Old") and all current (2013-14, referred to as "New") Third Year students were sent the **questionnaire**.

One of the current (2013-14) Third Year groups was chosen as a **focus group**. Given that groups were randomly selected it was anticipated this would be representative. From a group of 14 students eight agreed to attend.

Semi-structured interview candidates were selected from current active teachers (2 male, 3 female). One had a university appointment and was also a module organiser. Five semi-structured interviews were completed by which point it was concluded that little new material was being obtained.

METHODS

A brief **questionnaire** was developed and piloted on a group of third year students undertaking a summer elective in Medical Education. Most questions were closed requiring a response on a Likert scale. Questions examining the nature of feedback were adapted from the principles of feedback outlined by Nicol and Macfarlane-Dick.[8] The revised covering letter and questionnaire were loaded onto SurveyMonkey and circulated to current Fourth Year students (Old Third Year) in October 2013. The same questionnaire was sent to all Third Year medical students in March 2014.

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By this time all had experienced the new system.

The **focus group** was held in the Royal Victoria Hospital with the principal researcher acting as moderator. The group discussion was recorded discreetly for later transcription.

A guide for **semi-structured interviews** with teachers was formulated and piloted. Interviews were conducted in the offices of either the researcher or the teacher along the lines suggested by Bryman.[9]

DATA ANALYSIS

Statistical comparisons between years were based on a χ^2 distribution with one degree of freedom. When cells contained less than 5, adjoining cells were merged to avoid distortion of data. The 5% level of significance for two-sided tests was applied throughout. Percentages quoted in results section illustrate key contributors to any differences.

The open ended questionnaire responses were analysed using the Framework method of thematic analysis as were the focus group and semi-structured interviews.[10]

ETHICAL ISSUES

The protocol was approved by the Joint Research Ethics Committee of the School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast. Return of the e-mailed questionnaire was taken as implying consent. All focus group and semi-structured interview participants were given information sheets and signed a consent form. Data were collected and stored anonymously as required by University regulations and the Data Protection Act.

RESULTS

QUESTIONNAIRE QUANTITATIVE ANALYSIS

Overall response rates were 33.5% in the New Third Year and 27.0% in the Old Third Year.

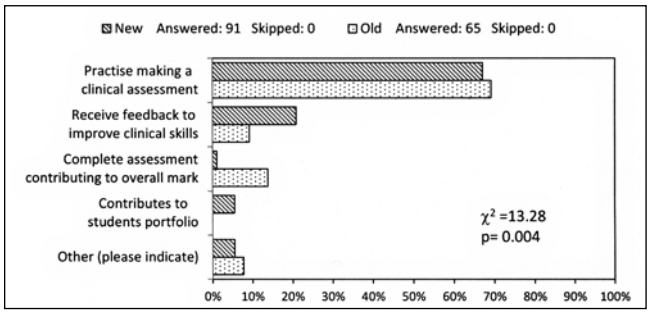

Fig 1. Student questionnaire responses about main purpose of case reports.

In deciding (Figure 1) the main purpose of case reports there was a change in the New compared to Old towards " feedback to improve clinical skills" (New v Old: 20.9 v 9.2%) and away from " contributing to overall mark" (New v Old: 1.1 v 13.8%).

Asked if the purpose of doing case reports was made clear, there was no difference between New and Old (Table 1). There was also no difference in the ability of students to gain access to patients, nor in the perception of whether patients were representative of clinical practice. There was a highly statistically significant change towards agreement that feedback always occurred in New compared with Old.

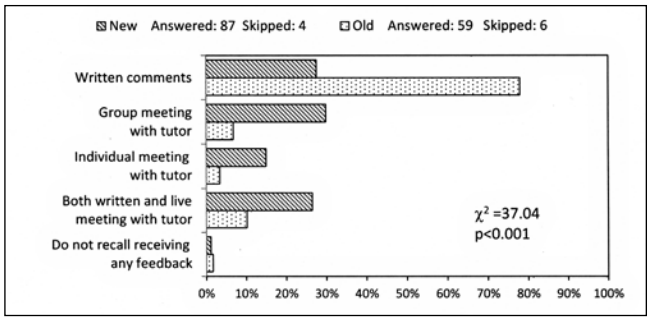

Fig 2. Student questionnaire responses about main mechanism of feedback.

The mechanism by which feedback was received moved (Figure 2) in the New Third Year towards group (New v Old: 29.9 v 6.8%), individual (New v Old: 14.9 v 3.4%) or combinations of written and tutor meetings (New v Old: 26.4 v 10.2%) and away from purely written feedback (New v Old: 27.6 v 78.0%). The timing of feedback (Figure 3) also changed towards earlier feedback with much less occurring 4 weeks after the end of attachment (New v Old: 2.3 v 20.3%).

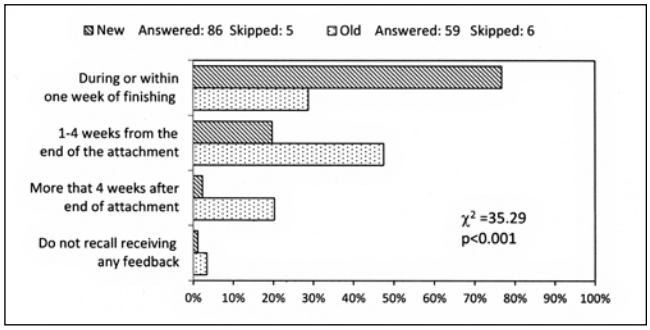

Fig 3. Student questionnaire responses about when feedback took place.

The New Third Year was more likely to consider the quality of feedback was excellent (strongly agree/agree, New v Old: 52.9 v 15.3%). Students were asked about markers of high quality feedback and agreed (Table 2) that feedback encouraged self-reflection and helped to clarify a good performance to a greater extent in the New compared with Old. The New Third Year believed that feedback encouraged dialogue with teachers but not with peers. They considered that feedback helped to close the gap between current and desired performance, and to identify specific actions to improve performance.

When asked (Figure 4) if at the end of clinical attachments students were confident in their ability to assess patients there was no difference in response between New and Old.

THEMATIC ANALYSIS OF QUALITATIVE DATA

Quoted questionnaire responses are identified by student year (New or Old), and respondent (R1, R2 etc). These were

TABLE 1:

Student questionnaire responses (in percentages) about arrangements for case reports.

	Purpose of case reports made clear		Easy to gain access to patients		Patients representative of clinical practice		Feedback always occurred	
	New	Old	New	Old	New	Old	New	Old
Strongly agree	17.6	25.0	18.7	15.6	10.0	14.1	27.5	12.9
Agree	55.0	51.6	51.7	57.8	65.6	64.1	51.7	32.3
Neither agree or disagree	13.2	14.1	20.9	12.5	21.1	15.6	5.5	8.1
Disagree	14.3	7.8	7.7	12.5	3.3	6.3	12.1	32.3
Strongly disagree	0.0	1.6	1.1	1.6	0.0	0.0	3.3	14.5
	$\chi^2 = 1.25$ p=0.263		$\chi^2 = 0.14$ p = 0.710		$\chi^2 = 0.11$ p = 0.738		$\chi^2 = 19.67$ p < 0.001	

considered with the focus group (identified F1 … F8) and semi-structured interviews (identified Interview 1 … 5) under three major themes.

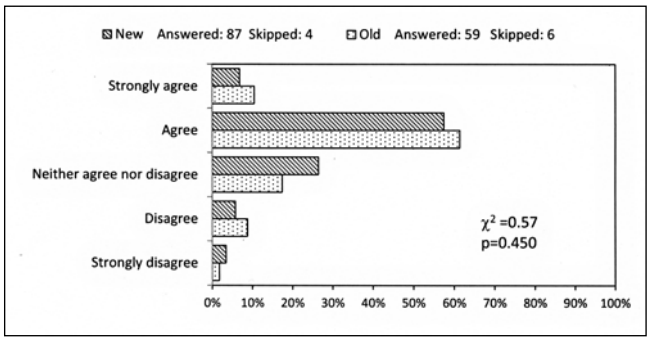

Fig 4. Student questionnaire responses about confidence in ability to assess patients.

FUNCTION

There was consensus amongst staff and students from both New and Old that the most important function of cases was to improve clinical skills:

" it's about getting them into the practice of taking a patient history and recording it in an accurate way and being able to set up the basic skills" (Interview 4).

Also seen in a positive light was experience navigating the patient record and hospital information systems. This allowed students to see the pattern and pace of investigation and management:

"Learnt about the structure and format of medical notes and how to extract the relevant information" (New, R3).

A downside was regurgitation of information copied from patient notes:

"made me speak to patients more, but not necessarily examine them as I just copied from the notes" (New, R45).

The potential to enhance patient contact was recognised in both student year groups. There was a perception amongst students and staff that this needed to be encouraged:

"I think it got some students actually seeing patients, especially those who may not have been too keen to be involved" (Old, R4).

TABLE 2:

Student questionnaire responses (in percentages) about indicators of high quality feedback.

	Encouraged self reflection		Helped clarify good performance		Encouraged dialogue with teachers	
	New	Old	New	Old	New	Old
Strongly Agree	6.9	3.4	4.7	1.7	8.1	3.4
Agree	52.9	32.2	46.5	25.9	43.7	13.8
Neither agree or disagree	18.4	30.5	19.8	27.6	25.3	31.0
Disagree	18.4	18.6	22.1	24.1	20.7	36.2
Strongly disagree	3.5	15.3	7.0	20.7	2.3	15.5
	$\chi^2 = 8.19$ p = 0.004		$\chi^2 = 8.54$ p = 0.003		$\chi^2 = 21.4$ p < 0.001	

	Encouraged dialogue with peers		Provided opportunity to close gap between current and desired performance		Helped identify specific actions to improve performance	
	New	Old	New	Old	New	Old
Strongly Agree	5.8	1.7	8.1	3.5	8.1	3.4
Agree	40.2	34.5	50.6	26.3	56.3	37.3
Neither agree or disagree	28.7	32.8	20.7	42.1	20.7	30.5
Disagree	20.7	25.9	13.8	19.3	9.2	20.3
Strongly disagree	4.6	5.2	6.9	8.8	5.8	8.5
	$\chi^2 = 1.08$ p = 0.298		$\chi^2 = 5.47$ p = 0.019		$\chi^2 = 6.46$ p = 0.011	

An additional purpose was to learn about disease, not just from the student's own case, but also those of fellow students. A perceived downside to detailed study of one patient was the time taken up with the commentary especially in shorter attachments:

"Cases in shorter placements made me focus on just one

patient and not enough in the whole spectrum of illness" (New, R14).

Cases were seen by teachers as a discriminating method of assessment, but there was concern that students put in less effort in the new system:

" students probably rightly think that they can get away with less work around the case" (Interview 1).

Furthermore there was a view that students needed some degree of summative assessment to give an idea of their ranking within the year even if the mark was not centrally retained.

FEEDBACK/QUALITY

Students and staff were positive about feedback and believed the absence of summative marks allowed them to focus on the attachment as a whole:

" it enabled me to focus on the patient more, their history, story and the impact of disease on their quality of life" (New, R33).

"We now actually have to sit down and give the student the 10 minutes" (Interview 2).

Students and staff saw the benefits of developing skills through an iterative process, to which feedback contributed, often with reflection on a good or ideal example:

"they ... look at the feedback before they then do the second and third cases because I see the whole purpose of this is to try and make their second case better and the third case even better" (Interview 2).

Students appreciated those teachers who took time to deliver feedback especially where it identified specific failings or recommendations for improvement.

Different formats to deliver feedback were described. Group work with oral presentation allowed common themes to be identified, but there was concern that feedback on written clinical notes was neglected. When group work went well it facilitated dialogue not just with the teacher but also amongst students.

The quality of feedback attracted criticism, especially on the written case commentary:

"Sometimes just written comments which were often brief, illegible or there was no comment left at all " (Old, R38).

This appeared to contribute significantly to a negative view of that part of the case report system:

"The discussion although interesting doesn't add anything to improving your clinical examination of the patient" (New, R5).

There was divergence amongst teachers as to whether feedback had improved in the new system. Two teachers, who already appeared to be delivering formative feedback at a high level, did not think the new system changed anything:

"I think the feedback arrangement is much the same. The only thing is I don't put a mark down anymore" (Interview 3).

PRACTICALITIES AND PROBLEMS

Not surprisingly some deficiencies were highlighted. Finding cases caused anxiety amongst students and there were complaints that some patients were unsuitable. Students acknowledged they acquired more confidence approaching patients later in the year.

Teacher time was a limiting factor in providing adequate feedback, which depended heavily on key members of staff. There was a perceived trade-off between giving feedback and other forms of bedside teaching. Providing good feedback depended critically on the assessor knowing the allocated case:

"they should know the case well and then they can give relevant feedback" (Interview 5).

A perception of poor standardisation of marking and inconsistency of advice about how to do cases was a frequent criticism across both year groups:

"one doctor wanted it done one way, another a different way" (New, R47).

DISCUSSION

CASE REPORTS IN LEARNING CLINICAL SKILLS

Students, as well as teachers, recognised the importance of cases in learning how to assess patients. There were striking comments about the need for students to cross the threshold from tutorial room to ward**.** There was less support for the commentary, which many found time consuming and burdensome especially within shorter attachments. Teachers expressed concern that students were not spending enough time on the ward, and by implication that more time with patients would increase competence. The limited evidence available does not support the contention that more clinical encounters alone improves clerkship performance.[11]

CASE REPORTS IN STUDENT ASSESSMENT

Students were pleased that cases no longer counted towards a summative mark, but teachers were concerned that the absence of a summative mark might lead to less effort by students. Perhaps eliminating all summative elements from clinical clerkships should occur only if and when both students and teachers embrace an approach to learning which is performance rather than goal orientated.[12] It is worth remembering that there is no reason why good feedback cannot be given after summative assessment,[13] nor are there practical reasons not to provide feedback rapidly to large numbers of students.[14]

Comparison with Mini-CEX[15-17] highlights a limitation of the case report system in that inferences were drawn from written cases and presentations and students were not observed

performing clinically. There is good evidence that students particularly value direct observation and feedback at the bedside.[18] Training in direct observation can increase the comfort of tutors in this type of activity.[19]

FEEDBACK

The questionnaire pointed to a major change in the quality of feedback in the New Third Year. There were also dramatic alterations in indicators of high quality feedback, such as encouraging self-reflection, encouraging dialogue with teachers, and identifying specific actions to improve performance.[8] The qualitative data highlighted examples of good feedback practice and identified development of feedback seeking behaviour amongst students.[20,21]

On the other hand, given the evidence that students do not always recognise feedback,[22,23] it is possible some differences were more perceived than real. In other words, the New Third Year students, having been told that there was to be greater emphasis on feedback, were better able to recognise it.

This study provides evidence that the practice of delivering feedback can be altered relatively quickly after a single year induction session. The majority of teachers had not received formal instruction in how to deliver feedback. It would appear wise to continue to develop the attitudes of students and staff to feedback.[22,23] It may be useful to investigate feedback practice in weaker students who might need it most.[24,25]

An important consideration is whether the structure of clinical attachments supports good feedback practice. Teherani and colleagues studied a longitudinally integrated model and compared it to traditional discipline-specific block clerkships.[26] The longitudinally integrated model was rated more favourably, however, formal opportunities to interact with faculty, peers and patients were essential.[27]

PROBLEMS AND DEVELOPMENT

Notwithstanding the progress made, there were difficulties with the case report system. The Old Third Year believed the marking system was inconsistent, and, even in the New Third Year, students found some advice and feedback confusing. It is hard to know in a course that spans many specialties as well as different sites, how uniform processes can be made. Nevertheless, certain shortcomings would be helped by clearer central direction. It was also apparent that "formal" feedback had been introduced at the expense of time otherwise spent on bedside skills, which presumably in previous years included activity not recognised as feedback.[28,29]

LIMITATIONS

An overall limitation of this work is that it included no objective assessment of student performance. We do not know if students in the New Third Year were more or less competent, but there was no difference in the students' confidence in their ability to assess patients. Many studies demonstrate that instruction in feedback improves reflective practice and approaches to learning.[23,30,31] There is good evidence that the clinical performance of trained physicians is improved by feedback,[32] but within clinical clerkships there is little hard evidence that clinical competence is improved.[33] A recent study within surgical clerkships showed benefits in knowledge and skill acquisition in those receiving feedback compared to a control arm receiving compliments, even though students found it hard to distinguish feedback from compliments.[22]

The response rate to the questionnaire was around 30%, and the sample of opinion from focus group and semi-structured interviews was small, but there is no reason to believe the data were unrepresentative. The New Third Year completed the questionnaire two thirds the way through the year, whereas the Old Third Year completed it four months after year end. The Old Third Year responses might be expected to have the advantage of mature reflection but miss important immediate issues. Comparable opposite considerations might have applied to the New Third Year.

WAY FORWARD

The results of this and previous studies allow some conclusions about case reports within clinical clerkships.

1. Students seeing cases (and preparing a report) remains a valued way of encouraging patient contact and developing clinical skills. The optimum amount of student time spent in this way, or number of cases that should be seen, is unknown.
2. Relatively simple changes can have a profound influence on student and staff attitudes to feedback.
3. A summative element to cases may be necessary to maintain student initiated patient contact.

CONCLUSION

This study highlighted the keen awareness of the need to optimise learning in the clinical environment amongst staff and students at Queen's University Belfast. The change in the New Third Year, placing greater emphasis on formative assessment and feedback, was well received. Although previous research suggests that better feedback should enhance student learning, it is not known if the clinical skills of students in Belfast improved following the changes.

ABBREVIATIONS

Mini-CEX : Mini clinical evaluation exercise.

ACKNOWLEDGEMENTS

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Letters

UPTAKE OF THE USE OF PATIENT-DOCTOR E-MAIL IN AN ENDOCRINOLOGY OUTPATIENT SETTING

Editor

E-mail communication between doctor and patient is becoming increasing popular, particularly because of the availability of electronic health care records (EHR) and *e*health resources such as 'Patient Portals'. E-mail can be utilized to enhance access to healthcare, health promotion, facilitating clinical management and in some settings, replacing the outpatient clinic visit.[1,2] Perceived advantages include a rapid response time, usage outside of normal working hours, improved patient-doctor communication and the ability to initiate management plans at an earlier stage. However, implementation of e-mail appears to be under-utilized. Possible explanations include presumed increased workload for the clinician, matching patient expectations, issues of confidentially and medico-legal implications.[3] Against this background we aimed to assess the rate of uptake of e-mail at a weekly new-patient endocrinology clinic.

TABLE 1

Various reasons for e-mails being sent

Reason for e-mail	Number n=37
Medical advice	11
Test results sent by patient for advice	7
Test results sent by GP for advice	7
Clinical query	6
Advice on medication	3
Scheduling of appointments	1
Scheduling of investigations	1
Medication side effect reported by patient	1

Methods

All patients were advised at their initial clinic visit of the availability of e-mail communication. The consultant's hospital e-mail was provided on the clinic letter patients received after their appointment. All patients were reviewed by one endocrinology consultant. Upon receipt, all e-mails were documented in the patient's clinical notes. Data was collected prospectively over a 12 month period between 1st January and 31st December 2015.

Results

224 patients (146 female, 78 male) with a mean age of 47 years (range 14-90 years) were included in the study. 11/224 (5%) of patients utilized e-mail over the study period. Of the 11 patients, 9 were female and 2 male, with a mean age of 45 years (range 22-87 years). A total of 37 e-mails were received, 30 from patients and 7 from general practitioners (GP's), six patients and three GP's sent one e-mail, one patient sent two e-mails, two patients sent three e-mails, one GP sent four e-mails, one patient sent six e-mails, and one patient sent ten e-mails. The reasons for e-mail correspondence are outlined in Table 1 and included seeking medical advice, advice on test results and scheduling of appointments and investigations.

Discussion

Online communication by e-mail in the outpatient setting has the potential to be convenient for patients and efficient for doctors.[4] This study's main finding is that uptake of e-mail between patient and doctor in an endocrine outpatient setting was low at 5%. Although the numbers were small it appeared that most users of e-mail were young and female and advice on tests results and medical advice were the most frequent queries. The uptake of e-mail from some GP's shows a willingness to engage in using e-mail as a form of communication and has the potential to be explored further. Various factors correlating with the uptake of patient-doctor e-mail have been explored in other large series and have included age, access to internet, patient health status, doctor specialty and workload.[5] However, the numbers were too small in this study to address these factors. Although the uptake of e-mail was low, the results are relevant and timely with the widespread use of electronic health care records in Northern Ireland and the potential for the development of an interactive multi-functional 'patient-portal' with the facilities for secure e-mail access to allow for more efficient communication between doctor and patient.

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TOXOPLASMA SEROPREVALANCE IN NORTHERN IRELAND

Editor,

Toxoplasma gondii is the causal agent of toxoplasmosis, a common parasitic infection of humans acquired either by ingestion of oocysts voided in cat faeces or tissue cysts in undercooked meat. In humans, infection is mainly asymptomatic or accompanied by mild self-limiting symptoms. Infection or reactivation in immunocompromised patients can have serious clinical consequences. Primary infection in pregnancy can lead to miscarriage, stillbirth or congenital toxoplasmosis. The majority of infected neonates do not have detectable disease at birth but carry a significant risk of developing ocular disease in later life. Historically, Northern Ireland has been considered and cited as the area with the highest toxoplasma seroprevalence in the UK at 40% in blood donors[1], 36% in diagnostic samples[2] and even higher seroprevalence rates in farmers in Northern Ireland of 73.5%[3] However all this data actually relates to samples tested several decades ago. There has been no data in the literature on toxoplasma seroloprevalence in Northern Ireland population for more recent decades. The impression within our laboratory is that the seroprevalence rate has fallen dramatically and was now more in line with rest of UK. We set out to determine if this was the case.

TABLE 1

Toxoplasma seroprevalence (IgG) data by age bands

Year of birth	Positive/total tested (% positive)	Equivocal
1920-1929	17/20 (85.00)	0
1930-1939	48/84 (57.14)	3
1940-1949	135/358 (37.70)	19
1950-1959	165/583 (28.30)	16
1960-1969	130/724 (17.96)	20
1970-1979	169/1139 (14.83)	10
1980-1989	179/1555 (11.51)	9
1990-1999	50/795 (6.29)	10
2000-2015	37/529 (6.99)	11
TOTAL	930/5787 (16.07)	98

Materials and Methods

A convenience set of 5787 samples received from January 2012 until September 2015 were tested routinely for *Toxoplasma gondii* IgG using either Vidas Toxoplasma IgG II assay (bioMérieux UK Ltd, Basingstoke, England) or Elecsys Toxo IgG (Roche Diagnostics, Rotkreuz, Switzerland)). Equivocal results were regarded as seronegative for purposes of analysis.

Results

Of 5787 sera tested, 16.07% were seropositive but there was a marked reduction in seroprevalence with younger age (table 1 and figure 1). A total of 85% of samples from patients born between 1920 and 1929 were seropositive contrasting with 6% for patients born between 1990 and 1999.

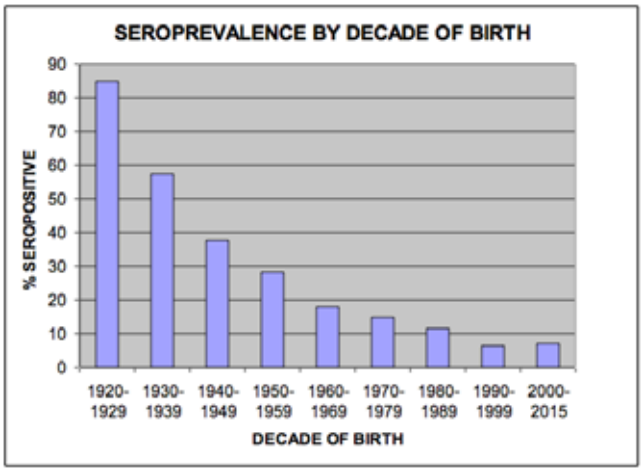

Fig 1. Toxoplasma seroprevalence by age band

Discussion

The most likely interpretation of this data is an age cohort effect suggesting that acquisition in childhood has decreased greatly over the past 50 years. It should be noted that the vast majority of the samples in the post-2010 DOB group were from babies and thus reflect maternal seroprevalence (similar to age cohorts 2 decades previously), hence explaining the slight apparent upward trend in this group.

Other countries such as France with previously reported high seroprevalence rates have seen marked decreases in seroprevalence[4]. It is likely that such decreases in toxoplasma seroprevalence are due to changes in animal husbandry and food exposure. Knowledge of current seroprevalence is important for understanding the epidemiology and determining approaches to congenital toxoplasmosis in Northern Ireland and similar countries.

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WHY ASTHMA STILL KILLS

Editor,

In May 2014, the RCP National Review of asthma deaths was published, entitled "Why asthma still kills"[1]. The report reviewed asthma deaths in the four UK countries over a 12 month period. One recommendation was that all asthma patients who have been prescribed more than 12 short acting beta agonist (SABA) reliever inhalers in the previous 12 months should be invited for urgent review of their asthma control[2].

Following on from this report, I conducted an audit of SABA overuse in asthmatics in a GP practice in West Belfast during my FY2 rotation.

Method: An EMIS search was conducted of asthma patients who had been prescribed 12 or more salbutamol inhalers from January 2014- 2015. Patients were contacted by telephone or sent a letter to invite them to attend for review of their asthma- starting with those issued the highest quantity of SABA inhalers. They were reviewed by FY2, practice pharmacist and two practice nurses.

Results: The total number of asthmatic patients prescribed salbutamol in the Year 2014-2015 was 576, with 145 prescribed 12 or more inhalers (25%). The largest quantity issued to a single patient was 44. The table below demonstrates the breakdown of number of inhalers prescribed.

Number of inhalers prescribed	Number of patients
12	**31**
13-19	**51**
20-29	**41**
30-39	**20**
40+	**2**

From January-March 2015, 98/145 had been offered appointments or contacted via telephone about their SABA overuse. 46/98 had a review and discussion about their asthma. Those who have failed to attend for review and had been receiving > 1 inhaler per prescription had their prescription reduced to 1 inhaler per script, with a note to make an appointment for review of their usage.

Discussion:

This audit suggested that around ¼ of asthmatics in the practice were poorly controlled. On further review, a large number had failed to attend for an annual asthma review (45%). In those patients reviewed between January and March, their SABA usage had started to reduce over the 3 month period. At review, they were assessed using the BTS/SIGN guidelines, which cover a spectrum of areas. It was evident that education was very important for them. They were provided with a personal asthma action plan to refer to if they became symptomatic. This audit was presented at the monthly practice meeting in order to update the GP partners and highlight the issue. We would recommend vigilance when prescribing inhalers – those with excessive usage may benefit from education and personal action plans with the goal of reducing avoidable mortality.

The authors have no conflict of interest.

Dr Rebecca O' Kane, FY2

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INAPPROPRIATE ED ATTENDANCES IN NORTHERN IRELAND: A REVIEW OF ATTENDANCES IN THE BELFAST HEALTH AND SOCIAL CARE TRUST

Editor,

Inappropriate attendances (IAs) at Emergency Departments (EDs) may impact on patient safety and flow through the unscheduled care system. These are attendances where care could have been provided safely and more appropriately in other locations, e.g., by a general practitioner (GP) or by self-management. This study aimed to identify the number and type of IAs at EDs in the Belfast Health and Social Care Trust.

Notes of two consecutive days' ED attendances at the Royal Victoria Hospital (RVH) and Mater Hospital (MIH), 11th and 12th January 2015, were reviewed. During these days there were no significant incidents that would have been expected to alter the number or type of attendances. IAs were identified as those where the ED team did not provide any change in management or add to the patient journey or where, although the team may have provided some management, care could have safely been provided in another setting.

There were 646 attendances during the review period. Most were appropriate; 93.5% at the RVH ED and 79% at the MIH ED.

Of the 75 IAs, 59 (79%) were in individuals who had self-presented. This included 22 patients at the RVH (5% of all RVH attendances) and 37 at the MIH (16% of MIH attendances). 16 IAs (21%) were in patients referred by a GP, who did not require ED care. This included 5 attendances at RVH and 11 at MIH.

Very few IAs were assigned a Manchester Triage Category of 5 (non-urgent) (Figure 1). 6 patients were categorised as Category 2 (very urgent) and 43 as Category 3 (urgent).

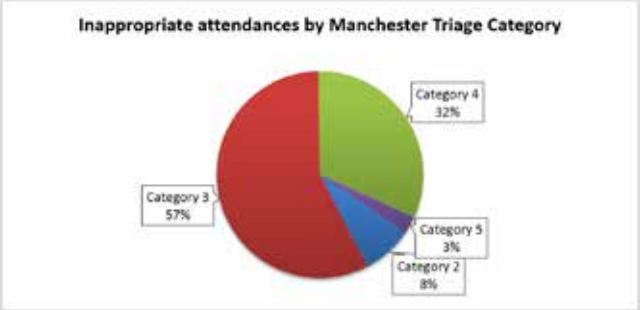

Fig 1. Inappropriate attendances by Manchester Triage Category

This study identified that most attendances were appropriate. The MIH had a greater proportion of IAs with larger numbers of both inappropriate self-presentations and GP referrals. This may reflect accessibility to primary care or a greater prevalence of chronic illness in the catchment area.

The proportion of IAs was 11.6% overall. This is similar to the findings of an analysis of attendances captured in a national ED dataset over one year, which identified 11.7% as inappropriate.[1] Other studies estimate a greater proportion of attendances to be avoidable. A systematic review suggested that 20-40% of attendances were inappropriate.[2] Analysis of the Royal College of Emergency Medicine Sentinel Site Survey, conducted in March 2014, identified around 15% avoidable attendances.[3] This variation may be due in part to the lack of a standardised definition of 'inappropriate' attendances.

Some patients may be being triaged into higher categories than their clinical condition would necessitate. A recent systematic review identified that the Manchester Triage System had both potential to under- and over-triage patients, impacting on safety in the ED and waiting times for patients.[4]

A limitation of this review is its small size. As it was carried out through retrospective note review, it is limited by the amount of information recorded on the notes. It may be possible that some presentations were wrongly categorised as inappropriate or appropriate.

This analysis has provided information on the proportions of patients attending ED in the Belfast Trust who have potential to be seen safely in an alternative setting. This may help to inform future investment decisions for those working in unscheduled care in Northern Ireland.

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DO THE PUBLIC GET WHAT THE PUBLIC WANTS IN NORTHERN IRELAND HEALTH AND SOCIAL CARE?

Editor,

Healthcare systems in Northern Ireland have undergone some degree of transformation over the last decade. Within the hospital sector, some services have relocated from smaller "local hospitals" to larger units. However, reorganisation of services has proven difficult, with evidence based proposals ignored and service alterations overturned by Government or judicial review, often as a consequence of "Save our hospital" campaigns by local community groups and political representatives. It is nonetheless unclear if these voices are representative of the population.

The recently published Donaldson Report recommends a major service reconfiguration to provide the Northern Ireland population with optimal secondary healthcare.[1] The subsequently appointed Northern Ireland Health and Social Care (HSC) Review Panel aims to determine the needs of the Northern Ireland population and describe a configuration of health and social care to best serve these.

Over recent years, increasing emphasis has been placed on empowering patients by offering more choice on treatment location and methods, similar to other consumer choices[2]. In this context, do patients employ a similar decision making process when contemplating healthcare decisions to that employed when purchasing other consumer commodities? We compared Northern Ireland public attitudes to healthcare with that of traditional consumer goods.

Methods

Questionnaires to assess public attitudes were distributed over a two-week period (18th-31st July 2014) in two locations-Belfast and Newcastle, County Down. Participants living

within the Greater Belfast area were considered to be urban dwellers, all others were considered rural dwellers. Data were analysed using SPSS (Version 21.0 Armonk, NY).

Results

One hundred questionnaires were completed. The participants rated accessibility of healthcare as more important than accessibility for traditional consumer products (Table 1). Participants would travel further for healthcare treatments than a variety of consumer products. Notably, participants would travel further for high quality products including healthcare treatments than for products of average quality (Table 2).

Table 1.

The importance of accessibility to healthcare and consumer items

	Importance of accessibility*
Sick children	4.63
Cancer treatment	4.63
Accident and Emergency	4.39
Cardiac surgery	4.16
Outpatient clinic	4.09
Bread	4.09
Everyday essentials e.g. shampoo	4.04
Large household appliances	2.78
Clothes for a special occasion	2.55
Television	2.51

*Accessibility was measured on a Likert scale from 1-5 with 5 being highest importance

Discussion

Consumers have similar attitudes to healthcare as they do to other consumer commodities. Consumers are willing to travel further for what they perceive to be specialised products or large one off purchases such as a fridge or television. Similarly, consumers are willing to travel further for traditionally perceived specialised treatments such as cardiac surgery, in comparison with GP or outpatient attendance. The public do want community based services such as their general practitioner to be nearby, similarly to frequently purchased consumer items such as bread. However, consumers are willing to travel on average more than one hour for secondary healthcare such as cancer treatment, particularly when the healthcare provided is of high quality. No longer should pressure be applied to maintain all local healthcare services at the expense of providing regional services of high quality. We encourage the HSC review panel to focus on the provision of high quality health and social care regardless of vocal opposition and suggest that implementation of a quality focussed system would meet the approval of the Northern Ireland population.

Table 2.

Acceptable travel time for healthcare and consumer items of varying quality.

	Average quality "Item" Travel time*	High quality "Item" Travel time*
Cardiac surgery	3.29	3.60
Clothes for a special occasion	3.05	3.20
Cancer treatment	2.98	3.56
Large household appliance	2.72	3.05
Television	2.67	2.96
Outpatient clinic	2.45	2.99
Accident and Emergency	2.38	2.96
Sick children	2.21	3.19
GP	1.92	2.59
Bread	1.16	1.48

Travel time was assessed using a Likert scale from 1-4 corresponding to the travel times below

1	2	3	4
0-15 minutes	15-30 minutes	30-60 minutes	more than 60 minutes

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ASSEMBLY OF SUCTION APPARATUS. AN ACQUIRED SKILL?

Editor,

Suction is an important aid in airway management. Correct assembly of the suction particulate trap apparatus is a pre-requisite for obtaining sufficient vacuum.[1,2] We sought to determine if the assembly of suction apparatus is an acquired

skill or a self-explanatory process. We also assessed if more recent apparatus used in hospitals in Northern Ireland can be assembled quicker. If the assembly of suction apparatus can be demonstrated to be an acquired skill then there may be indication for formal instruction to aid development of this skill by medical staff.

Our null hypotheses were:

1. If suction particulate trap assembly is a self explanatory process that does not require development of a specific skill then the time taken for senior doctors to assemble each apparatus should equal that for junior doctors.

2. The older Sep-T-Vac apparatus (Figure 1, panel A) is as easy to set up as the newer Vacsax apparatus (Figure 1, panel B)

One-way ANOVA test showed a significant difference between grade of doctor, irrespective of apparatus, which rejects the first null hypothesis ($p<0.05$). The Mann-Whitney test showed a significant difference between each apparatus with the Vacsax apparatus taking a significantly short time to set up in most instances ($p<0.05$).

Conclusion

The study showed that there is a significant difference between the times taken for the junior and senior doctors to correctly assemble the suction apparatus. This indicates that assembly is an acquired skill rather than a self explanatory process. We also conclude that it is easier to assemble the Vacsax apparatus and that hospitals should adopt this newer model.

Table 1

Grade of Doctor	Sep-T Vac Times of individual doctors (seconds)						Mean
	A&E		ENT		Anaesthetics		
Consultant	33	37	26	30	21	50	33
Registrar	77	160	34	57	48	67	74
SHO	79	115	30	125	98	127	96

Table 2

Grade of Doctor	VacSax Times of individual doctors (seconds)						Mean
	A&E		ENT		Anaesthetics		
Consultant	23	20	14	22	35	18	22
Registrar	19	19	17	18	17	24	19
SHO	27	38	30	25	32	34	31

Method

Six consultants, six specialist registrars and six senior house officers from three specialties involved in airway management were timed as they assembled a Sep-T-Vac suction particulate trap. The same method was applied for the Vacsax apparatus using different doctors with equivalent seniority. Doctor selection was random and was dependent on doctors who were available on the day of the study. Doctors had no previous training on apparatus assembly.

Results

For the Sep-T-Vac apparatus, the assembly time for the most senior grade is approximately one third of that taken by the most junior grade. Specialist registrars averaged the fastest times for the assembly of the Vacsax apparatus. The average times in all grades were faster for the Vacsax apparatus. The numbers in the study are too small to allow comparison between the specialties.

Fig 1. Sep-T-Vac apparatus (panel A) & Vacsax apparatus (panel B)

Assembly of suction apparatus is not straightforward and individual hospitals should consider formal instruction on the assembly and mechanism of action of their particular model.

Andrew Kelly, Nicholas Hope and Brendan Hanna

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TWO CONSULTANT SPINAL OPERATING: OPERATOR PERCEIVED BENEFITS

Editor,

There have been few documented studies looking at joint consultant spinal operating.[1-3] Within the Royal Victoria Hospital, it is routine for spinal consultants to operate in pairs for complex cases. The benefits of joint operating to either the patient or the surgeon are however unclear.

As a result, a study was undertaken to determine if participating surgeons felt there was any perceived benefit for either the surgeon or the patient. From the 27th September 2011 to the 26th September 2013, there were 43 documented joint consultant spinal operating cases at the main Royal Victoria Hospital site.

19 (44.19%) spinal stabilisation or fusion at any level.

18 (41.86%) Scoliosis operations.

6 (13.95%) Other (including tumour biopsy, wound wash out and kyphoplasty)

Q 1: Have you ever been involved in a joint consultant procedure?

Y/N

Q 2: If so, do you feel joint consultant operating is beneficial?

Y/N/NA

Q 3: What cases do you feel should be done/would like to do on a joint consultant basis?

- Complex spinal stabilisation or fusion at any level
- Posterior scoliosis correction
- Posterior fusion scoliosis
- Revision of Scoliosis fixation
- Complex spinal tumour operations
- Complex decompressions
- ACDF
- Free txt response

Q 4: What do you feel are the benefits of joint consultant operating?

- Shorter anaesthetic time
- Less blood loss
- Shorter stay in hospital
- Fewer post-operative complications
- Free text response

Q 5: Any other comments

Figure 1.

To assess if there was any operator perceived benefit, a 5 Question Survey was compiled. This was then sent to 300 Consultant Spinal Surgeons within the UK. A reply was received from 111 Consultants. Results were collated and both qualitative and quantitative data assessed (Fig.1).

The survey demonstrated that 94.50% had been involved in joint consultant operating and 93.64% felt that joint operating was beneficial. It was found that more complex and rarely performed cases were favoured for joint consultant surgery. A few responses, however, stated that consultants should be able to perform these operations by themselves. Although this is true the potential benefits for the patient would encourage joint operating.[1]

The perceived benefits for the patient included shorter surgery time, less blood loss and fewer post-operative complications. The perceived benefits for the surgeon included less stress with shared responsibility and experience. (Fig. 2)

Some Q 3 Free Responses

"Needed for any procedure if there is any concern or (if someone) is new to the team"

"Cases where there is significant risk of neurological loss".

Some Q 4 Free Responses

"Pooling of expertise/Combined thinking".

"Better legal position if patient develops complications".

Some Q 5 free responses

"it may impact negatively on the training of registrars".

"This is particularly important now as new consultants have little unsupervised pre-consultant operative experience".

"Should be considered… during the first year of new consultant appointments to ensure smooth transition into consultant practice".

Figure 2.

Conclusion: We believe joint consultant operating is an essential practice and should be used to share knowledge, increase skills and impact positively on patient outcomes. We also believe that this will be true for other surgical specialities. The survey analysis indicated that joint consultant operating is perceived by surgeons to be beneficial for both patient and surgeon. Conversely, there was some concern over registrar training, as opportunities to scrub would not be so readily available. Our feeling however is that actual operating time for the registrar is far outweighed by the invaluable

knowledge gained by assisting two consultants.

Research into this area has shown a reduction in operative blood loss, decreased stay in hospital and a reduction in complication rate.[1, 3] A local study, quantifying outcomes from single and joint consultant operating needs to be undertaken to determine if there is any actual benefit to either the surgeon or the patient.

The authors state that no funding was received to produce this study.

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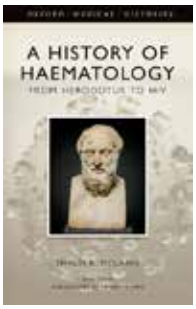
Book Reviews

A HISTORY OF HAEMATOLOGY. FROM HERODOTUS TO HIV (OXFORD MEDICAL HISTORIES).



Shaun R McCann, Oxford University Press 2016, ISBN 978-0-19-102714-7. RRP £39.99 Hardback

Did you know that some 17th century physicians suggested blood transfusion between spouses as a treatment for marital disharmony? Neither did I before reading "A History of Haematology from Herodotus to HIV" by Professor Shaun McCann, Professor Emeritus of Haematology and Academic Medicine at Trinity College Dublin. Although Haematologists make up a very small proportion of the medical workforce, most doctors have dealings with "blood" in their daily practice and should therefore find this well written book interesting and stimulating.

In his preface, Professor McCann tells of how he first met the editor of this series of books, Dr Christopher Gardner-Thorpe, at a dinner on the terrace of a mutual friend's house in Tuscany. He readily admits that the idea for the book was subsequently consolidated over an excellent lunch in London. The tone and style of the resulting book suggests that the dinner conversations on these occasions were enthusiastic, philosophical, wide ranging and entertaining. "A History of Haematology" is comprehensive and authoritative but never tiresome. When McCann tells us that in 500 BC Herodotus stated that "each person remembers something different-different and differently" he isn't revisiting the subject of marital disharmony, but preparing us for the fact that this is *his* history of haematology with emphasis on topics which he has judged to deserve attention. It is a thoughtful approach which rewards the reader.

He tells of his long-held fascination of the phenomenon of "people being written out of history" and certainly sets the record straight for many unsung heroes whose work continues to guide daily medical practice. I particularly enjoyed the story of Canadian blood transfusion pioneer Dr Norman Bethune (1890-1939), whose communist political outlook seem to have contributed to his omission from the historical record hitherto. McCann brings Bethune's story to life, setting the scene by telling us of his belief in the association between poverty and tuberculosis "ideas not widely held by the medical profession" at the time. Bethune's outlook was further influenced at a medical conference in Leningrad in the summer of 1935 by the idea that treatment was a "right of the individual, and not a charity". The swashbuckling Canadian took himself off to the Spanish Civil war to lead a surgical team to care for the wounded. where he developed a centralised blood bank in Madrid. He recognised the importance of transfusing casualties early, before they were transported behind lines to a hospital. He equipped a station wagon with an incubator, a fridge and an autoclave, establishing a mobile transfusion service across a 1000km war front. Bethune's premature return to Canada was caused by a combination of his reluctance to follow orders, his resistance to central control of his transfusion service, his heavy drinking and a number of sexual indiscretions. He ended up emigrating to China to work for Mao Zedong and is buried in the Revolutionary Martyrs' Cemetery in Shijiazhuang.

I found this book to be full of interesting facts, anecdotes, stories and opinions which provided me with stimulating topics for conversation over dinner in Derry/Londonderry. The book is dedicated to his wife; it seems that transfusion between spouses isn't required in the McCann household! "A History of Haematology" is highly recommended.

Dr F.McNicholl, Consultant Haematologist.

Ulster Med J 2017;**86(1):**51-54

Abstracts

Ulster Society of Internal Medicine
95th (Spring) Meeting
Friday 27th May 2016

Altnagelvin Hospital

PROGRAMME:

2.00 pm **Pneumocystis jiroveci pneumonia; The who and the where; identifying the population at risk.**

L McCorry. Dept of Microbiology, Kelvin Laboratory, RVH, Belfast HSC Trust, Belfast, UK.

2.15 pm **Pulmonary Embolism: A case requiring rescue percutaneous intervention.**

A.P. Gray, D. Flannery.

Department of Cardiology, Craigavon Area Hospital, Southern Trust, Northern Ireland.

2.30 pm **Pyoderma Gangrenosum in a Critically Ill Patient.**

P Collins, C Devereux, P Windrum.

Dermatology Department, Northern HSC Trust.

2.45 pm **Guest Lecture: "PCSK 9 inhibitors."**

Professor Maurice O'Kane, Clinical Chemistry, Altnagelvin Hospital.

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

Refreshments sponsored by **Sanofi.**

Poster 1 **Dysplastic Brain.**

D Cousins, E Kerr

Stroke Team, RVH, Belfast Trust.

Poster 2 **Complications after baby number three!**

L Kayes, D Comer, R Sharkey, MG Kelly, M McCloskey.

Respiratory Department, Altnagelvin Area Hospital, WHSCT.

Poster 3 **A case of voriconazole induced adrenal suppression in a patient with polyarteritis nodosa.**

S McDonald, N McKee, G Wright.

Musgrave Park Hospital, Belfast, N. Ireland

3.40 pm **Grand Rounds: Cases from Altnagelvin Hospital.**

4.10 pm **And the band played on! Hypersensitivity pneumonitis from wind instruments.**

G Gamble, E Toner, N Chapman & R Convery.

Respiratory Medicine, Craigavon Hospital. SHSCT.

4.25 pm **Granulomatosis with polyangiitis – cerebral involvement.**

McKnight J, Burns J, McCann S .

Rheumatology department. Northern HSC Trust, Antrim Area Hospital, UK.

5.10 pm Presentation of prize for the best abstract.

2PM ORAL

PNEUMOCYSTIS JIROVECI PNEUMONIA; THE WHO AND THE WHERE; IDENTIFYING THE POPULATION AT RISK.

L McCorry, Department of Microbiology, Kelvin Laboratory, Royal Victoria Hospital, Belfast HSC Trust, Belfast, UK

Pneumocystis jivoreci is an opportunistic pathogen which can lead to life threatening respiratory failure. It has a documented mortality of between 5-20%[1]. Historically it was almost exclusive to HIV patients however; an increase in immunosuppressive therapies has led to a reciprocal increase in the prevalence of Pneumocystis pneumonia (PCP) in this non-HIV population[2]. Despite clear guidelines for PCP prophylaxis in HIV, there is a haphazard approach in other immunosuppressed populations[1].

A growing body of evidence suggests that immunosuppressed patients are at an increased risk of PCP, but to what extent, or to whom that risk is greatest is not certain2.

Given this uncertainty we felt it prudent to review regional rates of PCP to develop a clearer understanding of the potential at risk population. We believe this is the first study of its kind.

We audited a random cohort of 103 patients who tested positive for Pneumocystis jiroveci over a 5-year period in Northern Ireland, who had documented pneumonia. We collated information on potential risk factors, morbidity and mortality.

The highest proportion of patients were cancer patients, however the most at risk population were rheumatology patients, with a 73% mortality rate in those who tested positive for PCP. Admission to ICU was 38% and mortality was 32%. Mortality was highest when prescribed three modalities of immunosuppression in combination, however prednisolone alone carries a mortality rate of 62%.

We feel that prophylaxis guidelines should be considered in these identified high risk groups.

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215PM ORAL

PULMONARY EMBOLISM: A CASE REQUIRING RESCUE PERCUTANEOUS INTERVENTION

A.P. Gray, D. Flannery

Department of Cardiology, Craigavon Area Hospital, Southern Trust, Northern Ireland

We present the case of a 35-year-old female with no past medical history who presented with a one-week history of exertional shortness of breath. She denied any additional symptoms suggestive of venous thromboembolism. She was haemodynamically stable with oxygen saturations of 99% on room air. Admission biochemistry was unremarkable except a D-Dimer elevated at >2 (reference range <0.5). ECG and chest x-ray were equally unremarkable. She was admitted under the medical team and treated with therapeutic enoxaparin for presumed pulmonary embolism. Her risk factors constituted raised body mass index and oral contraceptive use.

CT pulmonary angiogram confirmed large bilateral pulmonary emboli. Despite this she remained stable during admission however whilst attending for cardiac echocardiogram suffered a respiratory arrest. She was successfully resuscitated but subsequently arrested again twice. She received thrombolyis with Actilyase but remained haemodynamically unstable with oxygen saturations 70%, despite intubation and ventilation, and required inotropic support. She was profoundly acidotic (pH6.9) with a lactate of 20. On discussion with the tertiary referral centre it was felt that without intervention she was unlikely to survive. She was transferred to the cardiac catheterisation suite two and a half hours post arrest, remaining acidotic, hypotensive and hypoxic. Catheterisation of her pulmonary artery using a balloon tipped 6f swan ganz catheter was successful at restoring flow in both lung fields. Her haemodynamic status immediately improved with normalisation of oxygen saturations, pH and lactate. She was extubated the following day and was found to have GCS 15 with appropriate verbalisation.

230PM Oral

Pyoderma Gangrenosum in a Critically Ill Patient

P Collins, C Devereux, P Windrum.

Dermatology Department, Northern HSC Trust.

Pyoderma gangrenosum is a rare autoimmune condition which can lead to devastating skin loss if it is not diagnosed and managed promptly and appropriately.

A 72-year-old male was admitted to our intensive care unit with septic shock, requiring inotropic support. He developed progressive ulceration following surgical drainage of an abscess in his left axilla. This was managed as Necrotizing Fasciitis. A dermatological opinion was sought due to continued deterioration despite four further debridements. Clinically the ulcer was typical for Pyoderma Gangrenosum.

Clinical management was challenging as the patient required immunosuppressive treatment in the setting of his complex comorbidities of pneumonia and septicaemia. A multi-disciplinary approach involving dermatology, tissue viability team, intensive care physicians, surgical team and haematology was required.

Subsequent investigations have revealed this patient likely has a myeloproliferative disorder associated with his JAK2 positivity.

There have only ever been two reported cases of JAK2 positivity in Pyoderma Gangrenosum.[1]

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410PM ORAL

AND THE BAND PLAYED ON! HYPERSENSITIVITY PNEUMONITIS (HP) FROM WIND INSTRUMENTS

Gareth Gamble, Emma Toner, Naomi Chapman & Rory

Convery

Respiratory Medicine, Craigavon Hospital. SHSCT.

A male ex-smoker aged 70 presented with failure to recover following an episode of Streptococcal pneumonia. He started playing saxophone again after several years to 'strengthen' his lungs. Radiograph and serial CT chest showed evidence of mosaic infiltrate in keeping with HP. Empiric steroids failed to resolve his symptoms. A history review suggested reed fungal colonisation as potential trigger. Swabs confirmed Fusarium Dimerum as well as Staphylococcus Aureus. Advice re reed replacement/avoidance was given with good effect.

A 31-year-old female was investigated for right sided chest pain and found to have a nodular infiltrate in the right lower lobe. Open Lung biopsy confirmed an interstitial pneumonia, with MDT discussion suggesting HP. In depth history revealed exposure to stagnant secretions from a borrowed Euphonium several weeks before presentation. Recovery is ongoing.

Initially in susceptible individuals an acute type III and type IV reaction occurs in this complex dynamic clinical syndrome. Wind and brass instruments are rare causes of HP by virtue of biofilms or wooden reed fungal contaminants. Sterilizing instruments is advised but the best treatment is avoidance. Steroids can have a role in speeding up resolution.

425PM ORAL

GRANULOMATOSIS WITH POLYANGIITIS – CEREBRAL INVOLVEMENT

McKnight J, Burns J, McCann S.

Rheumatology department. Northern HSC Trust, Antrim Area Hospital, UK.

A 49-year-old male with a history of granulomatosis with polyangiitis was admitted acutely with a three-week history of headache, vomiting, nystagmus on lateral gaze and ataxia.

Granulomatosis with polyangiitis had been diagnosed 18 months prior; he initially presented with an ulcerating buccal mucosal lesion, epistaxis, nasal crusting, recurrent sinusitis and cavitating lung lesions identified on CT scanning. Previous biopsies of the buccal mucosal lesion confirmed the presence of a mixed inflammatory infiltrate with high concentrations of eosinophils. Initial serology confirmed elevated antibodies to PR3(>8 AI) and cANCA (40). Despite initially achieving disease remission with mycophenolate and high dose oral corticosteroid, the patient's compliance with maintenance immunosuppressive medication remained poor. He also had a history of chronic obstructive pulmonary disease (COPD) and continued to smoke between 40 and 80 cigarettes daily.

During his acute admission, his erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were noted to be markedly elevated. An MRI brain scan with contrast confirmed the presence of multiple enhancing nodular lesions which appear to be in continuity with the choroid plexus within the temporal horns and within the fourth ventricle. The lesions measured up to 2.7cm in diameter with significant adjacent oedema which also involved the brainstem.

Despite induction therapy with intravenous cyclophosphamide 750mg fortnightly and high dose corticosteroid, this patient's vasculitis remains active. He has now been commenced on a course of intravenous rituximab therapy in an attempt to obtain remission.

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POSTER 1

DYSPLASTIC BRAIN

D Cousins, E Kerr. Stroke Team, RVH, Belfast Trust.

A 26-year-old man with a history of migraine presented to the Emergency Department (ED) with headache and an episode of transient right arm heaviness. Neurological examination was normal. Blood pressure was 220/130mmHg. CT brain, urinalysis, ultrasound renal tracts and bloods were normal. The patient was commenced on Amlodipine and discharged with a diagnosis of migraine and probable essential hypertension.

8 weeks later the patient presented to ED with headache and a moderate, persistent right hemiparesis, dyspraxia of his right arm, mild dysarthria and a blood pressure of 156/90mmHg. MRI brain showed bilateral infarction in a 'watershed' distribution. CT angiography showed severe, irregular narrowing of both distal internal carotid arteries, and irregular narrowing with aneurysm formation of the right renal artery. A diagnosis of probable fibromuscular dysplasia (FMD) was made.

He with intravenous fluids, bed rest, discontinuation of antihypertensives and subsequent inotropic support to achieve BP >180/100. He deteriorated over the following days with recurrent stroke. He developed massive bilateral stroke with malignant MCA syndrome. He was not suitable for extracranial-intracranial bypass surgery or decompressive hemicraniectomy and died.

Family history revealed a florid history of 'migraine with aura' and transient ischaemic attack. MR angiography

revealed irregular stenoses of internal carotid arteries bilaterally in the patient's mother and sister. The family were referred to genetics.

DISCUSSION:

This patient had a diagnosis of fibromuscular dysplasia. This results in stenosis, aneurysms and dissections in any artery. The most commonly affected are the renal, carotid and vertebral arteries. 75% of people with FMD have renal artery stenosis and hypertension.

It is likely that this patient's cerebral perfusion had been maintained by hypertension, and introducing amlodipine precipitated reduced perfusion.

FMD has a strong genetic component and although this is a rare case it highlights the importance of an accurate family history in patients with atypical or hemiplegic migraine.

POSTER 2

COMPLICATIONS AFTER BABY NUMBER THREE!

L Kayes, D Comer, R Sharkey, MG Kelly, M McCloskey.

Respiratory Department, Altnagelvin Area Hospital, WHSCT, Londonderry.

This is the case of 28-year-old girl, with no past medical history, who at 34 weeks pregnant with her third child, was admitted on 12-09-2015 with abdominal pain and elevated inflammatory markers. No source of sepsis was identified and she had an exploratory laparotomy, appendectomy and caesarean section. She delivered a healthy baby.

Five days after surgery she developed chest pain and hypoxia. Chest x-ray showed left basal consolidation. CT pulmonary angiogram was normal. She became progressively more hypoxic and developed left lower lobe collapse. Over the next week she developed a complete collapse of her left lung due to mucoid impaction. She had a bronchoscopy on 01-10-2015 and there were copious tenacious secretions left lung. After this she improved. Four days later on 04-10-2015 she developed further left sided chest pain and chest x-ray showed a pneumothorax left lung. Chest drain was inserted and she improved and stabilised. Less than 24 hours later she became unwell again with worsening hypoxia and further chest pain. CT pulmonary angiogram now showed extensive thrombus right lung, left lung was still deflated. Her family were informed that she was gravely ill with significant right heart strain, oxygen requirements of 100% and that there was a high probability that she would not survive. She remained critically ill for seven days in Intensive Care.

Over the next few weeks she slowly improved and was discharged on 26-10-2016. At review she is very well. She does not want any further children but has yet to be sterilised.

This case is presented to discuss the numerous medical issues. Seven different medical specialties were involved in her care at consultant level and numerous investigations undertaken. No identifiable risk factors have been identified.

POSTER 3

A CASE OF VORICONAZOLE INDUCED ADRENAL SUPPRESSION IN A PATIENT WITH POLYARTERITIS NODOSA.

S McDonald, N McKee, G Wright,

Musgrave Park Hospital, Belfast, N. Ireland

ABSTRACT

A 78-year-old man with a long history of polyarteritis nodosa, ischaemic heart disease, chronic kidney disease and a cavitating lung lesion with mycobacterium malmoense was admitted with generalised muscular pain, fatigue, anorexia, decreased mobility and dizziness over the last month. His sputum had recently cultured aspergillus fumigatus and he had commenced on voriconazole six weeks prior. His maintenance therapy for polyarteritis was long term prednisolone and mycophenolate mofetil. His examination demonstrated that he was normotensive with generalised muscular tenderness, ankle oedema, an aortic murmur, bronchial breathing of the left upper lobe but was otherwise unremarkable with a normal postural blood pressure. Bloods demonstrated normal inflammatory markers, a new transaminitis, deteriorating renal function with urea of 37 and hyperkalaemia at 6.2, which required treatment. ANCA tests were negative. A synacthen test was inadequate with cortisol rising from 136 to 268 nmol/L at 30 minutes. Hypoadrenalism due to long-term steroid use was a working diagnosis. His prednisolone was increased to 20mg and he received intramuscular depomedrone 120mg. His voriconazole, mycophenolate and anti-tuberculous drugs were stopped 4 days post admission. He was discussed with renal who felt uraemia wasn't driving his symptoms and agreed there was no evidence of vasculitis relapse. A random morning cortisol checked 12 days post admission was 463nmol/L. He could now mobilise independently and his renal/liver function returned to baseline. It was felt that the voriconazole was the culprit agent and he didn't restart this on discharge, after consultation with respiratory.

Ulster Med J 2017;**86(1):**55-68

Abstracts

19th Meeting of the Irish Society of Human Genetics, Friday 9th September 2016.

Belfast City Hospital

SPOKEN PAPERS:

S01. Deep phenotyping and genomic analysis for Behcet's disease

A Coleman[1], F McKinley[2], A Gough[2], N Wheatley[2], H Xu[3], AJ McKnight[1].

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Behcet's disease (BD) is a complex, multifactorial rare disease, which is poorly understood. Genetic and environmental factors contribute to BD, but the process of diagnosis is challenging with inconsistent clinical manifestations. A recent survey of individuals living with rare disease(s) in Northern Ireland revealed ~50% of individuals receive ≥1 misdiagnosis with $^{1}/_{20}$ seeing >10 doctors.

Individuals with BD report a range of symptoms, which are variable in onset, severity, and frequency for this systemic vasculitis. Patients describe prolonged journeys to diagnosis with multiple healthcare professionals and medical specialties; there is no BD specialist in Northern Ireland. Using invitations via social media, voluntary groups, and direct contact we are using surveys incorporating micro-narratives, one-to-one semi-structured interviews, and focus groups to collect detailed family histories and stressor information to help characterise recurrent features in patients living with BD and their relatives in Northern Ireland.

BD is most often reported in populations along the Silk Road. The highest prevalence is reported in Turkey at 20-420/100,000, compared 1.5/100,000 individuals in the UK. Mapping through general practitioners revealed a much higher than expected prevalence of 12.6/100,000 in the Northern Ireland population. Clusters were observed in Co. Down and Co. Antrim and plotted with social-demographic information. This high 'UK' prevalence and the identification of several families with multiple members diagnosed makes NI ideal to explore genetic and epigenetic risk factors for BD.

This project involves deep phenotyping and strategies to improve recognition of Behcet's disease, build collaborative partnerships, improve data collection, enhance training, and information sharing.

S02. Capturing Irish Rare Disease activity, a must for improved cross border care and research

DM Lambert[1], SA Lynch[1], R Marron[1], D Gray[2], EP Treacy[1].

[1]National Rare Disease Office, Mater Misericordiae Hospital, Dublin 7, [2]National Clinical Programme for Rare Diseases, RCPI.

The National Rare Disease Office (NRDO), initiated in June 2015, collates and disseminates Irish rare disease (RD) information. The prevalent nature of RD (1 in 16 of the population, approximately 80% of which has a genetic basis) and the burden to the health care system is under-recognised and a neglected public health issue. Awareness of rare diseases is a challenge, especially for GPs who each care for > 90 RD patients.

The NRDO has made 58 presentations, lectures and publications and received numerous enquiries (58% of contacts from patients/families, 25% from health care professionals and 4% researchers). Mapping Irish RD clinical and research expertise is developing through Orphanet Ireland. Enrolment of clinical expert centres has increased by 50%,but only <10% of the most prevalent RDs are represented. This reflects well-developed services for some conditions, (e.g. vasculitis and ALS), but more disparate services for others (intellectual disability and multisystemic RD). A lack of coding and/or registries makes it difficult to identify rare patients within hospital systems. Numerous cross-border initiatives seek to maximize clinical and research outcomes through collaboration. However, < 1% of Irish RD research and <30% of RD clinical trials are registered on Orphanet. For European recognition and participation, Ireland must make its RD research visible, and 'count' RD patients and activity. Irish patients will be disadvantaged unless we develop systems to prepare for entry to European Reference Networks and become "trial ready". While progress is slow, these are early days and we are optimistic about future developments.

S03. PTEN Hamartoma Tumour Syndrome Screening Audit – Northern Ireland 2016

RS Moore[1], V McConnell[1].

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Aims: To assess the tumour surveillance advice given to patients in Northern Ireland with confirmed PTEN hamartoma tumour syndrome (HTS).

Methods: We used the surveillance advice laid out by the Pan Thames Cancer Genetics Group in 2014 to benchmark our

patients against. A coding search was carried out on our regional information management system to identify all patients with a confirmed diagnosis. The written/ electronic notes of these patients were reviewed. We adhered to the National PTEN audit inclusion criteria of including patients older than16 years, those with a pathogenic/likely pathogenic PTEN mutation or at 50% risk and those who had received advice between 01/08/10 - 01/08/2015.

Results: 21 patients were identified. All patients had a pathogenic PTEN mutation. 6 children were excluded. 1 adult was excluded due to lack of documented advice. 6 patients had a cancer diagnosis. 9 patients had a positive family history of cancer. Annual breast screening was recommended for 67% of patients which involved mammography in 83% and MRI in 17%. Annual thyroid USS and TFTs were recommended for 54% and 31% of patients respectively. 16% of female patients had gynaecology referrals completed. An annual dermatological review was recommended for 23% of patients. Widely variable colonoscopy and renal USS screening was recommended for 77% and 65% of patients respectively. No cases of Lhermitte-Duclos disease were identified vs 12% in the national UK audit.

Conclusions: There is a need for regional PTEN tumour surveillance guidelines to be produced and implemented through a regional PTEN specialist clinic.

S04. Post-mortem examination of an aggressive case of medullary thyroid carcinoma characterized by catastrophic genomic abnormalities

D Kelly[1,2*], S Das[3,4*], B Moran[3,4*], K Han[2,5], N Mulligan[2,5], C Barrett[2,5], PG Buckley[6], P Mc Mahon[1,2], J McCaffrey[1,2], HF Van Essen[7], K Connor[3,4], B Ylstra[7], D Lambrechts[8], WM Gallagher[3], DP O'Connor[3,4§], CM Kelly[1,2§] **Equal Contribution, § Senior co-authors.*

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Catastrophic genomic alterations can drive unusually aggressive cancer phenotypes. We describe a diagnostically challenging rapidly fatal case of medullary thyroid carcinoma (MTC) occurring in a young, morbidly obese man presenting with diffuse bone marrow involvement and disseminated intravascular coagulation. Whole-exome sequencing and shallow whole-genome sequencing was carried out for the primary tumour and multiple metastases. We identified three germline SNP's within the *RET* proto-oncogene which remained undetected using routine hospital genetic testing procedures. Indeed, one of the variants identified (L769L) has been previously reported in literature to be associated aggressive MTC presentation, yet remains untested for in the routine diagnosis of MTC. Supported by findings from shallow whole genome sequencing, we report for the first time in thyroid cancer, the occurrence of a catastrophic "chromothripsis-like pattern" (CTLP) event, which involved shattering of chromosome 4 leading to complete abrogation of normal chromosomal function, in addition to dramatic wide-spread copy number aberrations (CNA), across both primary tumour and bone marrow samples. We further describe the presence of loss-of-heterozygosity (LOH) in key genes involved in DNA repair mechanism pathways such as *ATM*, which possibly facilitated the CTLP event, in addition to LOH in other disease-associated genes such as *ALK* and *NOTCH1* as key drivers of the aggressive and rapidly fatal clinical course in this patient and unresponsiveness to the standard-of-care targeted agent chosen. Given a possible rapid generation of tumor neo-antigens as a result of the CTLP event, immunotherapy may have been more suitable as a treatment option. Moreover, the presence of disease-associated SNP's within the *RET* proto-oncogene, support their inclusion as part of routine *RET* genetic testing for aggressive MTC cases. These results provide a rationale for application of comprehensive genomic analysis of cancers presenting with unusually aggressive behavior to facilitate more appropriate therapeutic options and diagnoses.

S05. Target 5000: Genetic characterisation of a cohort of inherited retinal degeneration (IRD) patients

A Dockery[1], M Carrigan[1], C Malone[2], D Keegan[3], K Stevenson[3], J Silvestri[4], A Green[5], J McCourt[6], P Humphries[1], PF Kenna[1,2], GJ Farrar[1].

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The Target 5000 research project aims to provide genetic testing for the estimated 5,000 people in Ireland who have an inherited retinal condition. Many clinical trials are available for patients with sight loss, however, many such trials require patients to have their causative mutation identified in order to enter the trial. The objective of the study is to genetically characterise patients with inherited retinal degenerations (IRDs) in Ireland and in principle to make clinical trials more accessible to some Irish people suffering from sight loss. The study also seeks to identify previously undiscovered pathological mutations in a panel of known retinopathy genes evaluated utilizing target capture next generation sequencing (NGS).

Thus far in the study, as part of Target 5000 roughly 10% of the Irish IRD population has been sequenced and the results obtained are encouraging. Target 5000 offers not only a chance to discover new causative mutations, but is vital in giving patients access to information regarding the pathogenesis of their disease. Over 50 novel mutations have been discovered, as well as some previously ambiguous phenotypes resolved. More precise matching of genotype with phenotype from this study and similar studies

globally should start to enable clinicians to better formulate accurate future diagnoses and at times prognoses.

S06. Methylation quantitation trait loci and transcriptome analysis of differentially methylated microRNAs in end-stage renal disease

LJ Smyth[1], CE Neville[1], GJ McKay[1], AP Maxwell[1,2], JV Woodside[1], AJ McKnight[1].

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MicroRNAs are understood to play a functional role within the establishment of epigenetic marks and are in turn under epigenetic control. Emerging evidence suggests microRNAs are vital for both kidney development and renal function. This study aimed to identify differential methylation affecting microRNAs in patients with end-stage renal disease (ESRD).

Methylation status was determined for 485,577 unique CpG sites in 105 individuals with ESRD and 52 donor controls with no evidence of renal disease using the HumanMethylation450K BeadChip array (Illumina). Statistically significant associations ($P<10^{-8}$) were observed between case and control groups for both unique CpG sites within microRNAs and their target genes, identified using miRDB (an online database for microRNA target prediction and functional annotations).

CpG sites (n=11) within top-ranked microRNAs (n=42) alongside 848 CpGs in 198 target genes were evaluated in genotyped renal transplant samples to detect methylation quantitative trait loci (meQTLs) associated with ESRD. Following allelic association PLINK analysis, 116 SNPs were determined from the investigated CpG sites, 12 of which were located in genes previously linked with renal disease or microRNAs.

Blood-derived Ion Total RNA-Seq v2 analysis was performed on10ESRD samples and 29 controls (with no evidence of renal disease)to determine the expression levels of the microRNAs and target genes. Sequencing was completed using the Ion Proton™ (Thermo Fisher Scientific) and the most significant results were*MIR548H4* ($5.79x10^{-6}$) and *WASF3* ($5.59x10^{-9}$) respectively, showing increased expression within the ESRD samples.

This study has identified microRNA-related differential methylation with supporting gene expression data, associated with ESRD.

S07. Genetic overlap between amyotrophic lateral sclerosis and schizophrenia

RL McLaughlin[1,2], D Schijven[3,4], W van Rheenen[3], KR van Eijk[3], M O'Brien[1], Project MinE GWAS Consortium[‡], Schizophrenia Working Group of the Psychiatric Genomics Consortium, R Kahn[4], RA Ophoff[4,5,6], A Goris[7,8], DG Bradley[2], A Al-Chalabi[9], LH van den Berg[3], JJ Luykx[3,4,10], O Hardiman[2], JH Veldink[3].

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Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease characterized by rapid-onset loss of upper and lower motor neurones, resulting in progressive paralysis and death from respiratory failure. Schizophrenia is a neuropsychiatric disease with positive symptoms, negative symptoms and impairment over a range of cognitive abilities. We have recently shown that schizophrenia occurs more frequently than expected in the pedigrees of ALS patients, suggesting an aetiological relationship between both diseases. Using linkage disequilibrium score regression with summary statistics for GWAS of ALS and schizophrenia comprising over 100,000 unique individuals, we estimated the genetic correlation between ALS and schizophrenia to be 14.3% (95% CI 7.05-21.6; $p = 1\times10^{-4}$). Up to 0.12% of the variance in ALS was explained by schizophrenia polygenic risk scores ($p = 8.4\times10$). We leveraged the apparent pleiotropic relationship between ALS and schizophrenia to identify five potential novel ALS-associated genomic loci at conditional false discovery rate < 0.01. Diagnostic misclassification in the schizophrenia cohort did not contribute significantly to our observations (BUHMBOX $p = 0.94$) and we estimated that 4.86% (2.47-7.13%) of ALS cases would need to be misdiagnosed as schizophrenia to observe our genetic correlation estimate under a true genetic correlation of 0%. Our results indicate that the lifetime risk for comorbid ALS and schizophrenia increases from 1 in 40,000 to 1 in 34,336, which would require an incident cohort of 16,488 ALS patients to observe epidemiologically. Our findings suggest shared underlying biology between ALS and schizophrenia which will direct novel approaches in research and therapeutic development.

S08. Identifying clinically relevant imprinted gDMRs sensitive to a transient loss of DNA methylation in human differentiated cells

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Background: Imprinted genes are autosomal, but only expressed from one parental allele and are often clustered in small groups. They play an important role in the regulation of normal mammalian

development. Differentially methylated regions (DMR) on each allele are important in regulating the genes, with marks being characterised as primary or secondary DMRs, depending on whether they are inherited from the germ cells or arise later, respectively. Imprinting disorders such as Prader-Willi Syndome (PWS) and Beckwith-Weidemann Syndrome (BWS) arise either from uniparental disomy or faulty DNA methylation. We wished to determine 1) which of the loci are most sensitive to loss of methylation 2) to more precisely define the sensitive regions and 3) determine what happens at primary versus secondary imprints. Methods: Stable knockdowns of the maintenance methyltransferase DNMT1 were generated in hTERT-immortalised adult fibroblasts using shRNA. Genome wide methylation levels were assayed using the Illumina 450k BeadChip array and analysed using bioinformatic approaches. Results: We found that 1) the imprinted loci varied extensively in their sensitivity to loss of methylation 2) the extended locus involved in PWS was particularly sensitive 3) that loss of methylation at primary DMR appears to drive gains in methylation at secondary DMR. Conclusion: Our results point to a mechanistic link between primary and secondary DMR which may explain why imprints are difficult to reprogram in somatic tissues.

S09. Disease modelling with mesenchymal stromal cells and induced pluripotent cells uncovers the pathology of familial osteochondritis dissecans: from *ACAN* gene mutation to early onset osteoarthritis

M Xu[1], EL Stattin[2], G Shaw[1], D Heinegård[3], G Sullivan[4], I Wilmut[5], A Colman[6], P Önnerfjord[3], A Khabut[3], A Aspberg[3], P Dockery[7], T Hardingham[8], M Murphy[1], F Barry[1].

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Osteoarthritis (OA) is a degenerative joint disease that affects millions of people globally with no disease-modifying strategies yet available. Our understanding of the pathology of OA is inadequate and this impedes investigation of efficient diagnosis and treatment. To expand our understanding of the underlying cellular pathology of OA, we studied a monogenic condition, familial osteochondritis dissecans (FOCD), associated with a known mutation in the ACAN gene. Patients with FOCD develop early onset OA with multiple joint involvement.

The objectives of the project were to investigate the cellular pathogenesis of FOCD by studying (a) chondrogenesis of patient-derived bone marrow-mesenchymal stem cells (BM-MSCs) and (b) induced pluripotent stem cells (iPSCs) generated from patient fibroblasts.

Our findings revealed that the mutation resulted in a misfolded or unfolded aggrecan protein, which accumulated in the rough endoplasmic reticulum (rER) during protein production. The consistent accumulation resulted in ER stress throughout chondrogenesis. Moreover, the rER stress caused abnormal or disregulated global extracellular matrix (ECM) production and assembly. Importantly, ECM composition analysis indicated that the patient chondrocytes produced abundant amounts of OA-associated markers.

Using patient-specific stem cell models, we have discovered a cellular pathogenesis of FOCD involving abnormal cell function and defective tissue formation, contributing to the OA phenotype.

S10. Genomic insights into the population structure and history of the Irish Travellers

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Aims: The Irish Travellers are a nomadic population primarily found within Ireland and the UK. Consanguineous unions are common, and as a population they are socially and genetically isolated from the surrounding, "settled" Irish population. Previous low-resolution genetic analyses suggested a common Irish origin between the settled and the Traveller populations. It is not known, however, what is the extent of population structure within the Irish Traveller population, the time of divergence from the general Irish population, and the extent of autozygosity.

Methods: We recruited Irish Travellers from across Ireland and the UK. For inclusion, a participant had to have had at least three grandparents with a surname associated with the Irish Travellers. DNA was extracted from saliva samples, and genotypes were generated using the Illumina OmniExpress SNP genotyping platform. With this data, we investigated population structure using fineStructure, quantified the levels of autozygosity with PLINK, and estimated a time of divergence using a method based on Identity by Descent (IBD) segment sharing.

Results: We merged, cleaned, and analysed data from 42 Irish Travellers, 2232 settled Irish, 2039 British, 143 Roma Gypsies, and 931 individuals from 57 world-wide populations. We confirm an Irish origin for the Irish Travellers, demonstrate evidence for population substructure within the population, confirm high levels of autozygosity consistent with a consanguineous population, and for the first time provide estimates for a date of divergence between the Irish Travellers and settled Irish.

Conclusion: Our findings have implications for disease mapping within Ireland, and they additionally inform on the social history of the Irish Traveller population.

POSTER PRESENTATIONS:

P01. 16p13.11 duplications in a Northern Ireland Cohort

S McNerlan[1], V McConnell[2].

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Copy number variants at 16p13.11 have been described in association with a variety of neurodevelopmental disorders. While deletions of this region are perhaps better described, the clinical significance of the reciprocal duplication is less clearly defined. Phenotypes reported in association with the duplication include developmental delay, speech delay, behavioural difficulties and neurodevelopmental phenotype such as autism, schizophrenia and ADHD. However, the region appears to be subject to variable expressivity and incomplete penetrance.

To date we have detected duplications of 16p13.11 in 5 probands using oligonucleotide array CGH. Of these patients 3 showed duplications within the typical ~1.5Mb duplication region while 2 patients had a larger ~2.8Mb duplication, encompassing all of the above region. The clinical phenotype of these patients will be described. Two of these patients have inherited the duplication from their mothers, one was a de novo finding and the inheritance of the others is currently unknown. One of the maternal duplication carriers are also known to have a phenotype.

Our data provides further clinical information on the phenotypic features of patients with this syndrome and provides more evidence for the pathogenic nature of this duplication.

P02. NI Regional Cancer Genetics Service Patient Satisfaction Questionnaire

J Scott, T O'Neill, D Jager

Northern Ireland Regional Genetics Service

Introduction – Patients referred to the NI Regional Cancer Genetics Service for genetic counselling were sent a questionnaire to evaluate patient satisfaction. The questionnaire focused on satisfaction surrounding the referral process, waiting times and communication during and after the appointment.

Method – One hundred patients, whose episode of care was completed between November 2015 and June 2016, were sent an anonymised structured questionnaire by post. Patients were seen by a genetic counsellor for assessment of their family history of cancer, predictive testing and genetic mutation screening

Results – To date (23/06/2016) the questionnaire response rate is 34%. So far 91% have expressed satisfaction with the service that they received. Useful comments and observations have been feedback in the questionnaire to aid service improvement. Data collection will be completed imminently to allow for complete analysis.

Discussion – Useful data has been collected which reinforces the service currently being delivered by genetic counsellors whilst also highlighting areas of service development.

P03. Detection of the 3 primary mitochondrial mutations in Leber's hereditary optic neuropathy with a multiplex allele specific PCR / high resolution melt curve assay

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Leber's Hereditary Optic Neuropathy (LHON) is one of the most commonly inherited optic neuropathies and results in significant visual morbidity among young adults. 95% of LHON patients will present with one of three primary mitochondrial mutations; G3460A, G11778A and T14484C. We describe a novel real time diagnostic test to detect the three common mutations leading to LHON. The test uses a combination of multiplex allele specific PCR (ARMS PCR) in combination with high resolution melt curve analysis to detect the presence of the G3460A, G11778A and T14484C mutations.

PCR primer sets were designed to produce a control PCR product and PCR products only in the presence of the 3460A, 11778A and 14484C mutations in a multiplex single tube format. Products produce discrete well separated melt curves allowing clear detection of the mutations. The test has proved to be robust, cost and time effective with the real time closed tube system taking approximately 1 hour to complete.

This test provides a simple, robust, easy to read output that is both cost and time effective, thus providing an alternative method to individual endpoint PCR – RFLP, PCR followed by Sanger / pyrosequencing and next generation sequencing. It will also allow diagnostic laboratories to detect 95% of LHON causing mutations in a single tube assay allowing diagnostic laboratories to avoid costly NGS assays for the vast majority of LHON patients, thus allowing resources to be focussed on patients with unknown mutations requiring further analysis.

P04. TACE levels in patients at very high risk of Major Adverse Cardiac Events

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Atherosclerotic coronary artery disease (CAD) is a progressive chronic inflammatory condition that can lead to Major Adverse Cardiac Events (MACE) such as heart attacks. Currently there is no definitive test to predict MACE risk. Tumour necrosis factor alpha converting enzyme (TACE), also known as A Disintegrin And Metalloproteinase 17 (ADAM17) is a membrane-anchored protein responsible for the ectodomain shedding of a variety of transmembrane proteins such as cytokines, chemokines, growth factors and their receptors. TACE has been linked to several major acute and chronic inflammatory diseases including atherosclerosis. The aim of this study was to investigate if TACE may be a

valuable predictive biomarker for CAD and MACE risk. TACE levels were measured in the plasma of CAD patients including those with acute coronary syndrome (ACS) and elective patients attending the catheterisation laboratory for coronary angiogram. TACE levels were measured using ELISA and quantitative real time PCR. Levels were compared with control samples collected from apparently healthy individuals and a subset of patients with no CAD as evidenced by coronary angiogram. Other factors that might affect TACE detection were also measured including sample type and storage time. To date 207 consecutive CAD patients and 40 controls have been recruited to the study. Results demonstrate that CAD patients have higher levels of plasma TACE in comparison to controls. TACE protein levels were especially highest in those ACS and elective patients with a previous history of MACE. Results to date indicate that TACE may be a useful marker to predict disease progression and recurrent MACE in CAD patients.

P05. Investigating the role of a single nucleotide polymorphism in NRG1 in predisposition to breast and thyroid cancers

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Introduction: NRG1 (neuregulin1) is a candidate tumour suppressor gene. NRG1 encodes ligands for members of the ERBB family, and has been shown to be silenced by methylation in breast cancer[1]. Breast and thyroid cancers share some genetic loci (e.g. PTEN, STK11), and an increased risk of thyroid cancer has been noted in survivors of breast cancer[2]. A single nucleotide variant (C>G) in NRG1 (rs2439302), has been associated with increased risk of non-medullary thyroid cancer[3]. Aim: Our aim was to investigate the association between rs2439302 in NRG1 and predisposition to thyroid and breast cancers in an Irish population. Methods: A two-arm case-control study was undertaken. Patients with mutations in high-risk cancer susceptibility genes were excluded. Controls included adults with no personal or familial history of breast or thyroid cancers. Male controls were included in thyroid case- control analysis only. DNA was extracted from whole blood/buccal swabs by ethanol precipitation. Genotyping was performed using Taqman-based PCR. Results: 257 patients with thyroid cancer, 518 with breast cancer and 367 unaffected controls were genotyped. Homozygous carriers of the variant were found to have an increased risk of thyroid cancer (OR1.89 (1.21-2.95), p=0.005), but risk for mono-allelic carriers was not significantly increased (OR1.27 (0.87-1.84), p=0.21). The presence of the variant was not associated significantly with breast malignancy for mono-allelic (OR1.31 (0.95-1.8), p=0.095) or biallelic mutation carriers (OR1.15 (0.76-1.73), p=0.51). Conclusion: Homozygous carriers of the G allele were found to be at increased risk of thyroid cancer, but no association was observed between the variant and breast cancer. References:[1]Chua YL1, Ito Y, Pole JC *et al*, The NRG1 gene is frequently silenced by methylation in breast cancers and is a strong candidate for the 8p tumour suppressor gene. Oncogene. 2009;**28(46):**4041-52. [2]Nielsen SM, White MG, Hong S, *et al,* The Breast-Thyroid Cancer Link: A Systematic Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2016;**25(2):**231-8. [3]Liyanarachchi S, Wojcicka A, Li W, *et al*, Cumulative risk impact of five genetic variants associated with papillary thyroid carcinoma. *Thyroid*. 2013;**23(12):**1532-40.

P06. Expression and modulation of the family of *UGT1A* phase II metabolism genes by liganded Vitamin D receptor (VDR)

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The UGT1A gene family encode (UGT) activity that facilitate the transfer of glucuronic acid to a range of xenogenous and endogenous substrates, the polar end products of which are better suited for elimination through urine and bile. UGT1A genes exhibit an inducible pattern of expression regulated through the activities of such nuclear receptors (NRs) as pregnane X receptor (PXR) farensoid X receptor (FXR) and liver X receptor (LXR) that form a complex interactive network of 'sensors' to facilitate the elimination of potentially harmful metabolites and exogenous toxins. We have previously reported that activation of vitamin D receptor (VDR) through both synthetic agonists and nutritionally derived ligands, can induce the expression of both phase I metabolic (CYP3A) and phase III transporter (ABCA1) genes. Little is known however, as to how activated VDR may impact upon the regulation of phase II genes such as UGT1A1. In this study we demonstrate that ligand-activated VDR can significantly enhance the expression of several members of the UGT1A gene family. With particular respect to UGT1A1, we identify within the proximal promoter region of this gene a functional vitamin D response element (VDRE) also recognized by PXR but distinct from previously established regulatory elements that mediate FXR and LXR signalling. Based upon our data, we propose a model for VDR and circulating levels of vitamin D as maintaining stable expression of phase II and functionally related genes as a means to provide baseline protection against the effects of toxic xeno and endobiotic metabolites.

P07. Investigation of the oral microbiome for candidate markers of depression.

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Depression is a complex disorder with multiple symptoms, including a persistent low mood, anhedonia and cognitive impairments, and is currently the third leading cause of global disability. The underlying pathophysiology of depression is poorly understood but a growing body of evidence supports an important role for the microbiome in the aetiology of depression and other psychiatric disorders. While much interest is currently focused on the role of the microbiome-gut-brain axis in brain physiology and neurochemistry, the importance of the oral microbiome has received little attention. The aim of this study is to characterise the oral microbiome in adults with severe depression versus matched controls with no history of the disease. To achieve this, participants

were asked to complete an online validated mental health survey and to provide a saliva sample. We identified 46 individuals who met the DSM-V criteria for severe depression and 46 age and sex-matched controls with no history of depression. Bacterial DNA was extracted from the saliva samples and 16S rRNA surveys were conducted using next generation sequencing. Differences in the bacterial community composition of the oral microbiota between patients and controls were determined.Metagenomic analyses were conducted using machine learning and computational intelligence algorithms using the 16S RNA data to generate inferred metagenome feature sets. Charting the oral microbiome in depressed patients could therefore provide new insights into the development of the condition, and lead to the identification of novel diagnostic and therapeutic response biomarkers.

P08. Expression and modulation of genes of pharmacokinetic relevance within enteric cells by liganded Vitamin D receptor (VDR)

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The nuclear receptors (NRs) pregnane X receptor (PXR) and constitutive androstane receptor (CAR) modulate transcriptional networks that dictate the bioavailability of many endogenous and exogenous compounds such as steroid hormones and therapeutic drug compounds. Elucidating those factors that invoke PXR/CAR activity has been important for understanding the genetic basis for both metabolic disease and inter-individual variations in drug response. PXR is most closely related to Vitamin D receptor (VDR) for which there is relatively little is known for how this NR may impact upon these same physiological processes.

In this study, we employed enteric cell models and *ex-vivo* based human colon explants to examine how activated VDR may impact upon the expression of genes of a metabolism and transporter function. We find that in relation to PXR and other evaluated NRs, VDR is the most efficient and dominant receptor for induced expression of *CYP2B6*, *CYP3A4/5* and *ABCA1*. We note that upon activation with the synthetic agonist EB1089, VDR will achieve striking and sustained elevated expression of CYP3A4 at mRNA, protein and enzymatic level suggesting the potential for selective metabolic gene targeting through ligand design. In addition, we report members of the *UGT1A* gene family to be novel VDR regulated genes, thus extending the known metabolic effects of vitamin D to also encompass expression of phase II (conjugating) genes. This study intimates that systemic vitamin D status and/or activating VDR ligands may have pharmacokinetic relevance to co-administered drug regimes.

P09. Analysis of Genetic Disease Markers in Ancient Irish Genomes

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Ancient genomes are often typically analysed with regard to ancestry and physical phenotype. Less common is examination and identification of genetic diseases, primarily due to the very low numbers of samples sequenced and poor level of sequencing related to the difficulties in sequencing from ancient DNA.

Here we present the results of analysing 21 ancient Irish genomes. The data were screened for a wide range of pathogenic genotypes and markers. Giving information for the potential effects and prevalence of certain conditions as well as the earliest known confirmation of their presence.

Using records of the remains, we also examined if any displayed phenotypes correlated to identified diseases.

P10. The NLRP3 Inflammasome and related receptors as biomarkers for Atherosclerotic MACE

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Coronary Artery Disease is the largest contributor of CVD, the leading cause of death worldwide. It is caused by atherosclerosis, a build-up of cholesterol in the blood vessels and chronic inflammation. The NLRP3 inflammasome plays a critical role in the secretion of IL-1β, and there is significant evidence that it is involved in the pathogenesis of a number of inflammatory diseases including atherosclerosis. Recent studies demonstrate that particular cell surface receptors namely the scavenger receptor CD36 and the endocannabinoid receptor CB1 are involved in the activation and regulation of the NLRP3 inflammasome and they have also been implicated in the pathogenesis of atherosclerosis. The present study aimed to investigate expression and activation levels of the NLRP3 inflammasome, the CD36 and CB1 receptors in blood samples obtained from patients with atherosclerosis at very high risk of a Major Adverse Cardiac Event (MACE) such as a heart attack. The cell signalling processes involved in NLRP3 inflammasome activation were also investigated in a *THP1 in vitro* model of atherosclerosis. Results to date indicate increased expression of NLRP3 in patients at very high risk of MACE and also demonstrate that THP1 macrophages require both the CD36 and CB1 receptors for optimal NLRP3 expression in response to oxidized LDL. These preliminary findings provide an insight into the mechanism of action of the NLRP3 inflammasome in atherosclerosis and prompt further exploration of this protein complex and its regulatory receptors as potential targets for prognostic and or therapeutic development in the strive towards a more personalised approach to the management of coronary artery disease.

P11. An exploration of *de-novo* mutations underpinning chronic refractory epilepsy

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Approximately 30% of patients with epilepsy are refractory to anti-epileptic drug (AED) treatment and continue to have debilitating seizures that severely impact upon their quality of life. Exome sequencing in encephs etc has illustrated the importance of de-novo variants in the pathogenesis of rare neurological disorders. However, the contribution of *de-novo* mutations to pharmacoresistance in adult epilepsy is uncertain. In this study we investigated whether a trio whole exome sequencing paradigm could be applied to identify genetic causes of chronic, refractory epilepsy.

We selected adult patients (n=5) with onset of seizures after 5 years of age, had failed ≥6 AEDs and were still experiencing >4 disabling seizures per month. Patients were excluded if they had a potentially 'explanatory' lesion on MRI. Parents were exome sequenced to identify *de-novo* mutations and these were assessed bioinformatically for pathogenicity.

We confirmed the presence of coding *de-novo* mutations that were bioinformatically predicted to be functional and damaging in 3/5 patients. One of these occurred in the gene *DNM1L*, which was recently implicated in pharmacoresistant epilepsy (Vanstone *et al*. *EJHG*, 2015;Nov 25). This represents a potential diagnostic yield of 20% however more data is required and more trios are currently being sequenced.

We have demonstrated the potential diagnostic yield of whole exome sequencing in a small number of adult patients with chronic refractory epilepsy. Identifying genetic mutations underpinning this disorder may provide new insight into the underlying biology and offers the potential for therapeutic intervention in the form of precision medicine.

P12. Whole Exome Sequencing to Identify Candidate Mutations for Familial IgA Nephropathy

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IgA nephropathy (IgAN) is the most common form of glomerular nephritis worldwide[1]. Difference in incidences between ethnicities and familial inheritance patterns indicate this is a genetic disorder. An IgAN locus on chromosome 6q22-23 was identified via linkage analysis; however the causal gene remains elusive[2]. We set out to identify mutations underlying familial IgAN using whole exome sequencing.

DNA was collected on 25 (unaffected and affected) individuals across 6 families with IgAN. Families were chosen on the basis of having at least 2 affected members with IgAN. We carried out full exome sequencing on 12 of the affected members from these families. Depending on the pattern of inheritance in a given family, mutations that fitted a dominant, recessive or compound heterozygote model of inheritance were screened for. These variants were then filtered based on being shared between affected individuals within a family, their minor allele frequency, region, function and predicted deleterious nature.

We identified a number of potential candidate mutations in these families and including a mutation in the gene *COL4A5* which was previously described as pathogenic[3]. Mutations in *COL4A5* have previously been found in individuals with Alport syndrome, a disease which is often mistaken for IgAN. We are currently working to confirm these candidate mutations via Sanger sequencing and will be screening for segregation.

References: [1]Bisceglia *et al*. *Am J Hum Genet* 2006;**79(6):**1130-4. [2]Gharavi *et al*., *Nat Genet* 2000;**26:**354-7. [3]Zhou *et al*. *Am J Hum Genet* 1992;**50(6): 1**291-1300.

P13. A computational approach to increase understanding of atherosclerosis

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Atherosclerosis is a chronic inflammatory disorder that is responsible for approximately 71% of incidents of cardiovascular disease. A mathematical model of atherosclerosis has been developed, capturing the cell types and proteins involved in atheroma formation and describing the dynamics of disease progression. This is the first model of this type to be developed using open systems biology standards. We have predicted tertiary protein structures for all the proteins involved in this atherosclerosis model and all of their recorded mutations, using phase 3 sequence data obtained from the 1000 Genomes Project. By comparing the electrostatic potentials of these tertiary structures, we predict how the dynamics of atherosclerosis stratifies across population subgroups.

P14. A feasibility study investigating whether methylation of the oxytocin receptor (OXTR) can serve as a potential biomarker for response to oxytocin administration in women during and after labour.

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The aim of this pilot study was to test the feasibility of carrying out a large scale study using this design to investigate whether methylation of the oxytocin receptor (OXTR) can serve as a potential biomarker for response to oxytocin administration in women during and after labour.

Background: Oxytocin is a nine-amino acid peptide with hormonal and neurotransmitter functions during labour and lactation. We hypothesised that a difference in methylation levels of the oxytocin

receptor (OXTR) gene may impact the woman's ability to become established in labour and her response to oxytocin administration.

Method: Blood samples were taken pre-birth and postnatally from 21 women and subjected to DNA methylation analysis of the OXTR gene by pyrosequencing. Methylation status of CpG sites -924 and -934 upstream from the initiation transcription site (ITS) of the OXTR gene was determined. Expression of the OXTR gene before and after birth was measured using qPCR. Global methylation levels were examined using Luminometric Methylation Assay (LUMA).

Results: We found both hypo and hypermethylation of OXTR promoter at CpG sites -924 and -934 in individual samples, however we observed no profound changes in overall OXTR methylation levels within the patient cohort at these CpG sites. We found a strong correlation between OXTR promoter methylation levels found in whole blood and those found in matched PMBC samples. Global methylation analysis using Luminometric Methylation Assay (LUMA) revealed no significant differences between whole blood and PMBC.

Conclusions: A larger sample is required to determine whether OXTR methylation status is predictive of response to oxytocin administration. Whole blood sampling is a suitable alternative for OXTR methylation analysis in a larger cohort of women undergoing labour.

P15. Investigating microRNAs as Serum Markers of Elevated Blood Pressure

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Background: Cardiovascular disease (CVD) is the leading cause globally of morbidity and mortality. microRNAs (miRNAs) are small, non-coding RNAs which have a fundamental role in the pathology of various diseases including CVD. Circulating serum levels of miRNAs have been proposed as potentially valuable markers of heart failure, stroke, myocardial infarction and arterial hypertension, but the specific miRNAs involved and their function remains unclear. Therefore, this pilot study aims to profile miRNA expression in premature CVD patients to identify which miRNAs correlate best with hypertension.

Methods: The Multiplex Circulating miRNA Assay with Firefly™ Particle Technologies was used to profile 68 miRNAs on a cardiology focus panel in serum samples from 170 premature CVD patients recruited from Altnagelvin Area Hospital and screened for the C677T polymorphism in methylenetetrahydrofolate reductase, a risk factor for hypertension. Samples were collected at baseline and following intervention with riboflavin, a co-factor for MTHFR, which significantly lowers blood pressure specifically in adults with this polymorphism. Statistical analysis was used to correlate miRNA expression with blood pressure, MTHFR genotype and other relevant clinical data.

Results: The assay successfully measured miRNA expression in the sample set. miRNAs which expressed differentially between MTHFR genotype groups were highlighted and the functional significance of these miRNAs was assessed using bioinformatics to identify target genes involved in CVD.

Conclusions: The data provides further evidence that using specific miRNAs as serum markers could aid early prediction of CVD and may lead to better diagnostic modalities and therapeutic regimes.

P16. Investigating the association between genetic and epigenetic variability in the *5-HTT* and *BDNF* genes and depression in young adults.

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Gene-environment interactions, particularly in genes related to regulation of serotonin and neuronal function, have been implicated in the aetiology of depression. Allelic variations in the 5' flanking transcriptional region of the serotonin transporter gene (5-HTTLPR) and higher levels of promoter DNA methylation are associated with depression. Brain derived neurotrophic factor (BDNF) plays an important role in neuronal differentiation and survival, and is also involved in regulation of serotonin. A single nucleotide polymorphism in the BDNF gene, leading to a valine to methionine substitution at codon 66 (Val66Met), and increased methylation of the BDNF promoter have also been associated with depression. The goal of this study is to determine whether length of the 5-HTTLPR, prevalence of the Val66Met polymorphism of the BDNF gene and DNA methylation in both 5-HTT and BDNF promoter regions are associated with depression in the student population. First year students provided a saliva sample for genetic analysis and completed an online mental health survey. Presence and severity of depression was determined from survey responses based on DSM-IV criteria. Length of the 5-HTTLPR was determined by PCR and gel electrophoresis and presence of the SNP at BDNF rs6265 and examined using restriction fragment length polymorphism analysis. Bisulphite-treated DNA was amplified by PCR and pyrosequencing assays used to determine methylation patterns of *BDNF* and *SERT*. Our preliminary findings suggest that genetic and epigenetic variation in the 5HTT and BDNF genes are associated with depression in the student population and may be candidate biological markers to assist in diagnosis.

P17. The potential role of *Propionibacterium acnes* in prostate oncogenesis

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BACKGROUND: Prostate cancer is the most common male cancer in the UK, where it kills approximately 11,000 men annually. There has been growing interest in the role played by the anaerobic bacterium Propionibacterium acnes, an important component if the skin microflora, in the aetiology of the condition via a chronic, asymptomatic infection of the prostate leading to oncogenesis.

METHODS: A quantitative real-time PCR (qRT-PRC) assay for retrospective detection of P. acnes in formalin-fixed paraffin embedded sections from archived prostate samples was developed. An in vitro infection model of prostate infection with P. acnes is being optimised, which should allow us to get insight into the dysregulation P. acnes infection causes in prostate epithelial cells.

RESULTS: A total of 81 biopsy samples, representing one or both prostate lobes, were examined from 53 patients with prostate carcinoma, versus 111 samples from 60 patients whose biopsies were histologically normal, and the assay revealed that 35% of cancerous prostate samples were positive for the presence of P. acnes, compared with only 8% of the disease-free samples ($p<0.001$). Transcriptomic studies of chronically infected epithelial cells revealed a significant dysregulation of genes, previously associated with prostate cancer development, progression and metastasis.

CONCLUSIONS: Our study reveals that P. acnes is significantly associated with cancerous prostate tissue and has a capacity to initiate a host response in vitro, suggesting it may stimulate oncogenesis as a result of a chronic infection. Investigation is needed of the association of different phylogenetic types of P. acnes and their ability to initiate molecular dysregulation resulting in oncogenesis in vitro.

P18. Whole exome and total RNA sequencing reveals candidate drivers in the development of oral squamous cell carcinoma.

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Oral squamous cell carcinoma (OSCC) is one of the top ten most prevalent cancers in the world. Prognosis is poor and quality of life is commonly reduced for patients who survive. OSCC is thought to progress via a premalignant stage called dysplasia. Effective treatment of dysplasia prior to malignant transformation, or the ability to more accurately predict the 10-20% of dysplasias that will progress to OSCC, is an unmet clinical need.

With the aim to better understand the biology of OSCC development, and attempt to identify potential markers of early disease and therapeutic targets, we performed parallel whole exome sequencing and total RNA sequencing on 16 micro-dissected formalin-fixed paraffin embedded dysplasia and their associated OSCC. These are the largest omic analyses on matched patient samples from the oral cavity in non-HPV infected patients where all dysplasias are associated with progression to OSCC, that has been performed to date.

Whole exome analysis revealed that every OSCC and adjacent associated dysplasia sample did have a common clonal ancestor, with many shared potential drivers of progression, but that there is also considerable genomic heterogeneity between associated pre-invasive and invasive disease, as seen in a previous study[1]. RNAseq analysis revealed differences in the immune cell signatures present at different disease stages, distinguished early events in pathogenesis from later events and identified several novel coding and non-coding candidates with potential involvement in oral dysplasia development and malignant transformation. These findings merit further investigation in a larger retrospective longitudinal study of patients with oral dysplasia.

[1]Wood HM, Conway C, Daly C, *et al*. The clonal relationships between pre-cancer and cancer revealed by ultra-deep sequencing. *J Pathol* 2015; **237:**296-306.

P19. Evaluation of Potential Mitochondrial Therapies using a Novel Complex I Assay

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Many disorders involving tissues, which have significant energy requirements, involve mitochondrial dysfunction often due to mutations affecting the mitochondrial genome. Some such mutations can involve genes coding for subunits of complex I of the electron transport chain leading to a complex I deficiency in disorders such as Leber Hereditary Optic Neuropathy (LHON) amongst others. Mitochondrial dysfunction leads to a lack of energy production and ultimately the death of the cell. In disorders such as LHON, retinal ganglion cells (RGCs) are affected, leading to retinal dysfunction. These observations have prompted interest in exploring innovative therapeutics to modulate mitochondrial disorders involving complex I deficiency. The Farrar laboratory has explored candidate gene therapies for complex I deficiency using Ndi1, a yeast gene which is a complex I homologue.

In order to test the efficacy of candidate therapies, we have developed a robust, empirical assay of mitochondrial function. Previous assays measured the level of NADH oxidation in a sample, both before and after rotenone as a measure of complex I activity. To optimally distinguish between the activity of complex I and the potential therapeutic, the assay was modified with the addition of a second inhibitor which allowed specific measurement of the therapeutic, such as Ndi1. Given that this is an in vitro assay, it enables large-scale screening of potential therapeutics and ensures only those that show strong evidence of efficacy are then tested in vivo. In combination with other quantitative assays such as Reactive Oxygen Species (ROS) generation this allows detailed evaluation of the health of mitochondria within a sample.

P20. A Study of Genes that Function in the Centrosome for Involvement in the Aetiology of Schizophrenia and Associated Cognitive Deficits.

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Schizophrenia is an adult-onset mental illness with that impacts cognitive function. The largest GWAS has revealed 108 loci associated with schizophrenia risk but how variation affects genes and impacts brain function to increase risk is largely unknown.

The centrosome is the microtubule organising centre of the cell and seeds the growth of the primary cilium. The disproportionate number of brain disorders associated with centrosomal genes suggests the organelle underlies normal brain and cognitive development. Schizophrenia is neurodevelopmental and cognitive deficits are a core element of the disorder. We hypothesise that some of the newly identified risk genes for schizophrenia will function in the centrosome and variants in these genes will be associated with cognitive deficits.

Cross-referencing genes with centrosomal functions with genes from schizophrenia GWAS, identified six candidate genes; SDCCAG8, MAD1L1, GIGYF2, MPHOSPH9, PRKD1 and MAPK3. The effect of risk SNPs on cognition was examined using an Irish dataset of psychosis cases and controls (n=1,236) using linear regression. Among the associations identified, the SDCCAG8 risk SNP was shown to affect attribution style, a measure of social cognition (P=0.001). The MAD1L1 risk SNP was associated with poorer performance on episodic memory tasks (P=0.003).

A suitable replication dataset was not available for social cognition measures. We attempted replication for episodic memory results in UK and German samples but results were non-significant. Overall, we have identified a number of schizophrenia risk genes that function in the centrosome but further larger datasets are required to establish a role for these genes in cognition.

P21. Analysis of Candidate Schizophrenia Risk Gene *CHD7* and Associated Interacting Genes Suggests a Role in Cognition for Novel Network of Genes.

L Whitton[1], D Cosgrove [1], C Clarkson[2], D Harold[3,4], K Kendall[5], A Richards[5], K Mantripragada[5], MJ Owen[5], MC. O'Donovan[5], J Walters[5], A Hartmann[6], B Konte[6], D Rujescu[6], WTCCC2, M Gill[3], A Corvin[3], S Rea[2], G Donohoe [1], DW Morris[1]

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Epigenetic mechanisms are an important heritable and dynamic means of regulating various genomic functions, including gene expression to orchestrate brain development. These processes when perturbed are thought to contribute to schizophrenia (SZ). A core feature of SZ is cognitive dysfunction. GWAS have identified 108 genomic loci associated with SZ risk, containing 350 genes. My aim was to identify genes that have epigenetic functions which map to loci associated with SZ, and to test the associated SNPs for association with cognitive deficits. Risk SNPs in 8 genes: *BCL11B, CHD7, EP300, EPC2, GATAD2A, KDM3B, RERE* and *SATB2* were analysed using an Irish dataset of psychosis cases and controls (n=1235) who had completed tests across 5 cognitive domains. Five of the eight variants had significant associations with at least one cognitive task. Strongest associations were for *CHD7* (rs6984242) for IQ (p=0.001) and episodic memory (p=0.007). These results did not replicate in independent samples. We link rs6984242 to *CHD7* via a long range expression quantitative trait loci (eQTL) and *CHD7* has not been previously reported as a candidate risk gene for SZ. To further explore its novel association with SZ, we identified a set of 45 interacting genes and used SNPs across these genes to develop a polygenic risk score for SZ, independent of *CHD7* itself. This score was tested for association with cognitive function. Significant associations($p<0.05$) were found with 3 measures of IQ, 2 measures of episodic memory and 1 measure of working memory, suggesting a role for this gene network in cognition.

P22. Folate-sensitive differentially methylated regions: are we trying to predict the unpredictable?

A Harrison[1], K Pentieva[2], M Ozaki[1], H McNulty[2], A Parle-McDermott[1]

[1]Nutritional Genomics Group, School of Biotechnology, Dublin City University, Dublin 9, [2]Northern Ireland Centre for Food & Health, School of Biomedical Sciences, University of Ulster, Coleraine, Northern Ireland.

The relevance of nutrition and other environmental influences on epigenetic modifications including DNA methylation is a topic of considerable interest. Folate One Carbon Metabolism (FOCM) is the principal supplier of the methyl groups required for DNA methylation, giving folate status a strong biological plausibility of having an impact on an individual's and an offspring's DNA methylation profile at both the mitotic and meiotic level.

We sought to identify DNA methylation sites in the human genome that are sensitive to folate status i.e., Folate-sensitive Differentially Methylated Regions (FS-DMR) using a folic acid intervention trial in pregnant women known as FASSTT (Folic Acid Supplementation in the Second and Third Trimesters). To minimize the amount of DNA methylation 'noise' due to non-folate related factors such as other environmental stimuli and individual genetic variation, we

compared the DNA methylation profile of the same individual pre- and post- intervention to identify putative FS-DMR. We selected six healthy pregnant women, three from the folic acid intervention arm and three from the placebo arm of the trial. We performed MeDIP (Methylated DNA Immunoprecipitation) on all 12 samples and hybridized to a Roche Nimblegen Delux 2.1M promoter array. While we observed DNA methylation changes pre- and post- folic acid intervention in each individual, *the actual DNA methylation sites were not consistent across all three individuals*. Of course, it is possible that a more in-depth Next Generation Sequencing approach might yield our elusive FS-DMRs. However, the published literature to date does not appear to support such a promise.

P23. A Novel Approach to Promoter Identification – Development of a Ganglion Cell-specific Promoter for AAV-mediated Gene Therapy

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The loss of retinal ganglion cells (RGCs) is a hallmark of a number of retinopathies. There are a number of gene therapies being developed that have shown efficacy in preserving RGCs when administered using an AAV vector. Localising expression of any therapeutic to the target cell type (ganglion cell layer, GCL) would represent a significant optimisation of the approach. The packaging capacity of AAV (4.7kb) imposes a limit on the size of promoters and genes relevant for AAV-mediated gene delivery. Few GCL-specific promoter sequences have been defined of a size suitable for use in AAV-guided gene expression.

Exploring this, a panel of genes was chosen with GCL-limited expression profiles. A pipeline program was developed that analysed regions upstream of these genes for sequence conservation across placental mammals (as a proxy for putative promoter function), weighted by enriched GCL expression levels. Adopting this strategy, ganglion cell promoter 1 (GCP1), demonstrating the key features outlined above, was identified. To test its function, GCP1 (2.2kb in size) was engineered into an AAV2 virus expressing EGFP.

Here we demonstrate the effectiveness of GCP1 in localising EGFP expression to the GCL when administered via intravitreal injection. Furthermore, absence of EGFP expression was demonstrated when targeted towards photoreceptors via subretinal injection, verifying GCP1 tissue-specificity. Expression of AAV2.GCP1-EGFP was compared to expression from a non-specific promoter construct, AAV2.CMV-EGFP. GCP1-EGFP was shown to provide equivalent expression to CMV-EGFP in the GCL. GCP1 thus offers a tissue-specific promoter option, suitable for deployment within AAV vectors without compromising functionality.

P24. Targeting hypoxic prostate tumours using the novel hypoxia-activated prodrug OCT1002 inhibits expression of genes associated with malignant progression.

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Purpose: Hypoxia is a common hallmark of the tumour microenvironment. Recently we have shown the anti-androgen bicalutamide induces profound hypoxia in prostate tumours in vivo. This resulted in the promotion of epithelial to mesenchymal transition. Here we target tumour hypoxia using a novel unidirectional hypoxia-activated prodrug OCT1002 to enhance the anti-tumour effect of bicalutamide.

Experimental Design: The effect of OCT1002 treatment on LNCaP-luc cells was measured in normoxia and hypoxia *in vitro*. *In vivo*, tumour growth and lung metastases were measured in mice treated with bicalutamide, OCT1002 or a combination. Dorsal skin fold chambers were used to image tumour vasculature *in vivo*. Longitudinal genetic changes in tumours were analysed using PCR.

Results: Reduction of OCT1002 to its active form (OCT1001) decreased LNCaP-luc cell viability. In LNCaP-luc spheroids, OCT1002 caused increased apoptosis and decreased clonogenicity. *In vivo*, treatment with OCT1002 alone or with bicalutamide, showed significantly greater tumour growth control and reduced lung metastases compared to controls. Re-establishment of the tumour vasculature following bicalutamide-induced vascular collapse is inhibited by OCT1002. Significantly, the up-regulation of *RUNX2* and its targets caused by bicalutamide alone were also blocked by OCT1002.

Conclusions: OCT1002 selectively targets hypoxic tumour cells and enhances the anti-tumour efficacy of bicalutamide. Furthermore, bicalutamide causes changing genetic profiles during treatment, with development of a more malignant genotype; OCT1002 can block this effect. This study indicates that more attention should be attached to understanding genetic changes that may occur during treatment. Early targeting of hypoxic cells with OCT1002 can provide a means of inhibiting prostate tumour growth and malignant progression.

P25. Regulation of miR-200c and miR-141 by methylation in prostate cancer

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Background: In prostate cancer (PCa), abnormal expression of several microRNAs (miRNAs) has been previously reported.

Increasing evidence shows that aberrant epigenetic regulation is a contributing factor to their altered expression in cancer. In this study we investigate whether expression of miR-200c and miR-141 in PCa is related to the DNA methylation status of their promoter.

Methods: PCR analysis of miR-200c and miR-141, and CpG methylation analysis of their common promoter, was performed in PCa cell-lines and in FFPE prostate biopsy specimens. The functionality of miR-200c and miR-141 expression in prostate cancer cells was assessed by a series of in vitro bioassays.

Results: miR-200c and miR-141 expression correlates inversely with the methylation status of the miR-200c/miR-141 promoter in PCa cells. In PC3 cells, miR-200c and miR-141 expression is elevated by treatment with the demethylating agents suggesting their expression is linked to methylation. Expression of miR-200c and miR-141 in prostate biopsy tissue was inversely correlated with methylation in CpG sites closest to the miR-200c/miR-141 loci. Over-expression of miR-200c in PC3 cells inhibited growth and clonogenic potential, as well as inducing apoptosis. Expression of the genes DNMT3A and TET1/TET3 were down-regulated by miR-200c and miR-141 respectively. Finally, treatment with the soy isoflavone genistein caused demethylation of the promoter CpG sites closest to the miR-200c/miR-141 loci resulting in increased miR-200c expression.

Conclusions: Our findings provide evidence that miR-200c and miR-141 are under epigenetic regulation in PCa cells. Profiling their expression and methylation status may have potential in the improved diagnosis and prognosis of PCa.

P26. Folic acid supplementation in late gestation and the effects on DNA methylation in the offspring

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Increasingly accurate surveys of human health throughout the life course has led experts to propose that stresses on the child while still in the mother's womb can affect the individual's health much later in life. Such long-term effects on health are thought to be mediated by a semi-permanent trace on the genes of the affected person called an epigenetic mark. Epigenetic mechanisms, such as DNA methylation, are dynamic during pregnancy whereby epigenetic marks are seeded which persist throughout the lifetime of the developing child. It has been suggested that these patterns may be altered by the mother's diet, particularly folate – a key component in the DNA methylation cycle. Currently, mothers are universally recommended to supplement their diet with 400μg folic acid/day as a preventative measure against neural tube defects in the offspring prior to and during the first trimester. However, there remains no clinical recommendation as to whether mothers should continue supplementation during the final two trimesters and the potentially heritable effects on DNA methylation. Observational studies have suggested that folate-rich maternal diets are associated with changes in DNA methylation of the child during this period of gestation. We present here the results of a randomised control trial (FASSTT study) examining the effects of folic acid supplementation in late gestation (week 12 onwards) on DNA methylation of several gene classes in offspring cord blood samples. We report small but significant sex-specific differences between the two intervention groups. These preliminary results indicate that folic acid supplementation throughout pregnancy may exert significant effects on cord blood DNA methylation.

P27. Whole exome sequencing for the identification of variants associated with new-onset diabetes after transplantation

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[1]Nephrology Research Group, Centre for Public Health, Queen's University Belfast, [2]Regional Nephrology Unit, Belfast City Hospital

Introduction: New-onset diabetes after transplantation (NODAT) is a common complication of kidney transplantation which increases risk of subsequent graft failure, cardiovascular complications and death. NODAT is defined as the new requirement for oral hypoglycaemic agents or insulin as a result of hyperglycaemia after renal transplant. The first genome wide association study (GWAS) for NODAT was published by our group in 2014; seven of the eight top-ranked, common SNPs are implicated in β-cell apoptosis.

Methods: To further understand the genetic architecture of the NODAT phenotype we used whole exome sequencing for 134renal transplant recipients from a Northern Ireland renal transplant cohort. We sequenced 53 individuals with NODAT (cases)and 81 transplant recipients without NODAT (controls). Library preparation was performed using the Ion TargetSeq™ Exome Kit with samples sequenced on an Ion Torrent Proton sequencer. TheIon OneTouch 2 for emulsion PCR and Ion Enrichment System were used. Association analysis was performed using PLINK Version 1.9 to identify variants associated with NODAT (with age and weight at transplant included in the regression model).

Results: Following appropriate quality control, initial analysis identified 6 variants nominally associated with NODAT (P_{trend}<1x10^{-5})using the test for trend. The top two hitsrs2305765 (P_{trend}=2.50x10^{-6}; P_{LR}=1.0x10^{-4} OR:0.07(95% CI:0.02-0.26)) andrs8110964 (P_{trend}=4.47x10^{-6}; P_{LR}=1.4x10^{-4} OR:0.04 (95% CI:0.01-0.20))were in linkage disequilibrium (r^2=0.86) in the *MYO9B* gene. Variants in this gene have previously been associated with autoimmune diseases including type 1 diabetes. We propose *MYO9B* as a candidate gene for NODAT predisposition in immunosuppressed renal transplant recipients.

P28. Provision of a genetic testing service for five rare diseases in the Irish Traveller population: 'The story so far'

Michael Sweeney[1], Brónagh o hIcí[1], Ania Feder, David E. Barton[1,2], Jill Casey[2], SallyAnn Lynch[1,3], Shirley McQuaid[1]

[1]Dept. of Clinical Genetics (DCG), Our Lady's Children's Hospital, Crumlin, Dublin 12. [2]School of Medicine & Medical Science, University College Dublin, Dublin 4, [3]Children's University Hospital, Temple St., Dublin 1

The Irish Traveller community has a high incidence of autosomal recessive (AR) disorders due to consanguinity. The Division of Molecular Genetics at the DCG offers genetic testing, primarily to members of this community, for five specific pathogenic mutations found in five AR disorders. The pathogenic mutations are detected by bi-directional Sanger sequencing and the service includes:

Gene	Disorder/ Disease	Phenotype
LARS (leucyl-tRNA synthetase)	Infantile Liver Failure Syndrome 1 (ILFS1)	Infantile hepatopathy with failure to thrive (FTT) and developmental delay.
MCM4 (minichromosome maintenance 4)	Natural Killer Cell & Glucocorticoid Deficiency with DNA Repair Defect (NKGCD)	FTT, adrenocorticotropin hormone (ACTH) resistance, familial glucocorticoid deficiency (FGD), mosaic Fanconi anaemia and recurrent infections due to NK cell deficiency.
STRA6 (stimulated by retinoic acid 6 gene)	Autosomal recessive isolated colobomatous microanopthalmia (MCOPS9)	Microphthalmia, anophthalmia, coloboma. Specific *STRA6* mutation can also cause the Matthew-Wood syndrome [anophthalmia/ severe microphthalmia, with pulmonary hypoplasia/ aplasia]
LEPRE1 (Leucine- and proline-enriched proteoglycan 1) *syn. PH31*(prolyl-3-hydroxylase-1)	Type VIII Osteogenesis Imperfecta,	Variable phenoptype of bone fragility, susceptibility to fracture, short stature, bowing of the long bones and can be perinatally lethal.
ATP8B1 (ATPase, Class I, Type 8B, Member1)	Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) *syn.* Byler disease	Hepatic and systemic accumulation of bile acids, hepatic fibrosis, end-stage liver disease and growth retardation.

This study will detail (1) the service offered to users, (2) an audit of the test requests received over the last two years, (3) the challenges encountered in offering this unique service and (4) some interesting family pedigrees.

P29 The role of miR-210 in Prostate Cancer tumour development

N McElhatton, CP Walsh, DJ McKenna

Genomic Medicine Research Group, Biomedical Sciences Research Institute, Ulster University, Coleraine, BT52 1SA.

Background: Hypoxia in prostate tumours has been linked with promotion of disease progression and metastasis. miR-210 is a microRNA which is apparently affected by hypoxia, but this relationship has not been extensively studied in a prostate cancer setting. Therefore, in this study, we investigate the link between hypoxia and miR-210 in prostate cancer cells.

Methods: We have used 2D and 3D cell prostate cell models of hypoxia to investigate the functionality of miR-210. Expression levels of miR-210 have been measured by qPCR and functional bioassays used to examine its effect on prostate cell behaviour. Target genes have been identified and bioinformatic analysis has been employed to investigate a clinical significance for miR-210 in prostate cancer.

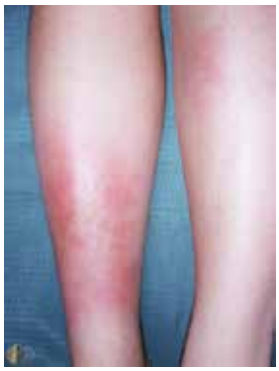
Results: miR-210 is induced by hypoxia in prostate cancer cell-lines. Over-expression of miR-210 impacts upon target genes, including SP1 and TPD52, which in turns affects cell proliferation. Data-mining of online repositories of clinical data and bioinformatic analysis of miR-210 cellular networks reveal that miR-210 plays a key role in a number of important cell processes, the dysregulation of which can lead to development of prostate cancer.

Conclusions: We propose that miR-210 could be an important microRNA in the pathogenesis of prostate cancer and has potential as a biomarker in this disease.

Curiositas (General Practice)

UNDERGRADUATE QUIZ

A 50 year woman presented to her GP with a 2 week history of a dry, intermittent, non-productive cough. She reported puffiness around her ankles and wrists. One week later she returned complaining of 'sweats' and arthralgia. A rash was present on her lower legs. Bloods were normal apart from an ESR of 24 mm/h.



Re-produced from DermNetNZ.org (http://creativecommons.org/licenses/by-nc-nd/3.0/nz/), no changes made

1. What is the rash?
2. What is the most likely diagnosis?
3. As the patient's GP, what radiological investigation would you request and what would you expect to see?

Dr Kieran McGlade (General Practitioner) and Dr Rachel Martin (GPST3 Research Registrar), Dunluce Health Centre.

HISTORICAL QUIZ

Can you name these two individuals and their significance to general practice in Northern Ireland?

Image 1

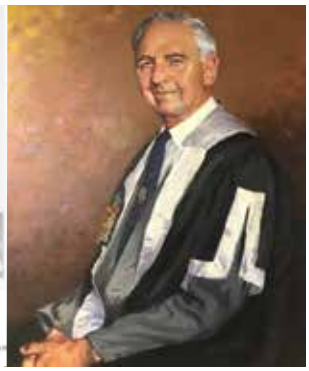


Image 2

Dr Nigel Hart and Dr Jenny Johnston (Senior Lecturers (Education), Centre for Medical Education, Queen' University Belfast). Images produced with the permission of the Department of General Practice, QUB.

CONTINUING MEDICAL EDUCATION QUIZ

A 69 year old non-smoking male attended the surgery giving a one week history of a cough productive of green sputum. He was diagnosed with community acquired pneumonia, issued an antibiotic, and advised to return if he was not improving in four weeks. Four weeks later, he had ongoing sputum production. A full blood picture revealed the following:

Complete Blood Count

Patient ID	Patient Name
Sex	Date Of Birth
Collected	Reported
Requested by	Requested from
Order Number	Status
Relevant Information	

Additional Information

Results:

Test Name	Result	Units	Ref. Range	Abnormality
HGB	145	g/L	130-180	Normal
HCT	0.436	l/l	0.40-0.54	Normal
WBC	9.4	10^9/l	4.0-10.0	Normal
PLT	*582	10^9/l	150-450	Above high normal
RBC	4.51	10^12/l	4.5-6.5	Normal
MCV	96.7	fl	76-100	Normal
MCHC	333	g/L	320-360	Normal
MCH	*32.2	pg	27-32	Above high normal
LYMPH	1.7	10^9/l	1.0-3.50	Normal
NEUT	6.9	10^9/l	2.0-7.5	Normal
BASO	*0.0	10^9/l	0.01-0.1	Below low normal
EOSIN	0.3	10^9/l	0.04-0.4	Normal
MONO	0.5	10^9/l	0.2-0.8	Normal

* Denotes Abnormal Result, ** Please check for comments where superscript characters exist

1. What is the most significant abnormality?
2. What can this abnormality commonly be due to?
3. What examination(s) would you consider:
   a. In this male patient?
   b. If the patient were female?
4. How would you proceed now?

Dr Carl Brennan (GPST3 Research Registrar, Carryduff Surgery) and Dr Paul Hamilton (Specialty Registrar in Chemical Pathology) Belfast Health and Social Care Trust.

POSTGRADUATE QUIZ

A 13 year old boy was brought by his mother to his General Practitioner with concerns about a skin lesion. The lesion on his upper chest appeared and grew over a 3 month period. He had no history of significant sunburn and no family history of melanoma. There was no history of bleeding, but the lesion had become itchy. On gross examination the lesion was 5x4mm, raised and darkly pigmented. The boy's mother was concerned that the lesion may be sinister in nature. How would you address these concerns?

Dr Nigel Hart and Dr Finbar McGrady (Academic General Practitioners, Centre for Medical Education, Queen's University Belfast). The authors would like to thank the patient and parents for their informed consent for use of these images.

ANSWERS See overleaf

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

Curiositas: Answers

UNDERGRADUATE QUIZ

1. The rash is erythema nodosum - the picture shows the classical red lumps (subcutaneous nodules) that often form on the shins, or less commonly on the thighs or forearms.
2. The dry cough, arthralgia, night sweats and erythema nodosum all point towards a probable diagnosis of sarcoidosis.
3. A chest x-ray would be appropriate and may show bilateral or paratracheal hilar lymphadenopathy

Dr Kieran McGlade (General Practitioner) and Dr Rachel Martin (GPST3 Research Registrar), Dunluce Health Centre.

HISTORICAL QUIZ

In 1958, Prof John Pemberton (Image 1) was appointed to the Chair of Social and Preventive Medicine at QUB.1 Pemberton believed that medical students should spend more time in General Practice. Among the benefits, he highlighted: "opportunities of seeing disease in its early stages" and "practising preventive medicine".2 He also recognised how a medical student, visiting the patients' homes with a doctor, would receive a practical demonstration of; the importance of overcrowding, ignorance of the simple rules of hygiene and strained human relationships in the aetiology of ill health.

In 1964 Dr William George Irwin (Image 2) was appointed as Chair of General Practice (the 4th in the UK). Professor Irwin was the first UK practitioner to establish a practice-linked department and following 9 years of hard work, 4 practices came together in the newly built Dunluce Health Centre. The centre offered tutorial rooms, a small library and state-of-the-art consulting rooms that, with patient consent, could avail of one-way mirrors and video cameras to facilitate learning. At the height of GP involvement in the QUB medical curriculum, all students took part in a family attachment during first and second year, with fourth year (four weeks) and fifth year (six weeks) mandatory clerkships based in GP and the wider community.

1. Harland R. The history of the teaching of the specialty of general practice in Northern Ireland. Presidential address to the Ulster Medical Society. *Ulster Med* J. 2001;**70(1)**: 5.
2. Pemberton J. Illness in general practice. *Br Med J*. 1949;**1(4598)**: 306.
3. Bengoa R. Systems, Not Structures - Changing Health and Social Care. https://www.health-ni.gov.uk/publications/systems-not-structures-changing-health-and-social-care-full-report Accessed 29th Nov 2016
4. O'Neill, M. Health and Wellbeing 2026: Delivering Together https://www.health-ni.gov.uk/publications/health-and-wellbeing-2026-delivering-together Accessed 29th Nov 2016.

Dr Nigel Hart and Dr Jenny Johnston (Senior Lecturers (Education), Centre for Medical Education, Queen' University Belfast).

CONTINUING MEDICAL EDUCATION QUIZ

1. Thrombocytosis.
2. Secondary causes[1]
   - infection
   - cancer e.g. of lung, gastrointestinal tract, ovaries or breast
   - trauma
   - splenic dysfunction
   - blood loss
   - iron deficiency anaemia
   - medication
3. A physical examination may incorporate assessments of the:
   a. Respiratory system - assessing for infection and signs of malignancy, and gastrointestinal system, assessing for signs of bleeding, ascites, organomegaly or other masses.
   b. Breast and pelvic examination for signs of malignancy.
4. Request an urgent chest x-ray and consider a red flag referral to a secondary care respiratory team due to a persistent chest infection with thrombocytosis[2].

Thrombocytosis can be a primary problem, or secondary to another condition.. It has been suggested that up to 40% of patients with a platelet count greater than $400x10^9$/L and no obvious secondary cause, have an underlying cancer. Such cancers are likely to be solid tumours[3,4]. Although this example quotes $400x10^9$/L, some laboratories have a reference range of $150\text{-}450x10^9$/L. Clinicians should consider underlying cancer in the absence of an identifiable secondary cause when the platelet count exceeds the reference range. The significance of thrombocytosis in relation to cancers is recognised in the NICE guideline for the recognition and referral for suspected cancer[2].

1. Platelet count. 2015; Available at: http://labtestsonline.org.uk/understanding/analytes/platelet/tab/test/). Accessed November, 16th, 2016.
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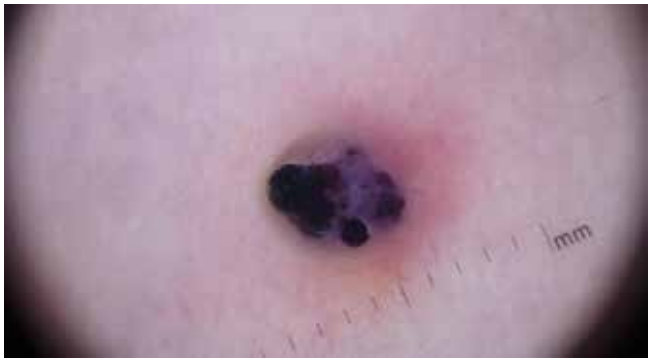
3. Lin RJ, Afshar-Kharghan V, Schafer AI. Paraneoplastic thrombocytosis: the secrets of tumor self-promotion. *Blood. 2014;* **124(2)**: 184-187.
4. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, et al. Paraneoplastic thrombocytosis in ovarian cancer. *NEJM. 2012;* **366(7)**: 610-8.

Dr Carl Brennan (GPST3 Research Registrar, Carryduff Surgery) & Dr Paul Hamilton (Specialty Registrar in Chemical Pathology) Belfast Health & Social Care Trust.

POSTGRADUATE QUIZ

When viewing a skin lesion with the naked eye, the outer surface of the epidermis *(the stratum corneum)* reflects light which reduces the ability to see what is happening in the deeper structures. Dermoscopy using a dermatoscope *(a device that combines a light-source with magnification)* is a non-invasive technique that allows visualization of microstructures of the epidermis, the dermo-epidermal junction and deeper into the dermis[1,2].

The use of dermoscopy has been shown to improve the ability of GPs to diagnose skin lesions as benign or malignant[3]. The lesion in the presented case was examined and photographed using a dematoscope with a camera attached.



Dermatoscopic view of the lesion on the upper chest wall

Dermoscopic examination of the lesion using polarised light is seen in *Image 2.* Dermoscopically this lesion can be described as: blue and purple clods and two structureless black areas with sharply demarcated edges. These findings give the diagnosis of a thrombosed haemangioma. *(Red and blue represent blood in different stages of oxygenation, purple is a mix of the two, and black is extravasated blood that has solidified. The whitish grey area correlates with fibrous stroma within the haemangioma).* On this basis, reassurance was given to the boy and his mother.

1. de Vries E, Coebergh JW. Cutaneous malignant melanoma in Europe. Eur J Cancer 2004; 40:2355–66.
2. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002; 3:159–65.
3. Argenziano G et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006 Apr 20;24(12):1877-82.

Dr Nigel Hart and Dr Finbar McGrady (Academic General Practitioners, Centre for Medical Education, Queen' University Belfast). The authors would like to thank the patient and parents for their kind informed consent for use of these images.

Book Case

The Editor recommends six books for the weary off-duty medic to enjoy.

AURORA: IN SEARCH OF THE NORTHERN LIGHTS.

Melanie Windridge (William Collins 2016. ISBN 978-0-00-815609-1, RRP £18.99 hardback)

I enjoy astrophotography but to take detailed photographs of distant galaxies from my back garden requires a night when there is no cloud, no wind and no moonlight – I don't get to enjoy my hobby very often!

In the last few years, I have turned to "night sky photography" taking photographs of the aurora borealis or phenomena such as noctilucent clouds - it's possible to do this with a digital SLR and a tripod and a little cloud, wind or moonlight doesn't present a major problem. The north coast of Northern Ireland is ideal for this and it's not too hard to choose a spot looking northward with very little light pollution.

I'm always keen to learn more about the aurora borealis and this book by plasma physicist Dr Melanie Windridge combines travelogue, history and up to date physics of our Sun and the Earth's magnetic field. The author travels to many spots associated with the aurora such as Canada and Iceland but also closer to home in Scotland and Scandinavia. Each chapter comprises a separate visit where she examines local culture and history in relation to the aurora, then goes observing with local guides and finally explains one aspect of the phenomenon per chapter and how it can fundamentally affect our radio transmissions, transatlantic flights, GPS and power grids. Our modern electronic world has become increasing vulnerable to the solar wind – a massive solar flare in 1859 resulted in household items such as candlesticks becoming statically charged and telegraph wires worked for hours with the power disconnected! Imagine the chaos if this "Carrington Event" was repeated nowadays – the closest we have come was the Quebec power grid failure in 1989. A very enjoyable combination of travelogue and physics!

THE OUTRUN

Amy Liptrot (Canongate Book 2016. ISBN 978-1-78211-548-9, RRP £8.99 paperback)

Small towns and islands can seem dull and oppressive to the young, so the author, Amy Liptrot, took the first opportunity to leave her native Orkney and travel to the bright lights of London. Her plan was to build on her success in writing short articles and blogs and develop a career in publishing. Initially, things went well but increasing addiction to alcohol resulted in her descent into the seamier side of life and brushes with the law. Eventually, she realises that staying in London can only take her further down and she returns home.

The book describes her isolated existence in Orkney as she struggles with sobriety and putting her life on an even keel. She turns to many of the familiar things such as seabirds, whales, the aurora and the dark night sky that she couldn't wait to leave before. This time around, she uses digital and social media not only to study and appreciate the natural phenomena but also to gain companionship from online communities. Her new interests lead to a conservation job with the RSPB and she joins an Orkney sea-swimming club (!) which in turn leads to scuba-diving amongst the wrecks scattered around the rocky coast. Eventually she rebuilds a stable existence.

This is a book about alcohol addiction and the acknowledgement that recovery is possible but things will be very different afterwards. It's about the rich natural world of Orkney and how to appreciate and share it in the 21st century. It's also very much about how small, isolated communities are embracing the new to preserve the old.

COLD: EXTREME ADVENTURES AT THE LOWEST TEMPERATURES ON EARTH

Ranulph Fiennes (Simon & Schuster UK 2014. ISBN 978-1-4711-2784-7, RRP £7.99 paperback)

In a way, this is another form of addiction. Sir Ranulph takes the reader through his long career as a polar adventurer (I think adventurer is the appropriate term to use here). The expeditions are listed chronologically and it's interesting to read how technology changes from Inuit hand-made fur parkas and map-reckoning to Gore-Tex protective clothing and GPS. I enjoyed the descriptions of drifting on broken shards of pack ice and the hazardous crevasses but a certain recklessness does permeate the book. Some examples:

We could easily have crossed the crevasse, if we had brought a crevasse ladder.

His injuries should not have been fatal but unfortunately, the doctor had not survived.

Then there is the self-surgery on frost-bitten finger tips.

Many of the expeditions follow in the footsteps of previous explorers and the history of the trail-blazers is well written. Often, the modern expeditions are much smaller and man-powered rather than involving dog-teams or even in the early Edwardian stages, Mongolian ponies.

The calorie expenditure from man-hauling sledges is enormous and despite advances in nutrition, severe weight loss is expected – the image of a skeletal Ran after an expedition in the colour plate section is disturbing. Constipation and piles are a consequence of a high calorie, low residue diet.

Often Ran is competing against other nationalities attempting the same route and much emphasis is put on expeditions being unassisted – even the air-evacuation of a sick team member is regarded as "assistance" since his rations will become available for the remaining team.

Eventually age, heart conditions and lack of digits catch up with Ran, so what does he decide to do? – climb Everest! One attempt ends with a severe anginal attack near the summit but eventually he is successful.

IN SHACKLETON'S FOOTSTEPS. A RETURN TO THE HEART OF THE ANTARCTIC.

Henry Worsley (Virgin Books, 2011. ISBN 978-1-905-26493-3, RRP £18.99 hardback)

This is one of my favourite books. In 1908, Ernest Shackleton led an unsuccessful pony-powered expedition to the South Pole. Ninety-seven miles from the pole, he decided to turn back as he knew the team would starve on the return leg – everyone got back safely.

In the years leading up to the Centenary, Henry Worsley, a descendant of one of Shackleton's team planned a repeat expedition along the same route.

This book describes Henry's attempts to get a team of "Shackleton descendants" together and attract sufficient sponsorship to pay for it all. In order to get to their start point, enormous logistic support is required and extremely brave pilots!

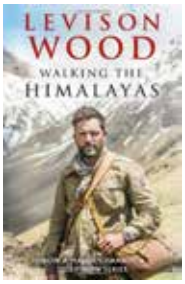
Once out on the ice, he charts their daily progress and contrasts the modern experience with excerpts from Shackleton's diary. Some of the modern photos mirror those taken in 1908.

Henry was older (48 years old in 2008) than the other team members and he describes his fears about his fitness and the need for self-maintenance in the unforgiving climate.

Eventually the team reach the South Pole which is now occupied by an enormous US base. Somewhat surreally, their journey ends at the pole with a greeting from an American officer in a jeep who offers them coffee and breakfast!

I was sad to learn that Henry died on a solo unassisted trans-Antarctic expedition in 2015/16. This was following the route of another unsuccessful Shackleton expedition. Henry's goal was to cross the entire continent by himself, hauling a 150kg sledge with no assistance (not even a sail/kite). Henry got to within 30 miles of his goal but succumbed to malnutrition which resulted in fatal peritonitis.

WALKING THE HIMALAYAS.



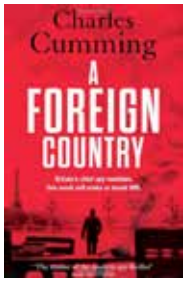
Levison Wood (Hodder and Stoughton, 2016. ISBN 978-1-473-62624-9, RRP £20 Hardback)

This is the book of a Channel 4 television series – I haven't seen the series and you wouldn't guess from reading the book that this was anything other than a modern day trek along the base of the Himalayas through several countries. The walk commences in Afghanistan and proceeds through Pakistan, India, Nepal and Bhutan.

I very much enjoyed the writing style which was sparse and concentrated on Levison's companions, the countryside and the people he meets, rather than himself. There is no journey of self-exploration here, just descriptions of stunningly beautiful but rugged terrain and the people who try to exist here. Some areas are lush and fertile, some are hard and unforgiving. Life can be cheap with remains of lorries littering the valley beneath a crumbling mountain road and rope bridges over snow-melt swollen rivers frequently giving way. Along the route, he makes close friends with his guides and his insights into their personalities and beliefs is one of the strengths of the book. The simmering feud between India and Pakistan over Kashmir makes one realise how little this conflict is reported in the West.

Highlights include meeting the Dalai Lama, who bridges the divide between the spiritual and modern, the commercialisation of Kathmandu and the enforced "Shangri La" happiness of Bhutan. Two colour plate sections illustrate the book. I'd recommend this to anyone who enjoys hill walking.

A FOREIGN COUNTRY



Charles Cumming (Harper, 2013. ISBN 978-0007346431, RRP £4.99 Kindle)

I don't often read spy stories but Charles Cumming was mentioned in Andrew Marr's recent television series about literary genres and I thought I should investigate further. I suppose the heyday of the spy novel was in the 1950s when the dashing hero had to save the world from a crazed madman with links to one superpower or another.

By contrast, there are no plans for world domination here, just a story of what happens when rivalry between two supposedly friendly intelligence agencies boils over into active hostility. Much of the book is based on patient and thorough observation rather than shooting – the first shot is fired on page 350 or so. The insights into the spy's "tradecraft" are illuminating – I didn't realise it was so easy to break into key card hotel rooms!

There is also an undertone of treachery throughout – the hero has already suffered from being the scapegoat for a politically inconvenient mission in the past and he knows that failure to succeed here will result in further isolation and denial of responsibility by those in power.

An interesting, modern take on the spy novel.

Game Changers

THE CHANGING ROLE OF THERAPEUTIC ENDOSCOPY IN GASTROENTEROLOGY: IMPROVING PATIENT OUTCOMES.

P. Agnew, I. Mainie

Department of Gastroenterology, Belfast Health and Social Care Trust

Endoscopy plays a critical role in the staging, sampling and curative resections of gastroenterology cancers, as well as the opportunity for non-surgical palliative techniques.

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been developed for the en-bloc removal of pre-cancerous and early malignant lesions in the GI tract, such as dysplastic Barrett's and early GI cancers.

EMR uses a suction cap or band ligation to snare the lesion, while ESD uses a specialised knife to dissect the submucosa below the lesion.[1] They provide the same curative outcomes with fewer complications than major surgery in early cancers and give a valuable alternative for patients who would not be fit for surgical intervention.

Radio-frequency ablation (RFA) is a technique where a circumferential ablation catheter or direct catheters use heat energy to remove dysplastic cells in Barrett's.[2] It has been shown to produce a high rate of eradication of dysplasia and decrease disease progression.

The introduction of Self Expanding Metal Stents (SEMS) for palliative oesophageal and obstructive colorectal cancer have greatly improved outcomes and decreased complication rates such as stent migration. This in turn improves patient quality of life, reduces the need for risky palliative surgical procedures and decreases re-intervention rates.

The role of endoscopy within the field of gastroenterology is always evolving giving more options for our patients with the aim of continued improvement in outcomes, now and in the future.

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2. Nicholas J. Shaheen, Prateek Sharma, et al. Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. *N Engl J Med May 28*, 2009; **360 (22)**:2277

ANTIFIBROTIC THERAPY IN IDIOPATHIC PULMONARY FIBROSIS

T. Scullion, P. Gorman, E. Gibson, R. Kelly, E. Murtagh, P. Minnis

Interstitial Lung Disease Service: Respiratory Medicine, Antrim Area Hospital, Bush Road BT41 2RL

Idiopathic pulmonary fibrosis (IPF) is a devastatingly progressive disease, characterized by a prognosis worse than many cancers, with a median survival of 3 years. Recent data suggests that Northern Ireland has one of the highest prevalence of IPF in the UK. Over the past decade, there has been a cohesive effort from patients, physicians, scientists and industry partners to find definitive treatments for IPF. Treatment aims have shifted from reversing the disease to slowing or preventing progression.

Two effective antifbrotic therapies are now available which offer hope to patients in slowing the inexorable decline in lung function. Pirfenidone (Esbriet®) a pleiotropic molecule that has antifibrotic, anti-inflammatory and antioxidant effects and Nintedanib (Ofev®) a tyrosine Kinase Inhibitor with potent triple inhibitory properties including activity directed against PDGF, vascular endothelial growth-factor, and fibroblast growth-factor receptors. Pooled analysis of the ASCEND and CAPACITY trials and subgroup analysis of the INPULSIS and TOMORROW trials demonstrate effectiveness in mild disease, currently not recommended by NICE.[1] IPF is often misdiagnosed as COPD as the majority of patients are ex-smokers. For these reasons early and accurate diagnosis of IPF is of paramount importance and requires expertise and multidisciplinary input.

At present there are 8 compounds undergoing phase 2 clinical trials, as well as trials exploring combination therapy with available antifibrotics concomitantly in addition to sildenafil.[2] There is inequity of treatment for Northern Irish IPF patients in comparison to the rest of the UK as our uptake of currently available antifibrotics has been poor and at present patients do not have access to untested novel treatments. Given the similarities to a cancer, difficulties in securing an accurate diagnosis and limited treatment strategies currently available in NI, a regional centre is urgently needed.

1. Guidance N. Pirfenidone for treating idiopathic pulmonary fibrosis Available from: https://www. nice. org. uk/guidance/ta282/resources/guidance-pirfenidone-for-treating-idiopathic-pulmonary-fibrosis-pdf. Accessed June. 2015;19.
2. Fraser E, Hoyles RK. Therapeutic advances in idiopathic pulmonary fibrosis. *Clinical Medicine*. 2016;**16(1)**:42-51.

Ulster Med J 2017;**86(1):**74-75

So you want to be an **Acute Physician**

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Accepted: 15th of November 2016

ACUTE INTERNAL MEDICINE

Acute Internal Medicine (AIM) is a relatively new specialty. In the past most acute medical admissions were managed by Consultants trained in General (Internal) Medicine along with a another specialty such as Respiratory Medicine. As the pressures of the medical take increased and the need for earlier expert input was recognised, certain individuals began to make acute care the focus of their work. Accompanying this was a realisation that the systems of acute care needed to change and Acute Medicine Units (AMU) were developed often with an Acute Physician as the lead. Acute Medicine was given subspecialty status before being recognised as a Specialty in its own right in 2009. It should be stressed that Acute Medicine is not the same as Emergency Medicine, although the two specialties work closely together.

The role of the Acute Physician encompasses the whole of acute care:

- Clinical - the prompt practical management of acute presentation of medical illness and the management of medical patients in an in-patient setting, often including the care of patients requiring more intensive levels of care than would be generally managed in a medical ward. In many units the Acute Physicians will be responsible for the first 24 – 72 hours of patients care; after which they may be well enough for discharge or triaged on to the appropriate inpatient specialty. Some units operate a 'next day specialty triage' system.
- Management and leadership within an acute medical unit – many acute physicians will be in charge of the Acute Medicine Unit with sessional input from other Internal Medicine trained colleagues
- Development of new patient pathways and services to maximise safe, effective care, for example, many AMUs now have Ambulatory Care facilities.

TRAINING

The first Acute Physicians were enthusiasts from the pool of G(I)M trained consultants but as AIM was acquiring specialty status it was recognised that an appropriate training programme was required. (Though many Consultants are currently still appointed from training programmes in G(I)M.)

Following completion of the Foundation Programme, training in Acute Medicine can start with either Core Medical Training (CMT) or, in some deaneries, Acute Care Common Stem (ACCS). In Northern Ireland recruitment is through CMT, and achieving the MRCP(UK) is necessary. Entry to specialty training is then via competitive interview.

Once successfully appointed, the AIM programme involves rotations through Respiratory Medicine, Cardiology, Care of the Elderly and Intensive Care Medicine, as well as time spent in the Acute Medicine Unit. Most trainees will complete a five year programme obtaining a Certificate of Specialist Training (CCT) in G(I)M as well as Acute Medicine but others locally have pursued additional training in Intensive Care Medicine and Stroke Medicine.

In addition to their core clinical training in Acute Medicine trainees are expected to develop a chosen specialist skill. This may be

- A procedural skill, such as, echocardiography or ultrasonography
- An additional qualification at diploma or masters level, e.g., in medical education or clinical leadership
- A Speciality Interest, such as Palliative Medicine or Intensive Care Medicine
- Research

THE GOOD AND THE BAD

The good…

- Acute Medicine offers a varied case mix with plenty of 'clinical detective work'.
- Acute Medicine Units are often run by teams, offering close support from a group of like-minded colleagues.
- Being a new specialty allows consultants to have input into the development of services.
- Shift working patterns allow work-life balance or the development of special interests.
- The AMU is an ideal environment to develop teaching and training.
- There is the opportunity to develop and practice specialist skills such as focused ultrasound.

The bad…

- The pressure of work can be intense.
- Continuity of care is limited.
- There is potential for conflict over triage decisions and boundaries of responsibility.

- You will not be 'the expert' opinion.
- A move to extended clinical cover will have the potential to make the hours of work more onerous.

THE FUTURE

Acute Medicine is a fast growing specialty and initiatives such as *Shape of Training* and the Royal College of Physicians' *Future Hospital Commission* promote the appointment of physicians who have the breadth of expertise to deliver care to the patients with multiple comorbidities presenting to hospital acutely. It is likely that appropriately trained physician will be in demand for the foreseeable future.

WOULD I DO IT AGAIN?

Yes, I initially trained in G(I)M with Clinical Pharmacology, but what I always really enjoyed was the acute take with its clinical problem solving and the management of acute emergencies. Acute Medicine has allowed me to be involved in the development and running of a new service when first appointed, it has allowed flexibility to experience hospital management and then to move on to roles in training and education. It has not been without difficulties, but I could not see myself in another specialty.

USEFUL WEBSITES

https://www.jrcptb.org.uk/specialities/acute-medicine

http://www.acutemedicine.org.uk/what-we-do/training-and-education/training-in-acute-medicine/

http://careers.bmj.com/careers/advice/view-article.html?id=20022363

https://www.rcplondon.ac.uk/file/383/download?token=wpfU3yC6

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

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

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.

If e-mail submission is not possible, A CD or memory stick containing the manuscript, tables, images and covering letter can be sent to the Editor at: Dr John Purvis, Consultant Cardiologist, Cardiac Unit, Altnagelvin Hospital, Londonderry, BT47 6SB, Northern Ireland.

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

Images and tables should be included as separate high resolution .jpg or .tif files and NOT embedded in the Word manuscript file. Images should be appropriately annotated and labelled.

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After peer review by the referee, a manuscript may either be accepted for publication, accepted with minor or major revisions requested within a deadline or rejected. The Referee's and Editor's decisions are final and not open to negotiation. A manuscript may not be re-submitted after rejection.

1. For full or short papers, the text should indicate the purpose of the paper, and should include an introduction, sections on materials and methods, results, and a discussion relevant to the findings. A brief factual summary/abstract should be provided at the beginning of the paper along with up to six key words. For case reports, these should be **novel** or particularly important cases and *not just good teaching points*, with a maximum of 10 references and appropriate patient consent for publication of photographs.
2. Letters to the editor should be less than 500 words with up to 5 references and 1 table and/or figure.
3. Audits are eligible for publication as letters to the editor but will not be considered as original papers.
4. Scientific measurements should be in SI units (DN Baron. *Units, Symbols and Abbreviations. A Guide for Medical and Scientific Authors.* 5th ed. London: Royal Society of Medicine, 1994). Blood pressure may be expressed in mmHg and haemoglobin concentration as g/dl.
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    4. the year.
    5. volume number and issue number (in brackets) **in bold**.
    6. first and last pages.

- *Example:* Devlin LA, Price JH, Morrison PJ. Hereditary non-polyposis colon cancer. *Ulster Med J* 2005;**74(1)**: 14-21.
- Book references should give the author, title, edition, town of publication, name of publisher, year of publication, and, where appropriate, volume and page numbers.

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