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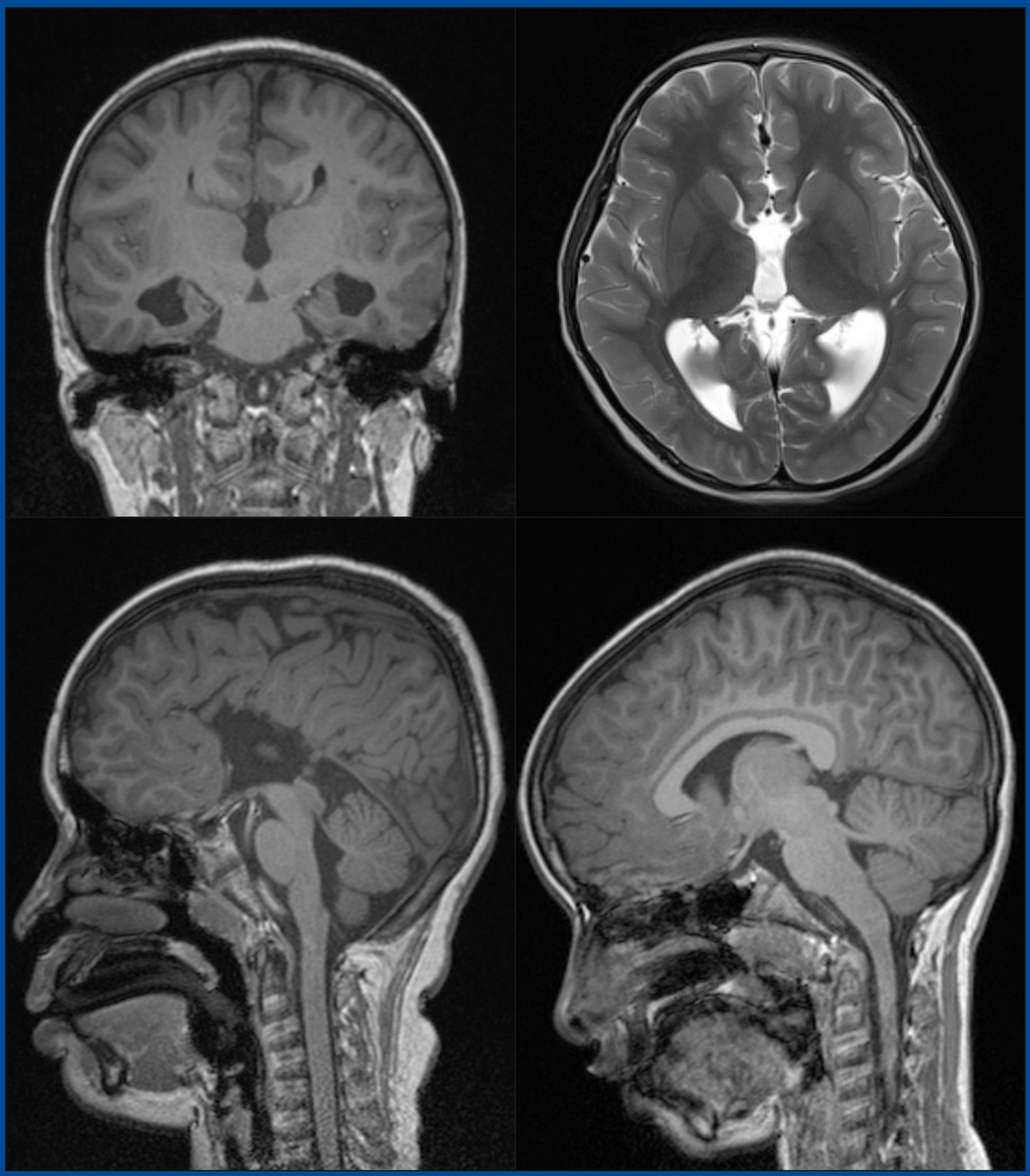

The Ulster Medical Journal

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Contact Details: All enquiries on submissions, subscriptions, permissions and advertising to the Editorial Office, The Ulster Medical Journal, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. United Kingdom.
T/ F: +44 (0) 28 9097 5780 **E:** umj@qub.ac.uk **W:** http://www.ums.ac.uk/journal.html

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Editorial

The Last Post

There is a temptation for your editor, at the end of his term, if not his rope, to get a few well-chosen things off his chest. I was reminded of Senator George Mitchell's concluding remark at the completion of the Good Friday Agreement in 1997, "I'm so sorry to leave but I can't wait to go." Yes, that resonates. Being editor can be a lonely berth at times channeling Coleridge's ancient mariner, and feeling 'alone on a wide wide sea.' However 'No man is an island', John Donne reminds us. True, except of course for Kenny Rogers and Dolly Parton, who were two islands. In a stream, to be precise. We are an island race.

By definition therefore, our shore defines us, literally. This Province (and our Society's symbol) is The Red Hand. There are many legends relating to this symbol's origin. Here are two. The Galician King of Spain, Milesius, in 500BC sent his three sons, Ir, Heber and Heremon, to claim Ireland, promising the island to the first son to touch its soil. Each of the parties raced towards the shore and one of the sons cut off his own hand with a sword and throwing it laid claim to the country. In another version, the captain of a Viking longboat, approaching Ireland promised that the first man to put his hand on the land could claim it. A mercenary on board named O'Neill used his sword to severe his own hand, and the mutilated appendage thrown ashore claimed it for him and his family, becoming the symbol for Ulster -the Red Hand.

Ulster generally and Belfast specifically is forever defined by one ship. A vessel so well known that it's name itself has become a metaphor: the *Titanic*. The *Titanic* sank at 2.20am on April 15th, 1912, about 400 miles from Newfoundland, struck by an iceberg on its starboard side. Titanic's name is synonymous with the power of nature, and the impotence and arrogance of man. The other ship that stands as metaphor, is, I would contend, the *Marie Celeste*. Possibly one of the most famous ships of all time the *Marie Celeste* is testament to the unsolved mystery and the ghost ship. Surprisingly its discovery, abandoned and tacking erratically, occurred as recently as December 1872. The ship, originally registered as the *Amazon* in Nova Scotia, had been reregistered as the *Marie Celeste* in New York. Probably the most likely theory is that barrels of alcohol held in inferior porous red oak casks emitted fumes, and an explosion ensued, frightening the crew. The captain ordered the lifeboat deployed (a tow line was found) but the life boat being cut adrift, meant death for its occupants, leaving the *Marie Celeste* intact, and sailing into mythology as an enigma.

I thought it might be interesting, for me at least, to map out my five year term in terms of world events. When I began the editorial cycle, there was lamentable pain in the Middle East, and also in another island, remote Iceland, that volcano with, for many of us, the unpronounceable name 'Eyjafjallajökull' (*Ah-uh-fyat-luh-yoe-kuutl-uh')* was spewing ash carried south by prevailing winds and paralysing the aviation industry. As I write this, a second Icelandic volcano -Bárðarbunga -lying under a thick glacier is excreting lava. Between these two events, Iceland went about its quiet industrious way, recovering from an economic crisis, and if the proposed energy interconnector with the United Kingdom is built, the citizens of Iceland are set to become rich enough to give the Sultan of Brunei run for his money. Sadly, the Middle East remains a different story. The constant in the chaos was the heartbreaking loss of so many innocent lives. As Wilfred Owen said, "My subject is war, and the pity of war. The poetry is in the pity."

The big news stories for 2010 were the BP oil spill from the Deepwater Horizon drilling platform in the Gulf of Mexico. Other events that year included the rise of The Tea Party, Obamacare, and in April, the launch of the iPad. Can you *imagine* life before the iPad? In 2011, on May 1, Osama Bin Ladin was killed. In Norway the Utøya massacre occurred killing 69 students from the Workers' Youth League; Adele released "21", and the Arab Spring began. In 2012 North Korea, his uber-nourished third son Kim Jon Un replaced the deceased Dear Leader Kim Jong Il and Oscar Pistorius became the first double amputee to compete in the Olympics. His après Olympic career however presumably wasn't what he had planned. In 2013 Pope Benedict resigned, the first Pontiff so to do in 600 years. His successor, an Argentinian Jesuit, took the name Francis, a first for papal nomenclature. Also in that year, Edward Snowden's whistleblowing revelations would reveal the extent of the USA's espionage activities.

Five years clocked up and I wondered what had been achieved? Building on the excellent advances of my predecessor, I wanted to emphasize medical education in its broadest sense. Firstly, I introduced Review Papers. Their primary purpose was to inform the readership about recent advances that had occurred in other people's specialties. An acknowledged expert would write each. There is no doubt in my view that an evangelical enthusiast is hard to beat. Again, paraphrasing Coleridge:

And when at last that face I see
I see the man that must hear me
To him my tale I teach.[1]

Next came the Grand Rounds. These articles were to assist those preparing for undergraduate and postgraduate

examinations and would be more practical than theoretical. The Pictorial Reviews and Game Changers are also extensions of that. The Bookcase section was my attempt to introduce a more holistic non-medical strand, and perhaps stimulate the occasional reader, if only with outrage. Social networking was the next step with a presence on Twitter and Facebook. QR codes followed these, but for us, are in their infancy. I was also particularly pleased to have introduced bilateral anonymity for reviewers and submitters and CME credits for reviewers. The anonymity has worked well, protecting both those submitting papers and reviewers alike. Wherever possible, I have invited reviewers from outside Northern Ireland, and indeed from outside the United Kingdom. I feel this adds to the Journal's perspective. The vast majority of reviewers provide very positive critiques, and this leaves a paper much stronger in the end. Being a reviewer is a hard station, so I was delighted to reward their endeavors with CME credits hosted by the Ulster Medical Society.

Case reports

Continuing my aquatic metaphor, identifying promise in a case report can be like looking for water in the desert. In that sense, the editor and reviewer resorts to dowsing, or divining:

Unfussed. The pluck came sharp as a string.
The rod jerked with precise convulsions,
Spring Water suddenly broadcasting
Through a green hazel its secret stations.[2]

Over the last five years I have used an alternative strategy: converting case reports into letters to the editor and with some success. The case report is of course the first tentative step for junior doctors (myself included) but there is a fundamental problem with it. It rarely has anything useful to add to medical literature's canon. I am very empathetic to the needs of trainee doctors in this respect. They have a requirement to be seen to pursue intellectual enquiry (let's call it 'research') as a means to professional advancement. Fair enough. The problem is that many of the case reports received are in fact straightforward expositions of uncommon conditions. A further complication ensues. In your editor's opinion, the worth suggested by the first author, very often is at variance with the experience of the more battle-scarred practitioner, and probably reflects the youthful blank canvas of that first author.

The postgraduate medical curriculum is now very full, planted thick with validated, targeted medical examinations to test the worthiness of the practitioner. Understandably therefore there is little room for research. I would suggest that it might be much more practical and targeted to employ a system of learning such as a Practice-Based Learning module, where critical appraisal of work can be done using accepted metrics and international norms. As the cited reason for case reports and papers is usually given as "the ability to critically appraise a paper", it would seem more appropriate to use this rather than embark on a relatively redundant case report. Anyway, I digress. By converting these case reports into letters to the editor, the trainee gets the work published, and cited, but for those interested in this kind of thing, it does not form part of the Journal's impact factor. This I would suggest is a win win.

It has been a privilege to have been at the helm, these five years. My final nod to Coleridge:

He rose as one that has been stunned
And is of sense forlorn
A sadder but a wiser man
He rose the morrow morn.[1]

Well, not sadder, but wiser. One leaves with the sense of what is achievable. One recognises a colleague who might help, and one that certainly won't. Most importantly, one has the wisdom to know the difference. I would especially like to thank Mary Crickard, Marie Murphy and the Journal's editorial board. They made the Journal better than when they found it and they did the same with me. I always thought there was an additional frisson to be had with me, notionally in charge, wondering in what month the September edition would actually be published. We always made it, but just. With my worthy successor, John Purvis, a cardiologist from Altnagelvin in *Legend -Derry*, deadlines will not be a problem. This will be a relief, not least for Peter Mahaffey, the long-suffering studio editor in Dorman's. Peter deserves great praise because despite my chaotic, entropic and scattergun approach, he always remained calm, and always delivered.

My very best wishes to John. He has worked tirelessly and methodically in preparation for becoming editor. There is I believe a Royal Navy exchange when the officer of the watch is relieved. The retiring officer says, "I give you the ship" and his replacement says, "I have the ship." He has indeed. Please do keep sending him your good papers.

Adieu

Barry Kelly
Honorary Editor

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Review

Perinatal Management of Major Congenital Heart Disease

Eiméar McGovern[1], Andrew J Sands[2]

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ABSTRACT

Congenital heart disease (CHD) is the most common form of congenital anomaly.

Prenatal diagnosis of CHD has been associated with decreased morbidity and mortality for some forms of major CHD. As most cases of major CHD are not identified prenatally, clinical examination of the newborn and pulse oximetry are also important means of identifying more cases.

Clinicians must suspect CHD as a diagnosis in a cyanosed or shocked neonate and be familiar with appropriate management, namely the commencement of prostaglandin if a duct dependent cardiac lesion is suspected.

Telemedicine can aid prompt diagnosis of CHD and therefore direct appropriate management.

INTRODUCTION

Congenital heart disease (CHD) is the most common form of congenital anomaly. If affects approximately 0.8% of all live births. Congenital malformations of the cardiovascular system accounted for 10.4% of infant mortality in Northern Ireland in 2010, excluding those infants with co-existent trisomy 13 or 18[1].

The correct management of neonates with suspected CHD is vital in improving the morbidity and mortality associated with these conditions. This may be facilitated by better prenatal diagnosis of CHD and the application of telemedicine in the form of transmitted echocardiography.

Major CHD is most often defined as a lesion that requires surgery or intervention catheter in the first year of life. Critical CHD may be defined as lesions that require surgery or catheter intervention in the first 28 days of life[2].

In the following paper we aim to summarise the role played by fetal echocardiography in the diagnosis of major CHD and also the identification and management of a neonate with major CHD. Both of these can be assisted by telemedicine.

PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASE

Prenatal diagnosis of CHD by fetal echocardiography is now a firmly established component of fetal medicine offered in many tertiary UK centres, including the Belfast Health and Social Care Trust. Image 1 shows an example of Hypoplastic Left Heart Syndrome (HLHS) identified on fetal echocardiography.

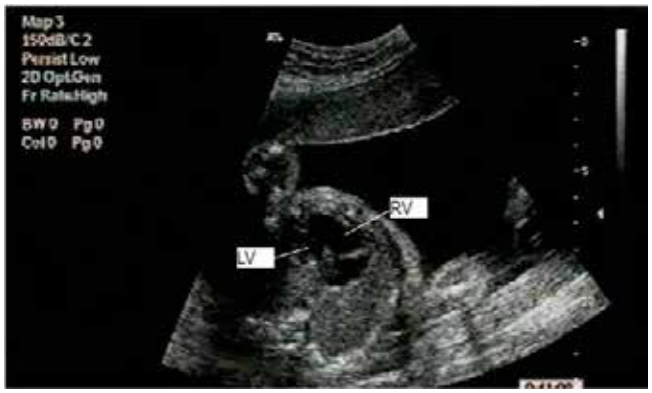

Image 1. Fetal Echocardiography of HLHS with a diminutive left ventricle (LV) and right ventricle (RV) seen.
Image provided by Dr AJ Sands

Prenatal diagnosis is increasingly playing an important role in paediatric cardiology. In the case of major or critical CHD it allows the opportunity to adequately counsel parents, to guide the timing and delivery of the baby in a suitable location and to plan perinatal management.

Approximately 90% of pregnancies affected by CHD occur in pregnancies where there are no known high risk features[3,4,5,6]. Therefore, initial antenatal diagnosis of CHD largely lies in the hands of those carrying out routine obstetric screening. Current national guidelines in the UK recommend that 4 chamber and outflow tract views are examined at the time of the fetal anomaly scan[6] as this allows for the possibility of >90% of major CHD to be detected[3,4].

When there is concern about the fetal heart on the obstetric anomaly scan or the pregnancy is deemed higher risk (refer to Table 1), referral is then made to a tertiary centre for fetal echocardiographic assessment.

Rates of prenatal detection of Congenital Heart Disease

Rates of prenatal detection of CHD vary considerably internationally and even nationally. In Northern Ireland between Sept 06 and Sept 07, 2.5 days of formal training on

[1]Paediatric Basic Specialist Trainee, Paediatric Department, Galway University Hospital. [2]Consultant Paediatric Cardiologist, Department of Paediatric Cardiology, Royal Belfast Hospital for Sick Children.

Table 1:

Pregnancies at high risk of fetal CHD that require referral for fetal echocardiography (excluding fetal indications)

Maternal Indications	Familial Indications
Maternal CHD	Paternal CHD
Maternal metabolic conditions, especially if poorly controlled in early gestation e.g. Diabetes Mellitus, Phenylketonuria.	Sibling with CHD or congenital heart block.
Maternal exposure to cardiac teratogens e.g Lithium, anticonvulsants, viral infections (rubella, cytomegalovirus, parvovirus, coxsackie) and toxoplasma	Chromosomal anomalies, gene disorders or syndromes with CHD in the family.
Maternal collagen disease with anti-Ro or anti-La	
Maternal use of Non-steroidal anti-inflammatory drugs after 25-30 wks	

Adapted from: Sharland G, Gnanapragasam J, Miller P, Narayanaswamy S. British Congenital Cardiac Association (BCCA) Fetal Cardiology Standards Working Group. Fetal Cardiology Standards. British Congenital Cardiac Association. March 2010. Revised March 2012.)[6]

fetal echocardiography was delivered to 90% of all obstetric radiographers in the province. The prenatal detection rate of major CHD rose significantly from 28% pre-training to 43% in the year of training[4] bringing Northern Ireland's rates close to the best previously quoted European rates of detection of 47%[7]. Diagnosis of four-chamber-view defects rose significantly from 38 to 54% and diagnosis of outflow-tract-view defects from 8 to 21%[4]. This study contributed to a change in regional guidelines, which now state that outflow tracts should also be routinely assessed during the anomaly scan.

Does prenatal diagnosis affect outcome?

The most important question is whether prenatal diagnosis of major CHD affects outcome of the infants. Some forms of CHD, namely those dependent on a patent ductus arteriosus, are associated with acute decompensation and risk of death often before a heart defect is suspected clinically. One would therefore expect that prenatal diagnosis of the defect and subsequent planning of the delivery with prompt postnatal management, would decrease the morbidity and mortality of the infant. This has however been hard to demonstrate. Prenatally diagnosed major CHD in some studies has been associated with a higher mortality. This is largely due to the fact that fetal echocardiography preferentially diagnoses the most severe/complex forms of CHD and there is also a higher frequency of associated extra cardiac abnormalities[3,4,8].

There have however been several studies since which have demonstrated that prenatal diagnosis of major CHD can improve outcome[9]. Research suggests that prenatal diagnosis of Transposition of the Great Arteries (TGA) and HLHS is associated with decreased perioperative morbidity and mortality[10, 11]. In coarctation of the aorta, collapse, pre-operative haemodynamic instability and death were more common in a postnatally diagnosed group[12].

POSTNATAL MANAGEMENT OF MAJOR CONGENITAL HEART DISEASE

Although the detection of major CHD in utero has improved substantially in recent years, many babies with CHD are undiagnosed at birth. This means that effective clinical examination of the newborn before hospital discharge and knowledge of the immediate management of a sick neonate with a duct dependent systemic or pulmonary circulation, is vital. Delayed or missed diagnosis of critical CHD accounted for 0.4-2.0 deaths per 10,000 livebirths in a UK series[13]. Perhaps the most important long term sequelae of delayed diagnosis in such patients who survive, is the risk of hypoxic/ischaemic brain injury. Periventricular leukomalacia has been reported on MRI imaging of the brain in up to 39% of neonates with critical CHD[13].

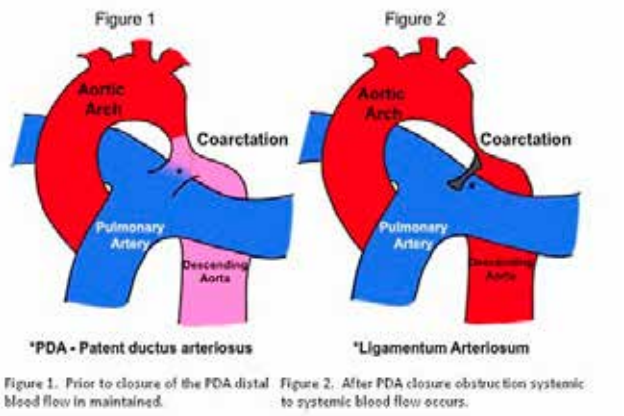

Fig 1. Duct Dependent Coarctation of the Aorta
Adapted from: http://www.uwhealth.org/american-family-childrens-hospital/pediatricpathways

Infants with a duct dependent systemic or pulmonary circulation and transposition of the great arteries are at risk of rapid demise and death in the first few days to weeks of life. Duct dependent systemic circulations often include the following conditions: HLHS; critical aortic stenosis; coarctation of the aorta; and interrupted aortic arch. Duct dependent pulmonary circulations may include the following conditions: pulmonary atresia; critical pulmonary stenosis; and tricuspid atresia. Circulatory collapse coincides with the closure of the ductus arteriosus and changes in the pulmonary vascular resistance. Figure 1 shows an example of critical

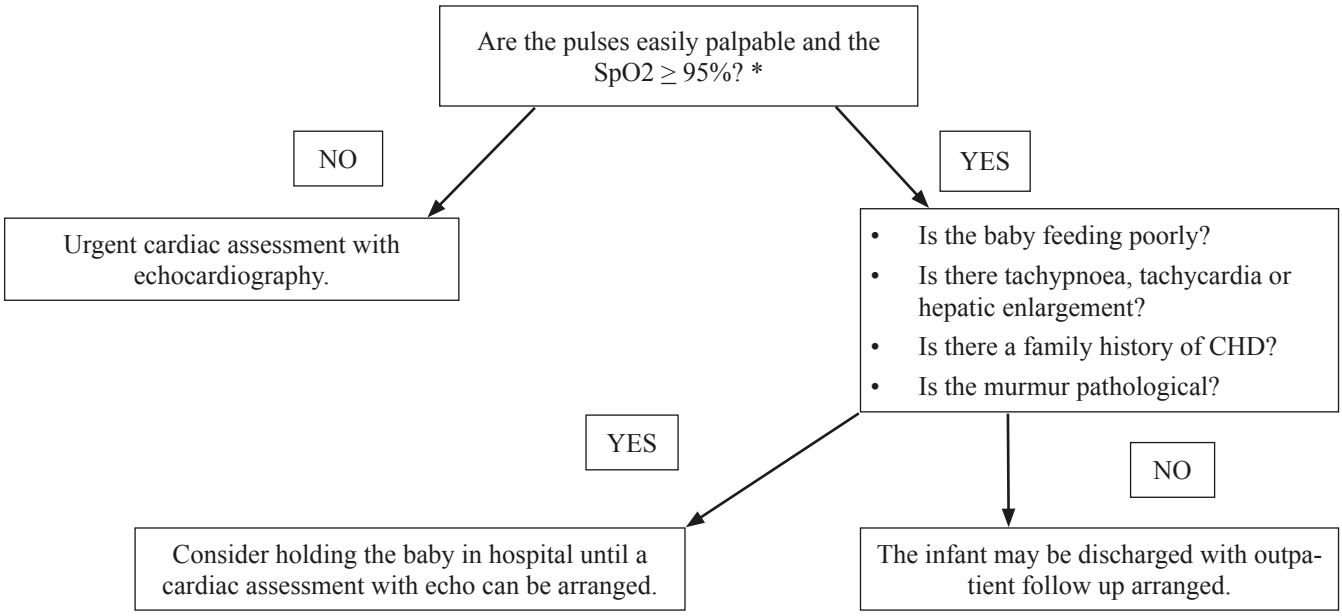

Fig 2. Assessment of a murmur heard on the newborn check pre-discharge.

*Confirming presence of femoral and brachial pulses should be mandatory before hospital discharge.

coarctation of the aorta where the systemic circulation is dependent upon a patent ductus arteriosus.

As these babies often look and examine well before these physiological changes occur, major CHD can go undetected at routine examination of the newborn. This is becoming even more problematic with a higher rate of early discharge of mother and baby after delivery.

Routine examination of the newborn

Routine examination of the newborn before discharge from hospital must incorporate the cardiovascular system. Signs such as cyanosis, heart murmurs and diminished peripheral pulses are sought and their discovery will prompt further expert cardiovascular assessment. As these signs are not always present before closure of the ductus and reduction of pulmonary vascular resistance, the clinical examination has low sensitivity. A study of 1590 babies with CHD in the UK showed that more than half were thought to have a normal cardiovascular system at their first routine examination and of these almost 40% presented with symptoms or died before their routine 6 week check[14]. Furthermore, the clinical examination is not specific. Cyanosis may be secondary to lung pathology and diminished pulses secondary to sepsis. However, discovery of these clinical signs will identify a sick newborn and further assessment and investigation must be undertaken with echocardiography often playing an important role in ruling out CHD as a cause. As heart murmurs have a prevalence of between 0.6-4.2% in all newborns, this decreases the specificity of the cardiovascular clinical examination of the newborn. The murmurs often represent physiological flow murmurs (e.g. mild turbulence in the branch pulmonary arteries), transient tricuspid regurgitation and small ventricular septal defects of no clinical significance. These babies may be wrongly suspected of having major congenital heart disease. Flow charts to help junior doctors and GPs decide when a neonatal murmur is significant may be useful as in figures 2 and 3.

Ongoing vigilance for CHD by the general practitioner and health care visitor is required, especially in cases of early discharge of the mother and baby.

Importantly, murmurs are often absent in major CHD and thus if any of the above features are present without a murmur, CHD must be ruled out.

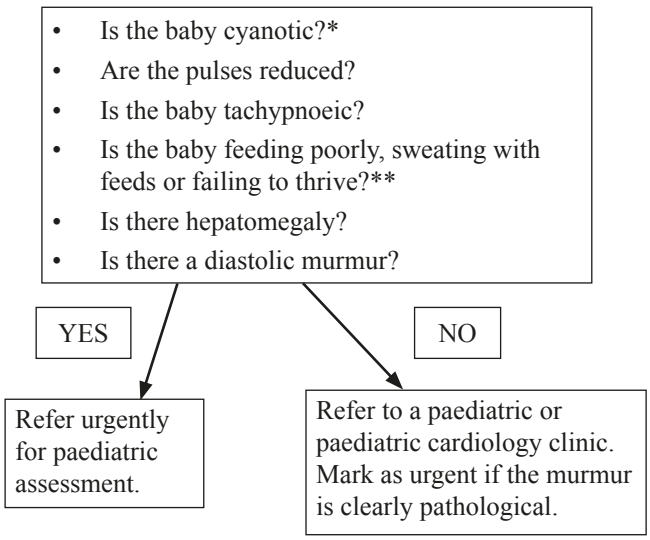

Fig 3. Assessment of a murmur heard on the 6 week baby check in primary care

*One must distinguish between peripheral and central cyanosis. SpO2 must be measured if there is any concern over cyanosis.

** Poor feeding may be the first sign of cardiac compromise

SpO2 screening with pulse oximetry

The addition of pulse oximetry screening to the newborn clinical examination has the potential to identify many more major congenital heart defects than clinical examination would alone. Post-ductal saturations (left hand or a foot) will be lower than pre-ductal (right hand) when there is mixing of pulmonary blood with arterial blood across the ductus arteriosus in duct dependent lesions. A positive result is post-ductal saturation of <95% or a 3% difference between pre and post-ductal saturations. A Swedish prospective study showed that introduction of pulse oximetry screening improved total detection rate of duct dependent circulation to 92%[15] and a case control study calculated that pulse oximetry had a sensitivity of 98.5% and a specificity of 96% for detecting these lesions[16].

Management of the collapsed neonate

As antenatal detection rates for major CHD remains around 50% at best and many cases are therefore unexpected, clinicians must have a high index of suspicion for CHD as a diagnosis in a cyanosed or shocked neonate presenting in the first hours or days of life. One must not forget that respiratory and metabolic conditions as well as sepsis can present very similarly and are more common than critical CHD. Nevertheless, if a duct dependent lesion is clinically suspected, commencement of prostaglandin infusion must not be delayed. Specialist paediatric cardiology advice must be sought as soon as possible. This will usually include echocardiographic assessment. In a remote hospital, a telemedicine facility would allow transfer of live echo images to a tertiary centre and avail of specialist opinion promptly. Of note, differentiating persistent pulmonary hypertension of the newborn (PPHN) from a duct dependent pulmonary circulation can be very difficult. Infants with PPHN may also show some improvement with the higher doses of prostaglandin. Use of echocardiography will often make a firm diagnosis, but usually the safest option is to commence prostaglandin in the interim.

Dose and rate of increase of prostaglandin may be administered as per the BNFC[17]. If a local protocol is available for both starting doses and rate of up-titration of prostaglandin, one must adhere to this.

The aim should be saturations between 75-85%, palpable femoral pulses and resolving acidosis. The dose may need to be doubled as frequently as every ten minutes if there is no improvement. However, at this point expert advice is required. When ductal patency has been established, attention must be paid to the balance between the pulmonary and systemic circulations. Pulmonary overcirculation will reduce systemic and myocardial circulation and so must be avoided. Measures to reduce pulmonary overflow include maintenance of systemic saturations between 75-85% and PaCO2 of 5-6 to avoid respiratory alkalosis, which may mean use of mechanical ventilation in order to achieve this[14]. Ventilation may also be required if the patient remains critically unwell (severe hypoxaemia, acidosis and/or cardio respiratory failure), suffers apnoea on administration of prostaglandin or on an elective basis when prostaglandin requirement reaches a pre-determined high level when apnoea becomes more common (e.g. >25nanograms/kg/min if PGE1 used)[18]. Apnoea is the most common side effect of prostaglandin, but other important side effects include hypotension, hypoglycaemia and fever.

If a baby is not responding to a prostaglandin infusion, there may be a variety of explanations[14,18]:

- Venous access may be inadequate.
- There may be inadequate flow across the duct and subsequently infusion rate may need to increase substantially (cardiology advice must first be sought).
- The patient may have been shocked and acidotic for a long period.
- The patient may have ventricular dysfunction secondary to an obstructed systemic lesion.
- The patient could have TGA with an intact atrial septum or obstructed total anomalous pulmonary venous connection. Specific catheter or surgical intervention may therefore be required urgently.

TELEMEDICINE

Telemedicine is a rapidly developing application of clinical medicine where medical information is transferred through modern telecommunications allowing for remote specialist consultation. Image 2 shows two doctors delivering a remote cardiac consultation via telemedicine. Images are received on the unit to the left of the picture and displayed on the television screen to allow viewing by those in the room. An audio unit seen on the table acts both as a microphone and a speaker to allow a conversation between both parties.

Telemedicine has proven to be very useful in paediatric cardiology. Transthoracic echocardiography is the gold standard for diagnosis of most CHD and thus transfer of echo images from district general hospitals to the specialist centre can aid prompt diagnosis. This is particularly important when dealing with duct dependent lesions in the newborn. In this situation, prompt diagnosis can improve outcome by rapid institution of the correct management and transfer to the appropriate centre. On the other hand, where cardiac disease is suspected but ruled out by expert viewing of echo images transmitted by telecommunication, transfer of the patient to the specialist centre can be avoided.

Accuracy of remote Echocardiograms

There have been many studies to determine the accuracy of remote diagnosis of congenital heart disease by telemedicine, which have largely shown very promising results. A review of the use of telemedicine for diagnosis of congenital heart disease in Northern Ireland over an 8 year period, confirmed that telemedicine diagnosis was accurate in 97% of cases[19].

Image 2. Telemedicine Suite in use, Royal Belfast Hospital for Sick Children.

Image provided by Dr AJ Sands

Telemedicine and prenatal diagnosis of Congenital Heart Disease

In addition to neonatal diagnosis of CHD and post-op follow up of surgical patients, tele-echocardiography can also be applied to prenatal diagnosis of CHD. A Northern Irish prospective study compared fetal echo performed by obstetric sonographers with live guidance and assessment by a fetal cardiologist via telemedicine, with fetal echo later performed by the specialist at the regional centre. This method was technically feasible, reliable and diagnostically accurate with diagnostic concordance in 97% of cases[20].

CONCLUSION

CHD is the most common congenital anomaly affecting approximately 0.8% of all live births.

Prenatal diagnosis of TGA, HLHS and coarctation of the aorta has been associated with decreased perioperative morbidity and mortality.

Clinical examination of the newborn will still miss many cases of major and critical CHD. The addition of pulse oximetry has the potential to detect of up to 92% of all cases of duct dependent circulations before hospital discharge.

Clinicians must have a high index of suspicion for CHD as a diagnosis in a cyanosed or shocked neonate presenting in the first hours or days of life. Prostaglandin infusion should be commenced promptly if a duct dependent circulation is likely.

Telemedicine has proven to be very useful in paediatric cardiology. Transfer of echo images from district general hospitals to the specialist centre can aid prompt diagnosis and therefore direct appropriate management.

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PUZZLING SYMPTOMS?

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	GAUCHER DISEASE	FABRY DISEASE	MPS I (mucopolysaccharidosis type I)	POMPE DISEASE (acid maltase deficiency)
Enzyme deficiency	β-glucocerebrosidase	α-galactosidase A	α-L iduronidase	Acid α-glucosidase
Substrate accumulation	Glucosylceramide – primarily in monocytes and macrophages	GL-3 - primarily in vascular endothelium	GAGs (heparan and dermatan sulphate) – primarily in connective and soft tissue, joints and cardiac cells	Glycogen – primarily in cardiac, skeletal and respiratory muscles
Spectrum of disease	Type I - Non-neuronopathic Types II & III - Neuronopathic	Both males and females affected, ranging from mild to classical phenotypes	Severe to attenuated (formally known as Hurler, Hurler-Scheie and Scheie)	Infantile to late onset
Incidence	1: 40,000–50,000 in general population[1] (1: 450 in Ashkenazi Jews[2])	1: 40,000 males[3] 1: 117,000 in general population[4]	1: 100,000[5]	1: 40,000 live births[6,7] (1: 14,000 in African Americans[8])
Inheritance	Autosomal recessive	X-linked	Autosomal recessive	Autosomal recessive
Key signs and symptoms	- Hepatosplenomegaly - Anaemia/ thrombocytopenia - Bone pain/crisis - Growth retardation - Avascular necrosis - Pathologic fractures - Osteopenia	- Cardiac dysfunction (esp. left ventricular hypertrophy) - Corneal/ lenticular opacities - Angiokeratomas - Renal dysfunction - Acroparesthesia/episodic pain crisis - Heat and cold intolerance - Cerebrovascular complications - Gastrointestinal manifestations	*Spectrum of clinical presentations from mild to severe* - Recurrent ear/nose infections - Corneal clouding - Enlarged liver and spleen - Obstructive airway disease - Valvular heart disease - Coarse facial features - Mental impairment in severe form - Musculoskeletal features - use pGALS to identify joint abnormalities and pattern of involvement; consider MPS I with toe walking / kyphoscoliosis / symmetrical joint contractures [in the absence of synovitis], especially upper limb [fingers / wrists / predominantly shoulder] involvement. Other features include hip dysplasia / trigger fingers / carpal tunnel syndrome	*Infants* - Cardiomegaly and/or cardiomyopathy - Profound, rapidly progressive muscle weakness - Respiratory insufficiency/frequent infections - Feeding difficulties/failure to thrive *Early childhood to late adulthood* - Progressive proximal muscle weakness - Respiratory failure/insufficiency - Gait abnormalities - Muscle pain
Diagnostic tests	Enzyme assay in leucocytes or cultured skin fibroblasts; bone marrow biopsy	Dried Blood Spot. Heterozygotes: DNA mutation or linkage analys	Lymphocytes assay Urinary GAGs	Dried Blood Spot with enzyme assay – or enzyme assay with blood leucocytes. Muscle biopsy and fibroblast skin biopsy
Lab assays	ACE, TRAP, CHITO, CCL-18/PARC	Plasma and urine GL-3	Urinary GAGs	Hex4, CRIM
	ACE: angiotensin-converting enzyme TRAP: tartrate resistant acid phosphatase CHITO: chitotriosidase CCL-18: CC-chemokine ligand 18 PARC: pulmonary activation-regulated chemokine	GL-3: globotriaosylceramide	GAGs: glycosaminoglycans pGALS: paediatric Gait, Arms, Legs and Spine	Hex: glucose tetrasaccharide CRIM: cross-reactive immunologic material

Lysosomal Storage Disorders Specialist Treatment Centres

If you would like further information please contact your local treatment centre:

SPECIALIST TREATMENT CENTRES

BIRMINGHAM
Inherited Metabolic Disorders Service
Birmingham Children's Hospital (Paediatrics)
Tel: 0121 333 9907

Department of Inherited Metabolic Disorders
University Hospital Birmingham (Adult)
Tel: 0121 627 1627 Ext 51592

CAMBRIDGE
Lysosomal Storage Disease Unit
Addenbrookes Hospital (Adult)
Tel: 01223 274 634

LONDON
Lysosomal Storage Disease Unit
Great Ormond Street Hospital (Paediatrics)
Tel: 0207 405 9200 Ext 5081

Charles Dent Metabolic Unit
The National Hospital for Neurology and Neurosurgery (Adult)
Tel: 0207 829 8778

Lysosomal Storage Disease Unit
The Royal Free Hospital (Adult)
Tel: 0207 472 6409

MANCHESTER
The Mark Holland Metabolic Unit
Salford Royal (Adult)
Tel: 0161 206 4365

Willink Unit
Royal Manchester Children's Hospital (Paediatrics)
Tel: 0161 701 2137

WELSH CENTRE FOR METABOLIC DISEASES

CARDIFF
Inherited Metabolic Diseases Service
University Hospital of Wales
Tel: 0292 074 6752

SCOTTISH CENTRE FOR METABOLIC DISEASES

GLASGOW
Inherited Metabolic Disorders Scotland
Managed Clinical Network
Tel: 0141 201 0786

NORTHERN IRELAND CENTRES FOR METABOLIC DISEASES

BELFAST
Genetics Department
Belfast City Hospital
Tel: 0289 504 8315

Royal Belfast Hospital for Sick Children
Tel: 0289 063 2002

IRISH CENTRE FOR METABOLIC DISEASES

DUBLIN
National Centre for Metabolic Disorders
Children's University Hospital
Temple Street, Dublin 1
Tel: 01 878 4317

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Paper

Academic Medicine – revolution, evolution or extinction?

Gareth W. Irwin[1], Roy. A.J. Spence[2], Danny F. McAuley[3], Richard D. Kennedy[4], Keith R. Gardiner[5], J. Stuart Elborn[3]

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INTRODUCTION

The role that academic medicine has to play in a medical career has been a hotly debated topic over the last two decades. A number of initiatives have been proposed to increase the number of clinical academics, the quality of research undertaken and to preserve research in a NHS driven by service provision.[1-3] These initiatives have generated discussion, solved some issues, but left a number of ongoing problems unanswered.

This review evaluates recent changes in academic medicine and describes how they apply to Northern Ireland. It also details the various opportunities for a medical undergraduate or postgraduate to access academic training to explore or enter a career in academic medicine.

In Northern Ireland, academic medicine is linked with Queen's University Belfast, the sole provider of medical education in Northern Ireland. The medical school has four research centres and one teaching and research centre: Centre for Cancer Research and Cell Biology, Centre for Experimental Medicine, Centre for Infection and Immunity and Centre for Public Health and the Centre for Medical Education which is responsible for the administration and management of the undergraduate medical course as well as education research.

WHAT IS ACADEMIC MEDICINE?

Most job descriptions for clinical academics include responsibilities for research, teaching and administration in addition to clinical practice. Clinical academics are often expected to have a role in inspiring and training the next generation of clinicians as well as introducing innovations in treatment and practice. Locally, new staff are appointed to a post within one of the five research or teaching centres, however, they are obliged to contribute to the overall needs of the school. These appointments are strategic to enable these centres to meet their research themes, as measured by the Research Excellence Framework, or teaching commitments, as evaluated by the General Medical Council.

The responsibilities of clinical academics evolve over the course of their careers and usually involve all of these roles. The time commitment to these different activities depends on contractual arrangements with academic clinicians having primary contracts in the NHS with honorary academic contracts or in the case of Clinician Scientists, their contract is with their university. Recently, the local preference has been for a person's substantive affiliation to be with the university and then for them to be offered an honorary position with a NHS Trust to undertake clinical work. In view of the crucial role of clinical research in the interface between basic science and clinical practice, clinical academics often make important contributions to the prevention, diagnosis and treatment of disease, teaching of medical students and the training of junior doctors.[4]

WHO ARE CLINICAL ACADEMICS?

A recent survey of staffing levels of medical clinical academics, in medical schools, identified that approximately 6% of the NHS clinical workforce are involved in clinical academia. The survey showed that there were 3162 (full time equivalent) clinical academics employed in the UK in 34 medical schools. Although this has remained steady over the last few years, the number is still lower than in 2000.[5] Since then, General Practice, Ophthalmology and Internal Medicine have seen an increase in clinical academics but all other specialties have seen a decrease, with the greatest reduction being observed in Pathology. In comparison to NHS consultants, medical academics tend to be older, however, there have been recent improvements in gender balance and diversity of ethnicity.[5]

WHAT HAS CHANGED?

In 2005, the Walport report was published by the academic careers sub-committee of Modernising Medical Careers and the UK Clinical Research Collaboration.[6] It highlighted three major issues that were barriers to an academic career: lack of a transparent career structure, lack of flexibility in training and a shortage of supported posts when training is completed. Building on the Savill Report[7], Walport also noted that a problem for clinical academics splitting their time between NHS and academic responsibilities is that they

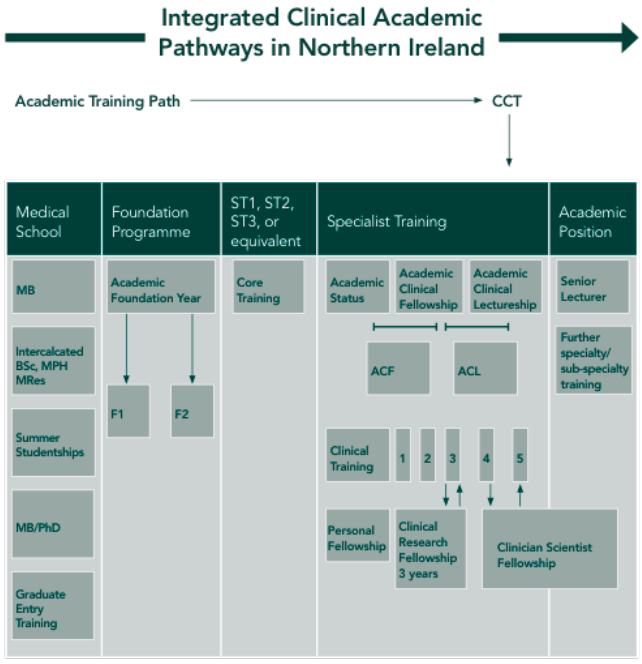
[1.] Centre for Cancer Research and Cell Biology, Queen's University Belfast.[2.] Belfast Health and Social Care Trust. [3.] Centre for Infection and Immunity, Queen's University Belfast. [4.] Centre for Cancer Research and Cell Biology, Queen's University Belfast. [5.] Northern Ireland Medical and Dental Training Agency, Belfast.

garethirwin@doctors.org.uk

Correspondence to: Gareth W. Irwin

are judged against the standard of their fulltime peers in both the hospital and university settings. This can be particularly problematic in craft specialties, where it can be a challenge to remain up-to-date, develop new technical skills in procedures or surgery and undertake the appropriate numbers of index operations/procedures as required by their respective specialty associations. They also have to meet high standards of the university with regards to lecturing, community engagement and research.

The Walport report suggested specific solutions to each of these deterrents by recommending the establishment of a distinct career pathway for those keen to pursue a career in clinical academia and increased flexibility allowing individuals to move easily between clinical and academic components. For the first time, it defined the academic pathway as consisting of three increasingly senior levels of post: Academic Clinical Fellowships, Academic Clinical Lectureships and Clinical Senior Lectureships for postgraduates, building on a more formalised undergraduate academic stream (Figure 1).



Type of Post	Duration
Academic F2 (AF2)	4 months during foundation training
Academic Clinical Fellow (ACF)	normally 2 years (25% Research)
Academic Clinical Lecturer (ACL)	normally 3 years (50% Research)

Fig 1. The integrated clinical academic pathway in Northern Ireland.[8]

UNDERGRADUATE OPPORTUNITIES

A systematic review, in 2006, stated that it was the duty of medical schools to ensure that their students were trained for future advances in clinical care, research and education and that they should aim to stimulate interest in academic medicine.[9] However, a recent study, based in Liverpool, found that 75% of undergraduates surveyed felt they had not been given opportunities to learn about academic medicine with 57% of students feeling that a career in academic medicine was less than 'quite appealing' for various reasons.[4] Many medical schools now offer several opportunities to gain some exposure to an academic career path. A group of medical students at QUB have formed an academic medicine society to promote research and academia to medical and dental undergraduates.[10] This society echoes the aims of INSPIRE, an initiative of the Academy of Medical Sciences, which seeks to coordinate current research opportunities and enhance the promotion of clinical academic training throughout the medical school and beyond.

INTERCALATED DEGREES – BSc, MRes, MSc IN PUBLIC HEALTH

Intercalated degrees allow an extra year of study at the end of 2nd or 3rd year, giving students an opportunity to explore an area of particular interest in greater depth. This year focuses largely on research and provides an opportunity to submit work for publication or to attend scientific meetings. Queen's University Belfast had 60 students, in 2013-14, in one of three programmes:

a) a Bachelor of Science at the end of 2nd or 3rd year in one of the basic sciences related to clinical training including Anatomy, Physiology, Pharmacology etc.,

b) a Masters of Research in translational medicine[11] which aims to inspire a new generation of innovative clinician scientists with an understanding of disease at a molecular level and a strong training in research methodologies and

c) a Masters of Science in Public Health, which aims to train the student in research methodology but also provides problem-solving skills to find solutions to practical health problems.[12]

As these options have become more popular, entry to these programmes has become more competitive. A review of a longstanding Masters' programme in Rheumatology, at another institution, highlighted that these schemes had the potential to maximize learning opportunities, to encourage critical reflection on professional practice, to promote the integration of existing knowledge and experience with new perspectives and develop the application of learning to the workplace.[13]

If a commitment to an entire year of further study seems too much, students can have a shorter 'taster' experience over the summer months through a Summer Studentship. This offers an eight-week exposure to laboratory or educational based research and could potentially be the foundation for a year-long research programme through an intercalated degree. This can be funded by the university or by some local and national charities keen to promote interest in their particular research area.

Recent studies have highlighted that students who undertake

an intercalated degree had better examination results and greater success when securing their preferred Foundation posts.[14 15] A recent BEME (Best Evidence Medical Education Collaboration) systematic review of the impact of an intercalated BSc on medical student performance and careers found that undertaking an intercalated degree may improve undergraduate performance, increase the likelihood of pursuing an academic career or make the student less likely to follow a career in general practice.[16] The extra year increases the financial burden of a medical student's time at university and could create an extra year of debt. The review highlighted that most students felt uninformed about the benefits of undertaking an intercalated degree.[16] One of the problems is that the benefits are soft and difficult to measure. At a bare minimum it is a topic to discuss at interview in which the interviewee should be an expert. More often the generic skills learnt can have a significant impact throughout a doctor's career. An attempt to introduce a compulsory intercalated degree at an Australian medical school required modification after it was found that some students lacked the maturity and autonomy required for such a programme.[17] However, it is a routine part of the undergraduate medical course at Nottingham University.[18]

MB/PHD PROGRAMME

In some UK universities an MB/PhD programme is offered to a small numbers of students.[19 20] This combines the undergraduate medical curriculum with a prolonged period of research working towards the award of a PhD. A recent review of graduates from a longstanding MB/PhD programme found that 79% of them were active in research and 90% had definite plans for further fulltime research.[20] They concluded that the scheme was successful at promoting scientific discovery and sustaining academic development.[20] However, some would question the optimal time at which to opt out from the undergraduate curriculum to undertake a focused period of research and would also ask whether or not it could result in the loss of recently attained clinical skills and loss of knowledge from the broad sweep of undergraduate medicine.

ACADEMIC FOUNDATION PROGRAMME – AF2

Included in the proposals from the Walport report was an option for new graduates to undertake an integrated academic foundation programme in their first or second postgraduate years. An academic foundation programme is a four-month research or teaching-intensive placement. It is designed to enable the foundation doctor to gain insights into clinical academic medicine through regular contact with academic clinical supervisors, scientific staff and postgraduate research students. It should allow foundation doctors to develop knowledge, skills and aptitudes for academic medicine and foster an interest in a long-term clinical academic career. A major feature is an opportunity to undertake a teaching or research project under the supervision of a senior academic.[8]

Recent evaluation of the foundation programme has highlighted that many found academic foundation posts provided good support to junior doctors and offered a wide range of learning opportunities.[21] Some, however, felt that the skills learnt were too generic and would have preferred an opportunity to focus their training at this stage.[21] The programme acted as a 'taster', allowing foundation doctors an opportunity to gain experience through an academic specific option early in their careers rather than having to progress to advanced clinical grades before academic training was a possibility.

ACADEMIC CLINICAL FELLOWSHIP - ACF

Academic Clinical Fellowships are targeted at doctors in the early years of specialty training. This is a two-year funded post that attracts an NTN(a) (National Training Number – Academic) and allows an opportunity to develop clinical skills and academic skills concurrently. The ACF is expected to complete ST3+ level training or equivalent with an integrated 25% of time spent in academic research. The aim is to obtain preliminary data to prepare a competitive application for a nationally funded research training fellowship working towards a higher degree. An AF2 post is not viewed as a pre-requisite for applying for an ACF post, however, it would be evidence of commitment to an academic career and it may be possible to develop a project undertaken during an AF2 into an academic clinical fellowship application.

An ACF post provides an opportunity to be trained in generic academic skills such as applied research skills, governance, communication and setting specific goals. Importantly, the scheme has a clearly defined entry point and an opportunity to exit academic training on completion of the programme.[22] A recent study highlighted that fellows felt that, as well as the opportunity to undertake and develop a research project, the major positive reasons for applying for a fellowship included stimulation, challenge and the opportunity to teach. However, it also highlighted that the negative factors of a fellowship included difficulty obtaining research grants, competing pressures between research, clinical work and teaching, lack of pay parity and concerns about availability of senior posts at the end of the fellowship (Table 1).[22]

ACADEMIC CLINICAL LECTURERS - ACL

Academic Clinical Lectureships are the most senior element of the integrated training pathway. They provide aspiring academic trainees with an opportunity to gain comprehensive research experience by working alongside internationally recognised researchers and clinicians. In England, these schemes are run by the National Institute for Health Research, who funded 122 of these posts in 2013. Similar schemes are run in the devolved nations. They are set up to allow 50% of time to be spent undertaking specialist clinical training and 50% undertaking research or education training. Some question whether this is enough clinical time during the final years of training in craft specialties such as surgery or anaesthetics. Applicants for these posts will be advanced in their specialty training and will have obtained a PhD/MD or equivalent or will be within three months of submission. The trainee is usually at ST3 level or above and will work towards gaining core clinical competencies to finish their training while continuing their academic development at

a post-doctoral level to enable them to run an independent research group.

NORTHERN IRELAND CLINICAL ACADEMIC PROGRAMME

The Northern Ireland Clinical Academic Programme is administered and run by Queen's University Belfast in collaboration with the Northern Ireland Medical and Dental Training Agency (NIMDTA). This enables the scheme to be accountable to NIMDTA for training purposes and quality assurance. The scheme also receives significant support from the Belfast and South Eastern Health and Social Care Trusts. This tripartite integrated model has enabled rapid roll out of clinically relevant research.

Indeed, a recent review by the GMC to find good practice in academic training schemes throughout the UK, highlighted flexibility in the Northern Ireland programme and also the effective integration with the local Trusts and good collaboration between the University, Trusts and NIMDTA.

Table 1:

Table highlighting possible positive and negative aspects of the clinical academic pathway

Positives	Negatives
Challenge of research	Lack of role models/mentors
Variety in work	Limited availability of senior academic positions
Intellectual environment/ stimulation	Longer training period
Teamwork	Difficulty in obtaining funding
Stimulation of teaching	Lack of pay parity
Stimulation of supervising research teams	Increased assessment burden due to different roles
Recognition by peers	No perfect stage in career at which to do this
Travel	Research may not 'work out'
Award of higher degree	Loss of skills especially in craft specialty
Development of critical appraisal skills	

CONSIDERING AN ACADEMIC CAREER?

As the Walport report has been implemented, some problems have been highlighted. One criticism of the new system is that doctors have to make decisions regarding their careers earlier than they would have historically. Consequently, some question whether clinicians who develop an academic interest later in their career are able to compete with those who have progressed along an academic career pathway since their Foundation Programme and, as such, may be excluded from the academic career pathway.[23]

Some further question whether the potential increase in financial burden placed on those who prolong their training through periods spent in research have been addressed adequately, potentially deterring clinicians capable of succeeding in an academic career (Table 1).[23]

Recent changes to medical school admissions have seen an increase in graduate entry.[24] The current academic training pathway may be less attractive to this cohort, with the requirement for further years of training and the resultant increased financial burden. Other models may be needed to attract these highly motivated students into academic medicine.

The relative lack of suitable role models has been highlighted for several years and has been perceived as a key element that needs to be addressed to encourage clinicians to enter and be retained in an academic career.[25] The Walport report recognised this and stated that one way to help students to understand the attractions of a career in academic medicine was to make 'sure that medical students are taught by leading clinical academics, among others'.[6] This requires teaching to be formally recognised in NHS or university contracts otherwise it may become overshadowed by other commitments as there can be very few opportunities for students to gain exposure to pure researchers.

Different specialties lend themselves more easily to the blend of academic and clinical training. Craft specialties, such as surgery, rely on regular practice to acquire and maintain skills with minimum numbers often being required to ensure competency in index procedures. Studies have already shown a reduction in the amount of time all surgical trainees are able to spend learning surgical techniques following the implementation of Modernising Medical Careers. It has been recognised that, in order to provide adequate training, the reduction in working hours must be offset by implementing measures to maximise the effectiveness of the limited training opportunities, such as simulation. This is an even more acute problem for those electing to undertake an academic training pathway.[26-28] The scrutiny of an individual surgeon's surgical outcome has recently increased due to national publication of these results. The Shape of Medical Training Review, chaired by Prof Greenaway (Vice Chancellor of the University of Nottingham), reported in the Autumn 2013.[29] It focused on the optimum balance of specialist and generalist training. It reinforced the role of academic training, but emphasised the need for the acquisition and maintenance of generalist skills until a Certificate of Specialist Training is obtained. A smaller number of individuals would then proceed to sub-specialist training after this by credentialling. The implementation of this report will have further implications for academic training.

STRATEGY FOR SUCCESS

So, what can be done to encourage success in this field? It is vital to ensure that the academic work undertaken by clinical academics addresses questions that are of clinical significance and of personal interest. If the subject is of personal interest and relevant to clinical practice then there will be a greater

desire to persevere during difficult times (unsuccessful grant applications; negative studies).

Secondly, an effective mentor is invaluable. The academic pathway, though now much clearer, still has many hurdles along the way. A mentor that can encourage, inspire, challenge and question at just the right time is indispensable in helping someone negotiate the academic training pathway.

Thirdly, cooperation between universities, health trusts and deaneries, as modelled in Northern Ireland, can enable the academic training pathway to operate effectively ensuring smooth transition between stages.

CONCLUSIONS

A career in academic medicine can be a very fulfilling one. However, time spent in academic medicine at any point in a medical career can provide an opportunity to learn valuable generic skills, improve clinical practice and provide an opportunity to develop critical thinking. These skills and experiences will be of benefit in career development but most importantly in improving the care of patients.

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Case Report

Transvaginal Oocyte Retrieval Complicated by Life-Threatening Obturator Artery Haemorrhage and Managed by a Vessel-Preserving Technique.

Ferdia Bolster[1], Edgar Mocanu[2], Tony Geoghegan[1], Leo Lawler[1]

Accepted 11th June 2014

ABSTRACT:

We report the case of a 36-year-old woman with secondary infertility who underwent routine transvaginal oocyte retrieval as part of IVF treatment. Four days following the procedure she presented with life threatening haemorrhagic shock. She underwent surgical laparotomy followed by CT and selective angiography, which demonstrated haemorrhage from a pseudoaneurysm of the obturator artery. The haemorrhage was successfully managed endovascularly with a vessel preserving covered stent.

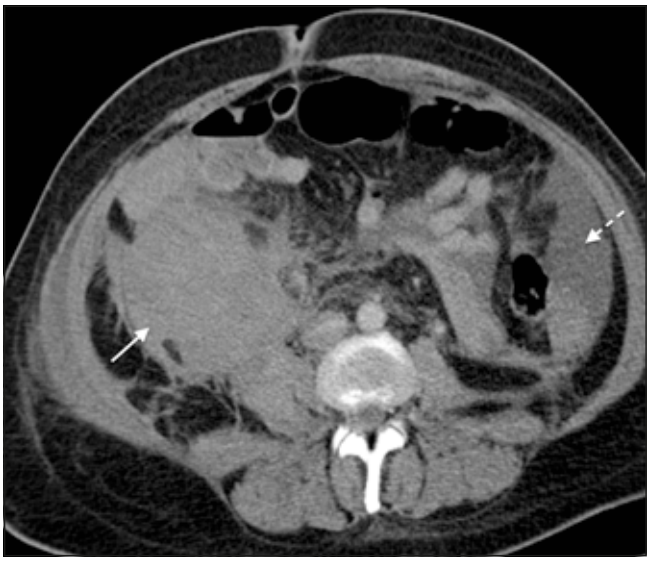

Fig 1. CT demonstrates a large right sided retroperitoneal haematoma (solid white arrow) and intra-abdominal free fluid consistent with haemorrhage (interrupted white arrow).

CASE:

A 36-year-old female with secondary infertility underwent ultrasound-guided transvaginal oocyte retrieval during her third IVF cycle. Postoperative discomfort persisted for longer than usual and she was admitted for observation. As she had persistent right sided back discomfort she remained in hospital while undergoing investigations. On the fourth day she developed light headedness and collapsed. The patient was resuscitated and underwent emergency laparotomy, which revealed a large right sided retroperitoneal haematoma. No further surgical exploration was pursued as no intraperitoneal bleeding was observed and because of the risk of severe bleeding associated with decompressing. She was transfused and haemodynamically stabilised with 5 units of packed red cells, 3 pools of plasma (Octaplase) and 2 pools of platelets and referred for radiological management. CT angiography (CTA) of abdomen and pelvis demonstrated active bleeding from a right internal iliac artery branch pseudoaneurysm and a large retroperitoneal haemorrhage (Figs 1 and 2). She was transferred directly to the angiography suite for emergency endovascular assessment and therapy.

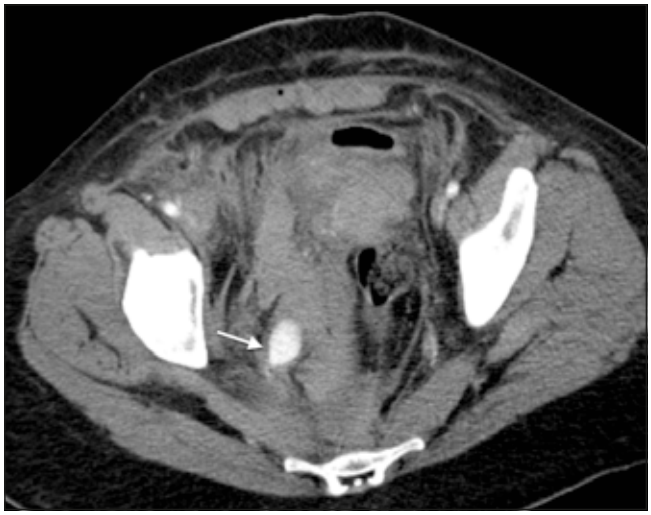

Fig 2. CTA demonstrates a vascular "blush" of a 2cm pseudoaneurysm and active extravasation from a branch of the right internal iliac artery (white arrow).

A retrograde 5Fr sheath was inserted into the left common femoral artery under ultrasound guidance. Up and over selective cannulation of the right internal iliac artery was performed and demonstrated a relatively large obturator artery pseudoaneurysm (see Fig 3). The pseudoaneurysm

1 Department of Radiology, Mater Misericordiae University Hospital, Dublin, Ireland. 2 Department of Obstetrics and Gynaecology, Royal College of Surgeons in Ireland, Dublin, Ireland

Correspondence to: Ferdia Bolster

Email: ferdiabolster@hotmail.com

neck was crossed with a combination microcatheter .014 wire. The bleeding site was treated with a 3mm x10mm coronary artery covered stent (Jo Stent Graftmaster) (see Fig 4). Subsequent DSA showed good stent position and cessation of extravasation of contrast (Fig.5). The patient made a rapid full recovery and a follow up CTA performed the next day confirmed good stent positioning with no extravasation of contrast into the treated pseudoaneurysm.

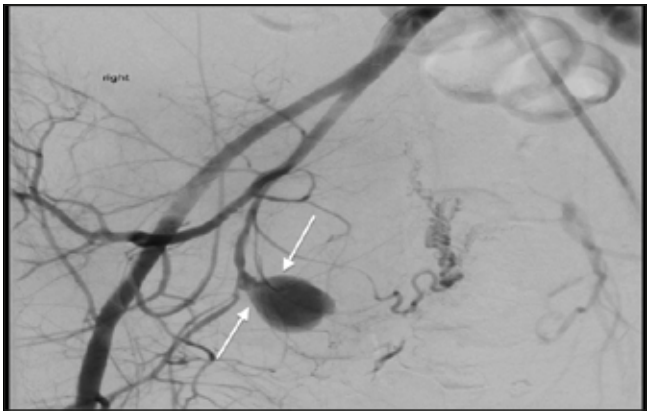

Fig 3. Up and over selective cannulation of the right internal iliac artery was performed and demonstrated a 2cm saccular obturator artery pseudoaneurysm (white arrows).

DISCUSSION:

Transvaginal oocyte retrieval is a frequently performed assisted reproduction technology (ART) procedure. Under direct ultrasound guidance an aspiration needle is passed through the lateral fornix of the vagina into the stimulated ovary with subsequent aspiration of follicles.

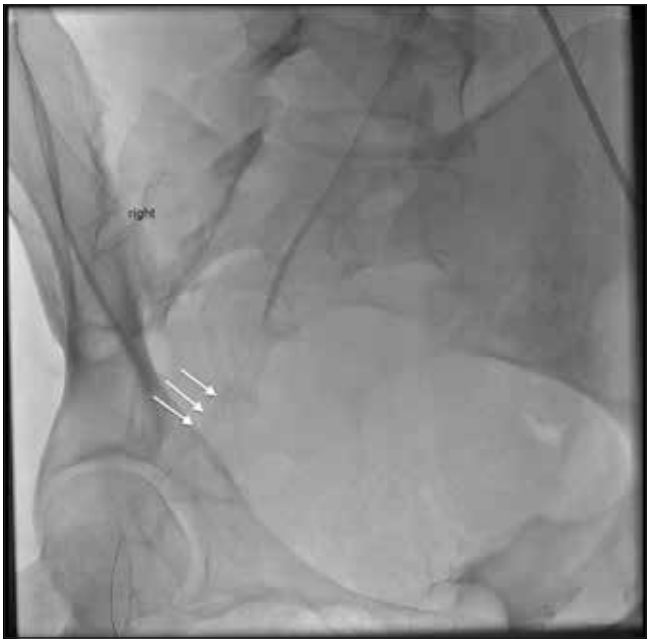

Fig 4. The bleeding site was treated with a 3mm x10mm coronary artery covered stent (Jo Stent Graftmaster) (white arrows).

The internal iliac arteries and their branches are potentially at risk as they lie in close proximity to the ovarian tissue. Pelvic conditions like endometriosis or severe PID, frequently encountered in patients requiring IVF can fix the ovary upon the pelvic wall increasing the risk of organ injury. Minor arterial/venous haemorrhage, thought to arise from direct trauma to the adjacent vessels, is a common complication occurring in 1.4-18.4% of punctures[1] but can usually be managed with local treatment such as local pressure.[2] Internal iliac pseudo-aneurysm is an extremely rare but potentially fatal complication of ART. It has only twice been reported in the literature[3,4]. Both previously described cases presented much later following initial oocyte retrieval with one patient presenting in the 29th gestational week and the other over 10 years after successful IVF[3,4] and neither case presented in extremis. Lifesaving laparoscopy or laparotomy may be required in cases of large bleeding[5].

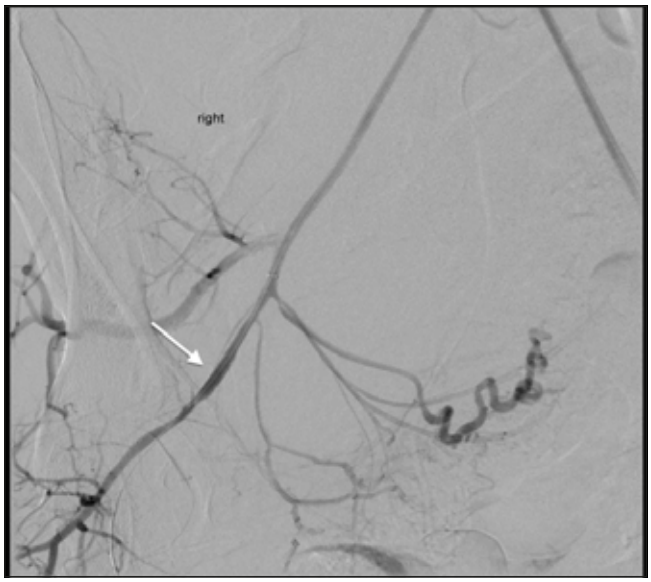

Fig 5. Post stenting DSA showed good stent position and cessation of extravasation of contrast with preservation of the native artery (white arrow).

We are not aware of another case of retroperitoneal bleeding reported to date. While the abdominal bleed or indeed the aneurysm can be easily diagnosed, a retroperitoneal bleed is usually concealed and requires specific management.

An endovascular approach offers an alternative with high success rate and the additional advantage of preserving fertility through organ preservation[6]. Traditionally selective uterine artery embolisation is performed with an embolic agent (e.g. coil, gelfoam, thrombin or glue) and typically involves vessel sacrifice.[5,6] To our knowledge this is the first case of an internal iliac pseudoaneurysm following transvaginal oocyte retrieval managed with an alternative vessel preserving stent technique.

Rapid access to advanced non-invasive and invasive diagnostic imaging was key to the successful management of this case. CTA permitted direct transfer to fast selective angiography. Microcatheter, covered stent techniques allowed immediate bleeding control and ultimately organ and vessel preservation. As the complexity of cases attending for ART is increasing and the procedure is performed on an ever

expanding number of patients it is important to recognize such complications and avail of rapid and efficient radiological diagnosis and treatment, particularly in the circumstances of concealed bleeding where the surgical intervention is limited.

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Grand Rounds

Prevention and Management of Acute Kidney Injury

John Harty

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ABBREVIATIONS

ACEi – Angiotensin Converting Enzyme inhibitors, AKI – Acute Kidney Injury, ARB – Angiotensin Receptor Blockers, ATN – Acute Tubular Necrosis, BP – Blood Pressure, CKD – Chronic Kidney Disease, eGFR – estimated Glomerular Filtration Rate, ESRD – End Stage Kidney Disease, GAIN – Guidelines and Audit Implementation Network, GFR – Glomerular Filtration Rate, MAP – Mean Arterial Pressure, NCEPOD – National Confidential Enquiry into Patient Outcome and Death, NICE – National Institute of Clinical Excellence, NSAIDs – Non Steroidal Antiinflamatory Drugs, SBP – Systolic Blood pressure

INTRODUCTION

Acute Kidney Injury (AKI) is common, expensive to manage, prolongs hospitalization and is associated with increased mortality. In 2009 the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a report into the care of patients who died with a diagnosis of AKI[1]. Only 50% of patients were deemed to have had a 'good" standard of care. The NCEPOD report identified inadequate assessment of patients at risk of AKI and deemed 60% of post-admission AKI was predictable and 21% was avoidable. Two thirds of patients had a significant level of AKI before a diagnosis was made and there was inadequate senior review of these patients. More severe AKI is associated with higher mortality. The in-hospital mortality rate for AKI has been reported at 24% and increases with more severe AKI[2]. In Northern Ireland, an audit of patients with severe AKI requiring dialysis demonstrated a 90 day mortality rate of up to 40% (personal communication) In 2013, the National Institute for Health and Care Excellence (NICE) published guidance on AKI[3] . NICE have calculated that if AKI was recognized and treated with attention to hydration and medication, 100,000 cases could be prevented and up to 42,000 deaths avoided annually. The National Clinical Director for Kidney[4] care has stated that management of AKI can provide a barometer by which we can measure and improve the care of the acutely unwell patient whatever the underlying cause. There is clearly a need for all clinicians to be competent in managing this common condition. The aim of this Grand Rounds article is to provide practical information on prevention and management of AKI.

DEFINITION OF AKI

The term AKI has replaced that of Acute Renal Failure. This is to recognize that there are varying degrees of kidney injury severity and to encourage early identification and management of AKI.

AKI is defined by an acute reduction in kidney function as identified by an increase in the serum creatinine and reduction in urine output.

The severity of AKI is reflected by the AKI stage[5] AKI 1 – 3 (Table 1), with Stage 1 defined as a rise of serum creatinine of ≥26 umol/L or 1.5 to 1.9 times the baseline serum creatinine. Such minor serum creatinine elevations are associated with increasing mortality[6] providing a rationale for the inclusion of this apparently small rise in serum creatinine in the AKI staging scheme.

Table 1:

Kidney Disease Improving Global Outcomes (KDIGO) staging classification for AKI

Kidney Disease Improving Global Outcomes (KDIGO) staging classification for AKI		
Stage	Serum creatinine (Scr) criteria	Urine output criteria
1	Rise in Scr of 26 umol/L within 48 hrs Increase of 1.5 – 1.9 x baseline Scr within past 7 days	< 0.5 mL/Kg/hr for > 6 consecutive hours
2	Increase of 2 - 2.9 x baseline Scr	< 0.5 mL/Kg/hr for > 12 consecutive hours
3	Increase of 3 x baseline Scr or Scr ≥ 354 umol/L or Commenced on dialysis	
Additional RIFLE Criteria reflecting outcome of AKI		
Loss	Need for ongoing dialysis for > 4 weeks	
Failure	Need for ongoing dialysis for > 3 months	

There are also two outcome stages – Loss and End Stage Renal Disease (ESRD)[7]. These stages recognize that AKI can subsequently lead to chronic kidney disease (CKD) and

Consultant Renal Physician, Daisy Hill Hospital, Northern Ireland.
John.Harty@southerntrust.hscni.net
Corresponding Author: Dr John Harty

ESRD requiring long term dialysis (Figure 1). Studies in the diabetic population[8] have shown that episodes of AKI double the risk of patients developing Stage 4 CKD (estimated GFR 15 – 29 mL/min/1.73m^2). Recent NICE Guidelines on CKD recommend monitoring of all patients who recover renal function following an episode of AKI for a minimum of 2 years to ensure early detection and management of CKD[3].

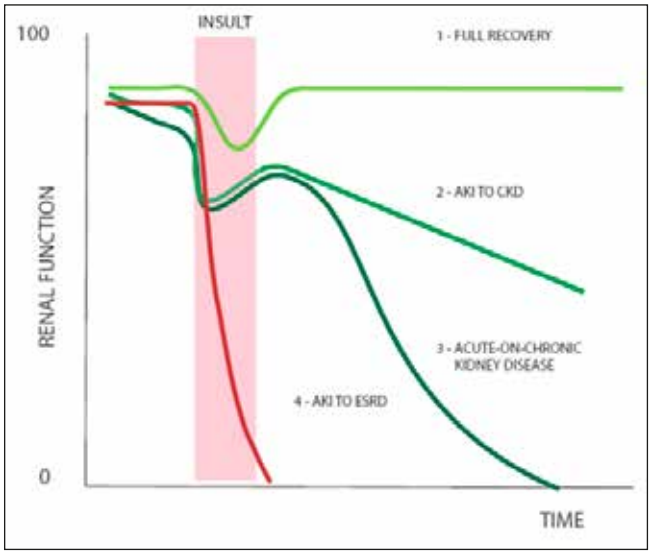


Fig 1. Potential outcomes following episode of Acute Kidney Injury

It is important to appreciate that the serum creatinine does not accurately reflect the Glomerular Filtration Rate (GFR) in a patient who is not in steady state. The serum creatinine is influenced by creatinine generation, volume of distribution and excretion. Thus a sudden fall in GFR is accompanied by a slow rise in serum creatinine which plateaus at between 7 and 10 days when creatinine production equals creatinine excretion. Large changes in GFR are initially manifested as small changes in serum creatinine. This may lead to a delay in recognizing the degree of AKI in a patient demonstrating an initial "minor" rise in serum creatinine. Similarly, during recovery from AKI, the serum creatinine may lag behind renal recovery.

E-ALERT FOR ACUTE KIDNEY INJURY

A national algorithm, standardizing the definition of AKI, has now been agreed for use in Northern Ireland. This has been integrated into the Regional Laboratory system and will identify patients with Stages 1 -3 AKI, based on change in serum creatinine, and create an E-Alert (Figure 2). This E-Alert will be highlighted on the results reporting systems and patient management systems (Northern Ireland Electronic Care Record) with a link to the Guidelines and

Fig 2. Example of AKI E-Alert

Audit Implementation Network (GAIN www.gain-ni.org) Acute Kidney Injury Algorithm (Figure 3). This alert will automatically identify patients with AKI and enhance clinicians' ability to recognize AKI and instigate early treatment.

CAUSES OF AKI

AKI is common with a recent study reporting an incidence of 25% in unselected medical admissions[9]. It is important to recognize that two thirds of episodes of AKI develop prior to the hospital admission. This affords an important opportunity to identify and prevent AKI in at risk patients.

For clarity the causes of AKI have been divided into three groups; Pre-renal, Intrinsic-renal and Post-renal. Table 2 lists some common causes.

In reality the majority of causes of AKI are not renal specific. The kidneys receive 25% of the cardiac output at rest are

TABLE 2

Causes of AKI

Pre-renal (hypoperfusion)	Intrinsic-renal	Post-renal
Volume depletion • Dehydration • Blood loss Hypotension • Sepsis • Medications • Cardiac failure	Acute Tubular Injury Interstitial nephritis Glomerulonephritis Vasculitis	Bladder outlet obstruction Bilateral ureteric obstruction. Obstruction of a single functioning kidney.

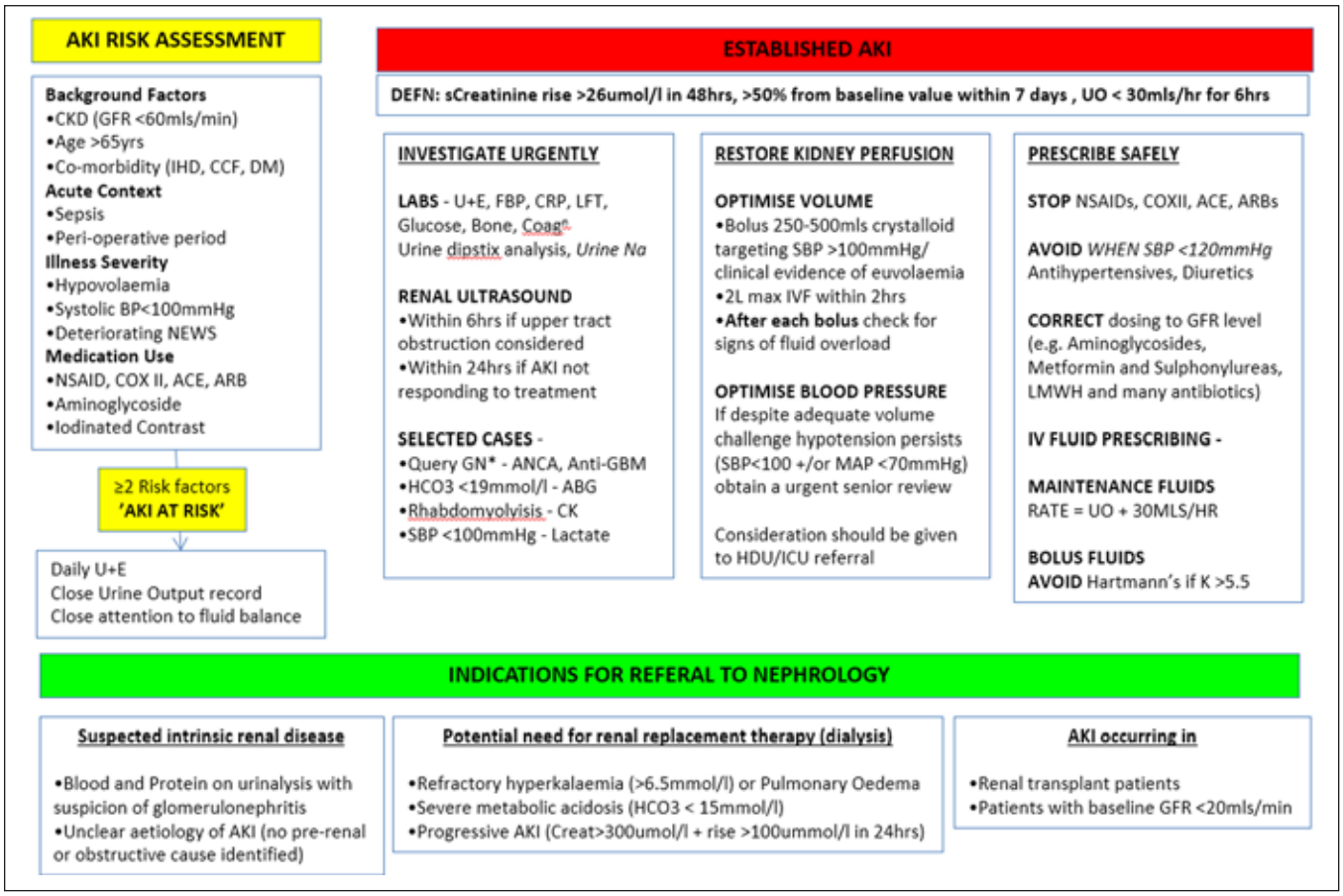


Fig 3. Northern Ireland GAIN AKI Algorithm

therefore sensitive to any systemic upset. In the largest trial of patients admitted to ICU with severe AKI[10] the most common causes (often in combination) were septic shock (47%), post major surgery (34%), cardiogenic shock (27%), and hypovolaemia (26%). . Deterioration in kidney function should provoke careful inspection for the common causes of haemodynamic compromise and sepsis throughout the body. Only when pre-renal causes have been excluded should specific attention return to consideration of intrinsic renal disease and renal tract obstruction.

PATHOPHYSIOLOGY OF PRE-RENAL AKI AND ACUTE TUBULAR NECROSIS (ATN)

Well perfused, healthy kidneys will produce on average 180 L of glomerular filtrate per day, the majority of which is reabsorbed leading to a usual excretion of 1.5 – 2 L of urine. Production of this volume of filtrate is dependent on an adequate glomerular capillary pressure which is the driving force for filtration. Normal glomerular capillary pressure is maintained by afferent arteriole vasodilation and efferent vasoconstriction. This mechanism is known as renal autoregulation. The ability to maintain renal haemodynamics becomes impaired at a renal arterial pressure below 70 mmHg[11]. When this occurs the GFR will fall in proportion to further reduction in blood pressure. The GFR will cease when the renal arterial blood pressure is ≤ 50 mmHg.

A reduction in renal perfusion due to hypotension results in prostaglandin mediated dilation of the afferent renal arteriole and constriction of the efferent glomerular capillary mediated by angiotensin II. However in patients with impaired autoregulation the GFR will fall even if the mean arterial pressure remains within the normal range.

Factors which increase susceptibility to renal hypoperfusion are listed in Table 3.

With prompt restoration of intravascular volume and blood pressure, normal renal haemodynamics can be restored resulting in complete recovery of renal function.

TABLE 3:

Factors increasing susceptibility to renal hypoperfusion

Failure to decrease arteriolar resistance • Structural changes in renal arterioles (old age, atherosclerosis, hypertension, CKD) • Reduction in vasodilatory prostaglandins (nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors • Afferent glomerular arteriolar vasoconstriction (sepsis, hypercalcaemia, hepatorenal syndrome, ciclosporin / tacrolimus, radiocontrast agents)
Failure to increase efferent arteriolar resistance • Angiotensin converting enzyme inhibitors • Angiotensin receptor blockers
Renal artery stenosis

However, in the face of persisting hypoperfusion, endogenous vasoconstrictors increase afferent arteriolar resistance. Causes of a low perfusion state are shown in Table 4.

TABLE 4:

Causes of Renal Hypoperfusion

Hypovolaemia • Extrinsic fluid loss (gastrointestinal, renal losses (e.g. diuretics), skin losses
Cardiac causes • Congestive cardiac failure, tamponade, valvular disease
Reduced peripheral vascular resistance • Sepsis, hepatorenal syndrome, drug overdose, vasodilators (e.g. antihypertensives)
Local renal hypoperfusion • Renal artery stenosis, malignant hypertension

Renal hypoperfusion reduces glomerular capillary pressure and the GFR. The post-glomerular capillary bed which perfuses the tubules will also have diminished blood flow leading to a subsequent ischaemic structural injury to the renal tubules often referred to as ischaemic Acute Tubular Necrosis (ATN)[12]. This state is characterized by a rising serum creatinine and a reduced urine volume refractory to further increases in intravascular volume and renal perfusion pressure. Management of this state includes avoidance of fluid overload, maintenance of an adequate mean arterial pressure (≥ 65 mmHg), correction of electrolyte disorders (potassium) and treatment of the underlying precipitating condition. Such patients may require a temporary period of dialysis support.

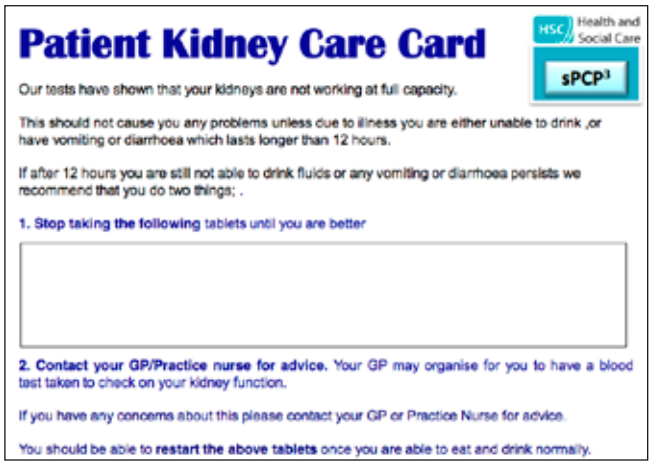
AKI in hospitalized patients can be thought off as a two hit process. Susceptibility factors create an admission patient group vulnerable to a subsequent 'second hit' - hypoperfusion events[13]. This can be seen in studies of AKI in critically ill patients[10] where the median length of inpatient stay prior to the development of severe AKI is 5 days. This delay is an opportunity to both prevent and reduce the severity of AKI in hospitalized patients.

PREVENTION OF AKI

Community Acquired

Patients in the community with CKD (eGFR < 60 mL/min/1.73m^2) and patients with normal renal function who are treated with an ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) are at increased risk of AKI if they develop an illness associated with hypovolaemia and hypertension. Such patients can be identified, educated and issued with a Kidney Care Card (Figure 4). This provides instructions for temporary cessation of certain medications, which may in this setting, induce, exacerbate and complicate AKI. These drugs can be remembered by the mnemonic DAMN (diuretics, ACEi/ARBs, metformin, NSAIDs).

Hospitalised patients


Patient Kidney Care Card

HSC Health and Social Care

sPCP[3]

Our tests have shown that your kidneys are not working at full capacity.

This should not cause you any problems unless due to illness you are either unable to drink ,or have vomiting or diarrhoea which lasts longer than 12 hours.

If after 12 hours you are still not able to drink fluids or any vomiting or diarrhoea persists we recommend that you do two things; .

1. Stop taking the following tablets until you are better

2. Contact your GP/Practice nurse for advice. Your GP may organise for you to have a blood test taken to check on your kidney function.

If you have any concerns about this please contact your GP or Practice Nurse for advice.

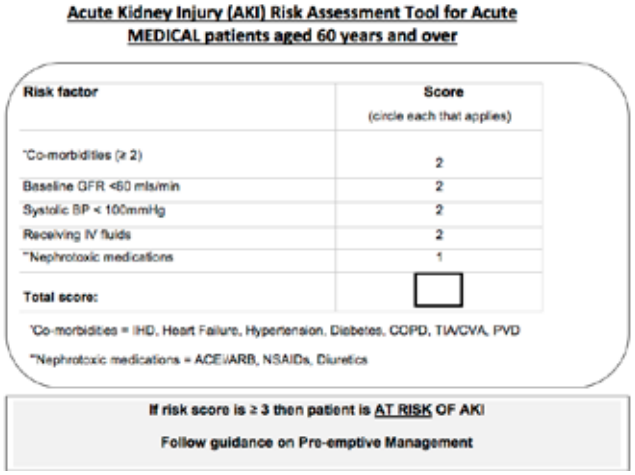
You should be able to restart the above tablets once you are able to eat and drink normally.

Fig 4. Community Kidney Care Card

Prevention of AKI should follow the following principles;

Risk Assessment

All patients, both on admission and during their hospital stay should be assessed regularly for their risk of developing AKI. Figure 5 gives an example of a risk assessment tool used in the Southern Health and Social Care Trust. NICE have identified the following patient groups (Table 5) who require special attention.


Acute Kidney Injury (AKI) Risk Assessment Tool for Acute MEDICAL patients aged 60 years and over

Risk factor	Score (circle each that applies)
*Co-morbidities (≥ 2)	2
Baseline GFR <60 ml/min	2
Systolic BP < 100mmHg	2
Receiving IV fluids	2
**Nephrotoxic medications	1
Total score:	

*Co-morbidities = IHD, Heart Failure, Hypertension, Diabetes, COPD, TIA/CVA, PVD

**Nephrotoxic medications = ACE/ARB, NSAIDs, Diuretics

If risk score is ≥ 3 then patient is AT RISK OF AKI

Follow guidance on Pre-emptive Management

Fig 5. Example of an admission AKI risk assessment tool

Perioperative AKI is common. Recognition of patients who are at risk will allow measures to be undertaken to reduce exposure to renal insults and maximize renal recovery should AKI occur[14]. An similar risk assessment tool for use in Surgical patients is shown in Figure 6.

Optimisation of fluid balance

Fluid volume status should be carefully assessed with respect to both fluid depletion and fluid overload. Patients at risk of dehydration due to prohibited or poor oral intake should be prescribed maintenance IV fluids.

Optimisation of blood pressure

Hypotension systolic blood pressure (SBP) < 110 mmHg

/ mean arterial pressure (MAP) < 65 mmHg) needs urgent assessment and treatment with IV fluid challenges and vasopressor agents where indicated.

TABLE 5:

Patients at risk of AKI

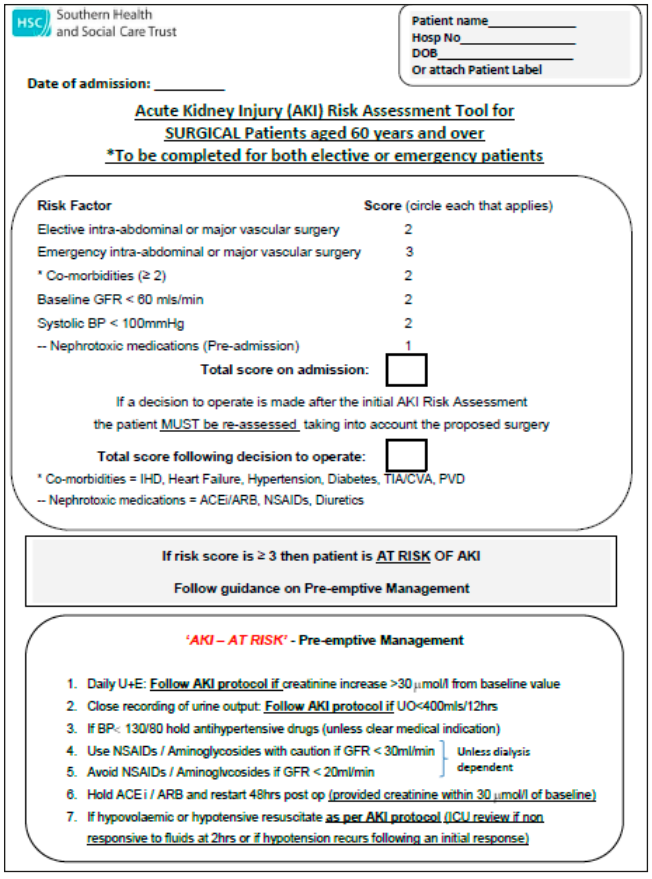
Age over 65 years
Existing CKD (eGFR < 60 mL/min/1.73m^2), Previous episode(s) of AKI
Co – Morbidity (Cardiac / Liver failure, Diabetes Mellitus
Use of nephrotoxic drugs (Diuretics, ACEi/ARBs, NSAIDs)
Diagnosis of sepsis
Hypovolaemia / Hypotension / Oliguria (< 0.5 mL/kg/hr)
Deteriorating Early Warning Scores
Symptoms / history or condition that may lead to urinary tract obstruction
Use of iodinated contrast agents within the previous week

Medication review

Temporary cessation of ACEi and ARBs is appropriate in patients with dehydration, hypotension (systolic blood pressure < 110 mmHg) and / or deteriorating renal function. In patients who continue to be prescribed ACEi or ARBs, alteration of timing of drug prescription to 6 pm will allow adequate time to assess clinical state and review their renal function in case there is a need to temporarily hold these medications.

Where clinically indicated aminoglycosides can continue to be used paying careful attention to renal function and drug levels.

Fig 6. Example of a Surgical AKI risk assessment tool


Southern Health and Social Care Trust

Patient name_____
Hosp No_____
DOB_____
Or attach Patient Label

Date of admission: _____

Acute Kidney Injury (AKI) Risk Assessment Tool for SURGICAL Patients aged 60 years and over
To be completed for both elective or emergency patients

Risk Factor	Score (circle each that applies)
Elective intra-abdominal or major vascular surgery	2
Emergency intra-abdominal or major vascular surgery	3
* Co-morbidities (≥ 2)	2
Baseline GFR < 60 mls/min	2
Systolic BP < 100mmHg	2
-- Nephrotoxic medications (Pre-admission)	1
Total score on admission:	☐

If a decision to operate is made after the initial AKI Risk Assessment the patient MUST be re-assessed taking into account the proposed surgery

Total score following decision to operate: ☐

* Co-morbidities = IHD, Heart Failure, Hypertension, Diabetes, TIA/CVA, PVD
-- Nephrotoxic medications = ACEi/ARB, NSAIDs, Diuretics

If risk score is ≥ 3 then patient is AT RISK OF AKI

Follow guidance on Pre-emptive Management

***'AKI – AT RISK'* - Pre-emptive Management**

1. Daily U+E: Follow AKI protocol if creatinine increase >30 μmol/l from baseline value
2. Close recording of urine output: Follow AKI protocol if UO<400mls/12hrs
3. If BP< 130/80 hold antihypertensive drugs (unless clear medical indication)
4. Use NSAIDs / Aminoglycosides with caution if GFR < 30ml/min
5. Avoid NSAIDs / Aminoglycosides if GFR < 20ml/min

Unless dialysis dependent

6. Hold ACE i / ARB and restart 48hrs post op (provided creatinine within 30 μmol/l of baseline)
7. If hypovolaemic or hypotensive resuscitate as per AKI protocol (ICU review if non responsive to fluids at 2hrs or if hypotension recurs following an initial response)

Reducing the risk of contrast induced AKI

AKI secondary to radiological contrast media typically occurs within 72 hrs of receiving such agents. The risk of contrast nephropathy can be reduced by temporary cessation of potentially nephrotoxic medication and adequate volume expansion (Table 6)

TABLE 6:

Prevention of Contrast Nephropathy

Identify risk	• eGFR ≤ 30 mL/min/1.73m^2 • eGFR 30 – 60 mL/min/1.73m^2 and risk factors (Table 5)
Manage risk	• Hydration – IV 1.4% sodium bicarbonate / 0.9% saline at 3 mL/kg/hr 1hr pre and 1 mL/kg/hr for 6hrs post procedure • Omit potentially nephrotoxic medications (ACEi/ARBs / NSAIDs / metformin on day of procedure and do not restart until renal function stable at 48 – 72 hrs • Use low osmolar agents in the lowest dose. • Recheck renal function 48 – 72 hrs following the procedure

ASSESSMENT OF AKI

Clinical assessment

This should begin with a search for the cause of AKI focusing on clinical evidence of hypoperfusion states (volume depletion and hypotension) and urinary tract obstruction. AKI in the setting of resistant hypotension suggests significant underlying sepsis, the source of which may not be immediately apparent especially in cases of intra-abdominal sepsis.

Intrinsic renal disease in the form of vasculitis may present with a typical rash, uveitis and / or arthropathy. Intrinsic renal disease should always be considered where AKI is occurring in the absence of significant dehydration, hypotension and obstruction.

The effect of AKI should also be assessed, paying particular attention to evidence of volume overload – often manifest by peripheral and pulmonary oedema and increasing oxygen requirements. In severe AKI (Stage 3) pericarditis and encephalopathy may be present.

Dipstick urinalysis is part of the clinical assessment and should be done as soon as urine is available for testing. Hypoperfusion states are suggested by a raised urine specific gravity (≥ 1.020). In the absence of haemodynamic upset and

sepsis, the presence of blood and protein in the urine should prompt consideration of a vasculitis / glomerulonephritis rather than a urinary tract infection.

Laboratory and Radiological Investigations

The GAIN AKI Algorithm (Figure 3) lists the required investigations.

In patients suspected of underlying sepsis, a serum lactate and arterial blood gas are essential in defining the severity of the metabolic upset.

Where there is no obvious precipitating factor for AKI, a renal immunology screen (including antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies (anti-GBM), serum electrophoresis and serum free light chains) should be sent urgently as the clinical management of such cases requires prompt specialist treatment.

In addition the finding of AKI, anaemia and thrombocytopenia with a normal coagulation profile should prompt a search for haemolysis (blood film, haptoglobulins) which occurs in Haemolytic Uraemic Syndrome, malignant hypertension, scleroderma and pre-eclampsia.

A chest x-ray can provide both evidence of a cause (pneumonia, pulmonary shadowing in vasculitis) and also help evaluate potential volume overload.

Renal tract ultrasound should be done within 6 hours where obstruction is considered. The presence of bilateral hydronephrosis and an empty bladder will require an urgent non-contrast CT scan to identify retroperitoneal obstruction to the ureters.

The presence of AKI should not prevent the use of contrast enhanced CT scanning to diagnose the source of sepsis, especially if a surgically remediable condition (intra-abdominal abscess, ischaemic bowel) is being considered.

MANAGEMENT OF ESTABLISHED AKI

Restore Renal Perfusion

As the majority of cases of AKI occur in association with volume depletion and sepsis, it is essential to restore effective renal perfusion as soon as possible. This will allow early recovery of renal function and help to avoid the development of acute tubular necrosis.

Optimise intra-vascular fluid volume.

Volume status should be carefully assessed and an attempt should be made to categorise the patient into one of three states; hypovolaemic, euvolaemic or hypervolaemic.

Hypovolaemic patients may have clinical signs of dehydration, are oliguric (urine output < 30 mL/hr) often with a concentrated urine (Specific Gravity ≥ 1.020)

There is no gold standard to definitively identify dehydration. However, hypotension (SBP < 110 mmHg), a postural fall in blood pressure with increase in heart rate, reduction in peripheral perfusion / skin turgor and dry mucous membranes are indicative signs.

Hypovolaemia should be promptly corrected with repeated boluses of 250 – 500 mL of crystalloid up to an initial total of 2 litres over 2 hours.

Hartmann's solution or 0.9% sodium chloride solution should be used. Hartmann's solution contains a small amount of potassium (5 mmol/L) and should be avoided in patients with significant hyperkalaemia (Potassium ≥ 6 mmol/L). Large volumes of 0.9% sodium chloride can provoke a hyperchloraemic metabolic acidosis.

Failure of the patient to maintain an effective blood pressure following this regime should raise the possibility of underlying sepsis or significant ongoing losses. Both these latter scenarios require senior assessment rather than continuing to prescribe increasing large volumes of fluid in the face of poor urine output. Fluid accumulation resulting in a positive fluid balance is a frequent event in critically ill patients with AKI. Such fluid accumulation (> 10% fluid weight gain) is independently associated with increased mortality[15] fails to improve renal function and is associated with worsening respiratory function.

Euvolaemia is characterised by an absence of clinical signs of dehydration, haemodynamic stability and an absence of volume overload. Oliguria in this context often reflects established ATN and will not respond to increasing fluid challenges, which put the patient at risk of fluid overload. In this phase, recovery of an adequate urine output is impossible to predict. Fluid intake should be restricted to a match daily output / losses. For patients who require ongoing maintenance IV fluids, one regime is to prescribe hourly crystalloid at a rate of the previous hours urine output + 30 mL.

Patients should be carefully assessed for signs of hypervolaemia. Features may include a raised JVP, peripheral and pulmonary oedema (clinically and radiologically). Calculation of total fluid balance since admission should alert clinicians to the potential of fluid overload. In the presence of AKI, hypervolaemic patients are vulnerable to pulmonary oedema and should be fluid restricted. There is no definitive evidence that the use of loop diuretics alters outcome in such patients. However, it is appropriate to consider a short trial of loop diuretics in patients with features suggestive of pulmonary oedema provided the patient has a reasonable perfusion pressure (MAP ≥ 65 mmHg, SBP ≥ 110 mmHg). Failure to respond is an indication for urgent haemodialysis and ultrafiltration.

Optimise Blood Pressure

Blood pressure is key to driving ultrafiltration at the glomerulus. Within the glomerulus the systemic blood pressure creates a hydrostatic pressure of 70 mmHg. This is opposed by the colloid oncotic pressure of 30 mmHg and hydrostatic back pressure from the tubules (20 mmHg). The

net filtration pressure which drives the production of up to 180 litres of glomerular filtrate is only 20 mmHg.

Absolute hypotension (defined as a SBP < 90 mmHg) has been shown to be associated with the development of AKI following sepsis and major surgery[16]. However, relative hypotension (where there is a decrease in BP from pre-morbid levels in the absence of overt hypotension) has been shown to be an independent contributor to the development of AKI in elderly patients[17]. Maintenance of SBP according to pre-morbid values may play an important role in preventing kidney injury in hospitalised patients.

In patients with AKI and hypotension, blood pressure should be targeted to a MAP of ≥ 65 mmHg. This can be achieved by three interventions.

1. Withholding drugs that interfere with renal autoregulation (ACEi / ARBs). Temporary cessation of all drugs that induce hypotension. This includes antihypertensives, diuretics, and agents such as nicorandil and opiates.
2. Correction of hypovolaemia as described above.
3. Consideration of vasopressor therapy (i.e. noradrenaline) in patients refractory to adequate correction of hypovolaemia. Vasopressors should be considered early in such patients to avoid needless fluid overload. Patients should be clearly identified as being suitable for vasopressor therapy and referred to Critical Care Teams. It should be stressed that there is no evidence for a role for "renal dose" dopamine in the management of AKI. In addition, dobutamine has significant vasodilatory effects which can aggravate hypotension and worsen renal perfusion in patients with sepsis and AKI.

Prescribe Medicines Safely

Patients who develop AKI require revision of all prescribed medications.

Drugs interfering with renal perfusion

These include those medications interfering with renal autoregulation (ACEi/ARBs, NSAIDs) and those medications with the potential to reduce blood pressure. Antihypertensive medications (including diuretics) should be withheld in patients with both absolute (SBP < 90 mmHg) and relative (SBP < 120 mmHg) hypotension. Patients treated with beta blockers need careful consideration of the risk / benefit of temporary cessation.

Drugs requiring dose reduction or cessation

All medications that are metabolized and excreted by the kidneys should be dose adjusted for an assumed eGFR of < 10 mL/min/1.73m^2. Such drugs include fractionated heparins, opiates, penicillin-based antibiotics, sulphonylurea-based hypoglycaemic agents, and aciclovir. Although metformin is not specifically nephrotoxic, it will accumulate in renal failure and is associated with life threatening lactic acidosis.

Drugs requiring close monitoring

These include warfarin and aminoglycosides. Gentamicin in particular demands careful consideration. It should not be withheld where there is a clear benefit to its use (life threatening sepsis). If used, the daily trough level should be < 1 mg/L .

Drugs aggravating hyperkalemia

All drugs which block renal excretion of potassium (trimethoprin and potassium sparing diuretics (spironolactone, amiloride) should be stopped. In addition, both beta-blockers and digoxin can inhibit the sodium / potassium ATPase pumps which move potassium inside cells. The presence of these drugs can render the patient resistant to insulin/glucose treatment of hyperkalaemia.

Referral criteria to a Nephrology Team

Whilst AKI is common, less that 10% of such patients require direct care by Nephrologists[2]. Studies show that less than 4% of hospitalized patients with AKI are treated with dialysis[2].

The indication for dialysis is based on the complications of AKI rather than an absolute value for serum urea, creatinine or GFR. There is no clear benefit for undertaking dialysis solely on the basis of a low GFR. Instigation of dialysis carries with it risk (access issues, haemodynamic instability) and can delay the identification of recovery of independent renal function.

The Northern Ireland GAIN guidelines[18] recommend referral of the following groups of patients (Table 7).

TABLE 7:

GAIN AKI referral guidelines.

Referral Indication	Comments
Complications of AKI requiring dialysis	Refractory hyperkalaemia, pulmonary oedema. Severe metabolic acidosis due to kidney failure (pH < 7.2). Uraemic pericarditis and encephalopathy.
Suspicion of a diagnosis that may require specialty Nephrology treatment	For example; vasculitis, myeloma, interstitial nephritis or glomerulonephritis.
AKI occurring in patients with CKD	Stage 4 or 5 CKD (eGFR ≤ 30 mL/min/1.73m^2)
AKI occurring in renal transplant patients	Complex interactions with immunosuppressive medications. Infection can provoke acute rejection.

Nephrology – Critical Care interface

Many patients develop AKI in the context of multiple organ failure. They often manifest hypotension, severe metabolic acidosis and hypoxia due to pulmonary oedema. Such patients may require mechanical ventilation and vasopressor therapy to support renal replacement. This level of care is best delivered in an Intensive Care Unit rather than on a Renal ward and early involvement of the Critical Care team should be sought.

Nephrology – Conservative care interface

It should also be recognized that AKI may reflect a terminal event in a hospitalised patient. Such patients usually have suffered a very severe episode of illness complicating the progression of advanced, untreatable co-morbidity.

In such patients, provision of dialysis therapy is futile, is likely to prolong suffering and lead to false hopes of survival.

Senior medical staff should identify these patients early in the course of their deterioration an if necessary discuss with the Nephrology team the ceiling of care for renal support.

TWO SCENARIOS

Case 1:

A 78 year old woman is admitted to the surgical ward with a left iliac fossa pain and a clinical suspicion of acute diverticulitis. She has a background of CKD (eGFR 35 mL/min/1.73m^2), hypertension treated with perindopril and type 2 diabetes treated with metformin. One week before admission she developed dysuria and was empirically prescribed trimethoprim. Despite a poor oral intake during the week she continued to take all of her medication. On admission she was febrile (38^{o}C), hypotensive (BP 80/50 mmHg), and heart rate 120 bpm. Oxygen saturation was 96% on room air. Urine output was 5 – 10 mL/hr. Investigations reveal; stage 3 AKI (creatinine 480 umol/L), hyperkalaemia – Potassium 7.1mmol/L, acidaemia (pH 7.25) with a high anion gap metabolic acidosis, elevated plasma lactate (8 mmol/L), CRP 235. She was treated with IV Tazocin® / gentamicin and insulin/glucose for her hyperkalaemia. Over the next 24 hr despite 6 L of Hartmann's solution she remained hypotensive and oliguric. Her serum creatinine rose to 650 umol/L. She became increasingly hypoxic with radiological evidence of pulmonary oedema and was transferred to ICU for mechanical ventilation, vasopressor support and dialysis. A CT scan of abdomen demonstrated a perforated sigmoid diverticulum with generalized peritonitis. She underwent a left hemicolectomy but 2 days later whilst still vasopressor dependent in ICU suffered a cardiac arrest from which she did not recover.

Learning points:

Prevention: This lady was at extremely high risk of developing AKI in the community. She has pre-existing CKD, is elderly with significant co-morbidity and is treated with an ACEi. Such patients should be identified with from the GP register, provided with a Kidney Care Card and counseled to temporarily stop potentially nephrotoxic drugs (including metformin) during periods of poor oral intake. In addition, trimethoprim should be used with caution in patients with Stage 4/5 CKD due to its potential to cause hyperkalaemia.

Treatment: It is essential to restore an effective blood pressure within the first 4 hr of hospital admission. Failure to achieve an adequate BP (MAP > 65 mmHg) despite an initial rapid infusion of up to 2 L of crystalloid is a marker of illness severity. In the absence of obvious fluid / blood loss or cardiogenic shock, such patients should be regarded as being in septic shock and should be referred to the Critical Care team for consideration of vasopressor therapy. In this case additional fluids failed to restore an effective perfusion pressure, failed to improve renal function and contributed to the development of pulmonary oedema. Finally this case demonstrates the high mortality associated with AKI where the renal insult is simply a talisman for serious underlying pathology.

Case 2:

A 60 year old man is admitted to a medical ward with a 2 week history of cough, arthralgia and reduced appetite. He had been prescribed doxycycline and a NSAID one week previously. He had a background of type 2 diabetes and hypertension treated with ramipril. On admission he was febrile (37.5^{o}C), hypoxic (oxygen saturations 92% on 40% oxygen). His BP was maintained at 124/80 mmHg. His white cell count was elevated at 16.9 and CRP was 279. His serum creatinine was 250 umol/L. An initial urinalysis was reported as 'clear'. Chest X-Ray showed multiple nodular opacities. Despite treatment with antibiotics, his renal function continued to deteriorate (serum creatinine 570 umol/L by day 3). A repeat urinalysis demonstrated 4+ blood and 3+ protein. A subsequence vasculitis screen was positive (cANCA 120, PR3 > 8). His presentation was consistent with a diagnosis of Granulomatosis with Polyangiitis (previously known as Wegener's Granulomatosis) and he was transferred to Nephrology. He was empirically treated with pulse methyl prednisolone and IV cyclophosphamide. A subsequent renal biopsy confirmed vasculitis. Two months after presentation his GFR was 50 mL/min/1.73m^2 and his pulmonary nodules had resolved.

Learning Points:

This patient was initially suspected to have AKI due to a combination of pneumonia and concomitant NSAID and ACEi therapy. However there were three key pointers to the possibility of an intrinsic renal insult

1. The lack of a hypotensive insult during his hospital admission.
2. The presence of dipstick blood and protein.
3. The failure to improve despite appropriate antibiotic therapy targeted against pneumonia.

In patients who develop AKI apparently out of proportion to the clinical insult it is important to validate the urinalysis findings. The presence of dipstick positive blood and protein should suggest a glomerulonephritis / vasculitis and an urgent renal vasculitis screen is mandated. The presence of a positive vasculitis serology in the appropriate clinical context will allow for commencement of immunosuppressive therapy prior to obtaining histological confirmation maximizing the chance of renal recovery.

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Presidential Address

RADIATION – FRIEND OR FOE?
Presidential Address to Ulster Medical Society
4th October 2012

Professor Roy Spence

Accepted 4 May 2014

The Ulster Medical Society was formed in 1862 with the amalgamation of the Belfast Medical Society (which had been founded originally in 1806) and the Belfast Clinical and Pathological Society (founded in 1853).

The Belfast of those early days of the 19th century was a parish of 20,000 inhabitants and in the second half of the 18th century the Charitable Society Poor House gave shelter to the old, infirm and orphaned children. Linked to the poor house was a small hospital[1]. In 1792 the Belfast dispensary opened a small fever hospital in Factory Row (Berry Street). A 'lying in' hospital was founded in1793 in Donegall Street and in 1815 the General Hospital was built in Frederick Street.

Against this background 19 physicians and surgeons came together in 1806 to form the Belfast Medical Society, with the first President being Dr SS Thompson. However, after discord the Society was dissolved in 1814 and reconstituted in 1822[2].

The Belfast Clinical and Pathological Society was founded in 1853 with its first President being Dr TH Purdon. This new Society, proposed by Dr Malcolm, included town and country doctors and by the end of its first year had 96 members. Remarkably its first President, Dr Purdon (born in Chichester Street, Belfast in 1806) entered Trinity College Dublin, at the young age of 13 years and in due course qualified in Medicine.

However, by 1861 discussions took place about having one single society and on April 30th 1862 the two old societies joined to become the Ulster Medical Society. The first President of the Ulster Medical Society was Professor JC Ferguson – born in Tandragee in 1802. He studied medicine in Trinity College and was appointed the King's Professor of Practice of Medicine in Dublin University in 1845. In 1850 he was appointed to the Chair of Medicine at Queen's College, Belfast[3].

The Society flourished and there were many well-known Presidential names over the years, including William Whitla, Robert Esler, Alexander Dempsey, John Byers, Thomas Sinclair (Professor of Surgery) (to whom I shall return), Johnston Symington (Professor of Anatomy and Fellow of the Royal Society) and so many others – truly giants of Ulster Medicine.

These giants of Ulster Medicine, who became Presidents of the Ulster Medical Society continued throughout the 20th and 21st century to my predecessor Professor Patrick Johnston (President of the Society 2011-12), recent Dean of Medicine in Queen's University and latterly appointed Vice-Chancellor of Queen's University.

One of the remarkable changes in my 40 years of working in medicine has been imaging in diagnosis in all specialties and, of course, the therapeutic value of radiation in the treatment of our cancer patients. However, radiation – either in its diagnostic or therapeutic use, is not without its sequelae and my journey for my Presidential Address and this paper is "Radiation – Friend or Foe?"

IN THE BEGINNING:-

As I have already alluded, Professor Thomas Sinclair was Professor of Surgery in Queen's College and President of this Society in 1895-1896. Thomas Sinclair succeeded Prof Alexander Gordon to the Chair of Surgery at 27 years of age. He was appointed to the Chair in 1886 and held the Chair for 37 years – a great technical surgeon and superb teacher. He was a surgeon to the British Expeditionary Force in the Great War and was appointed CB. He is remembered for performing the autopsy on Baron Richthofen (The Red Baron)[4,5]. It was said of Sinclair – 'No man has ever stood in higher regard with his professional brethren that Professor Sinclair'[5].

During Sinclair's Presidential year of the Ulster Medical Society a world shattering discovery was made on the evening of Friday 8th November 1895 by Roentgen in Wurzburg.

Wilhelm Conrad Roentgen was born on 27th March 1845 in Lennep in the German Rhineland. As a child he moved to Holland and later was expelled from Utrecht school! He later

Professor of Surgery and Consultant Surgeon, Belfast Trust, Centre for Medical Education, Queen's University Belfast, Mulhouse Building, Grosvenor Road, Belfast BT12 6BA.

Correspondence to Professor Spence

roy-spence@belfasttrust.hscni.net

studied mechanical engineering in Zurich and was inspired to follow a career in physics in the University of Wurzburg (Germany) – where (in 1883) he became Professor of Physics. (*fig 1*)

Fig 1. Wilhelm Conrad Roentgen, 1845 – 1923

He noticed late on 8th November 1895 that his 'Crookes tube' caused some adjacent barium platinocyanide crystals to 'light up'. The crystals were lying accidently on the adjacent table. He reasoned the tube was emitting some 'new' ray which produced fluorescence – if a metallic object was placed between the screen of barium platinocyanide and the tube, it cast a shadow. Roentgen is supposed to have said to his friend Boveri – 'I have discovered something interesting …..' He coined the phrase X-ray ('X-strahlem' in German) because the nature of the rays was uncertain.

His first paper on the new X-rays was given to the President of the Physical Medical Society on 28th December 1895. In his paper he showed an X-ray picture (the first) of the bones of the hand. (*fig 2*) The paper was printed immediately and an English translation was published in Nature on 23rd January 1896 and within weeks (long before modern communication) the news spread worldwide. Within a year there were 1000 publications on X-rays[6]. Lord Kelvin wrote a congratulatory letter on 17th January 1896 – in which he wrote 'I was very much astonished'[7]. (*fig 3*)

Roentgen worked on after his discovery – as industrious as ever. Honours were heaped upon him – including the Nobel Prize for Physics in 1901. Following the death of his beloved wife in 1919 he was lonely and unhappy and he died in Munich in 1923 of bowel cancer. His ashes were laid to rest in Giessen.

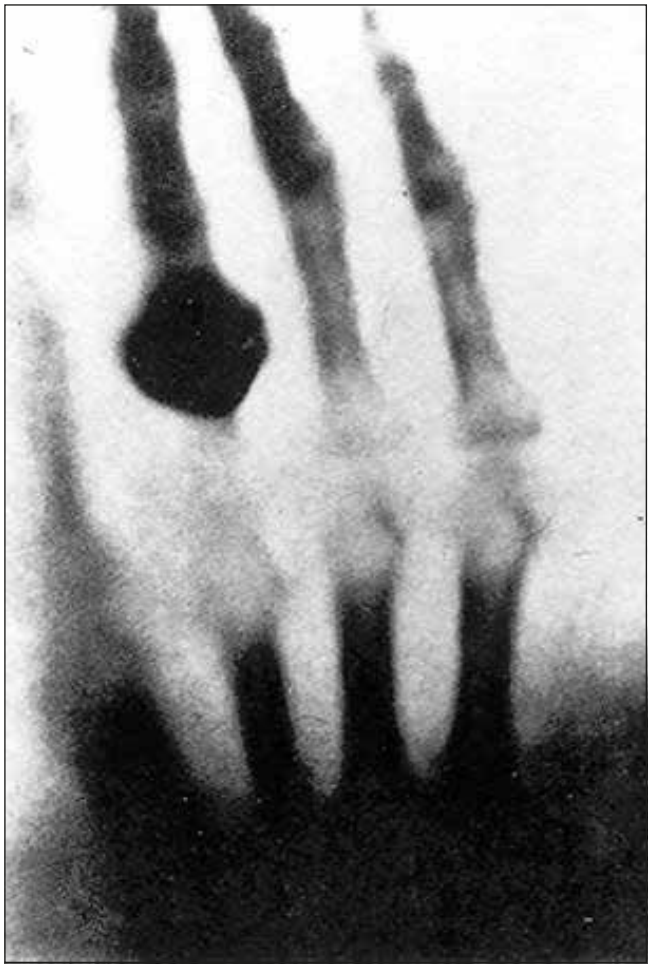


Fig 2. The first X-ray – bones of the hand (possibly Fräulein Roentgen)

His life and work are well reviewed by Mould in 1995[8]. Roentgen was a modest man who shunned publicity – writing only three papers on his remarkable discovery. As with others who have made such discoveries he had his critics – others had made accidental X-ray photographs in the course of research – such as Goodspeed in Philadelphia and Crookes in England (the latter had altered the shape of the cathode ray tube in 1879)[9]. However, neither of these scientists had appreciated the importance of their discoveries[10].

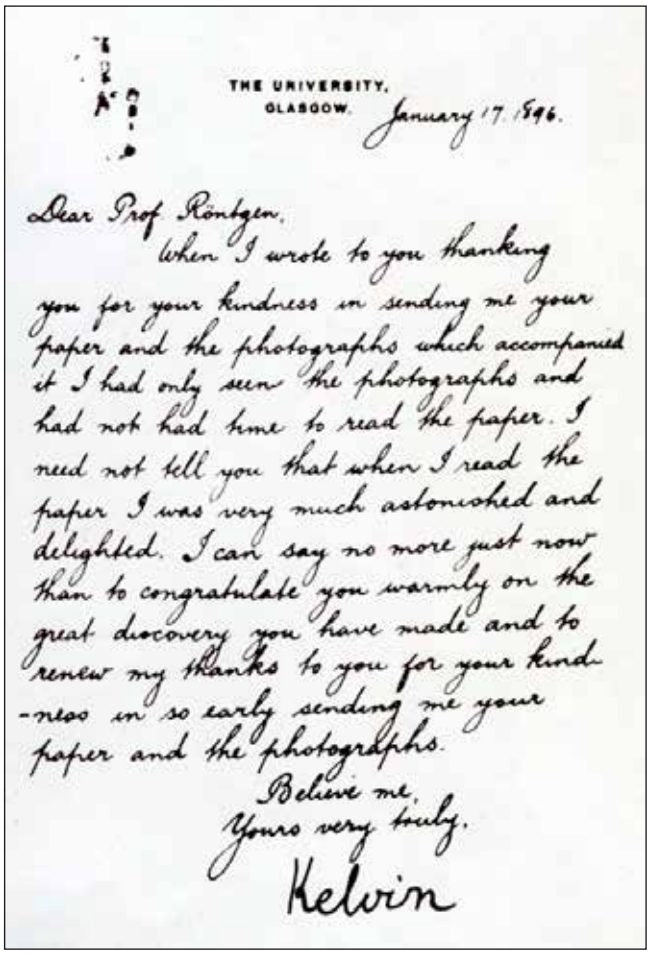
It is remarkable how word spread in the 19th century after Roentgen's discovery – only a day after his announcement Dr JR Ratcliffe in Birmingham, England, X-rayed his hand with a sterilised needle beneath the skin of his palm[9]. A day later a lady with a needle embedded in her hand had an X-ray taken in Queen's Hospital, Birmingham and a surgeon removed the said needle, guided by the radiograph[11].

Remarkably by January 9th 1896 American newspapers published the news of Roentgen's discovery[12]. In February 3rd 1896 a radiograph was taken of the left wrist of a 14

year old boy who had sustained an ulnar fracture[10]. Initially radiographs were used for skeletal abnormalities and location of foreign bodies. The British were the first to use radiographs for war casualties[11].

By 1898 bismuth subnitrate was used to study the gastrointestinal tract of humans[13]. Fluoroscopy, developed in 1896, was used widely in quality control of metal products, detection of fraudulent documents and paintings[11].

The spread of the news of these new 'X-rays' was remarkable. It was first reported in Britain on 6th January 1896 in the Daily Chronicle and the first note in a scientific journal in Britain was in The Electrician of 10th January 1846[14]. The Lancet on 11th January 1896, followed by the British Medical Journal reported the new phenomenon. Robert Jones also reported the use of the new X-ray to locate a bullet in the wrist of a 'lad aged 12 years' – with a 2 hour exposure[14]! There was an explosion of papers in 1896 – 18 published by John McIntyre of Glasgow, including the demonstration of a kidney stone. Over 1000 articles on Roentgen's X-rays were published in 1896. As Posner (1970)[14] has indicated it is difficult to think of any 'event', certainly in medicine which spread throughout the world with such speed until the first heart transplant in 1967 - all the more remarkable for the lack of electronic media which was not widespread until nearly a century later.



THE UNIVERSITY,
GLASGOW. January 17. 1896.

Dear Prof Röntgen,
When I wrote to you thanking you for your kindness in sending me your paper and the photographs which accompanied it I had only seen the photographs and had not had time to read the paper. I need not tell you that when I read the paper I was very much astonished and delighted. I can say no more just now than to congratulate you warmly on the great discovery you have made and to renew my thanks to you for your kindness in so early sending me your paper and the photographs.
Believe me,
Yours very truly,
Kelvin

Fig 3. Congratulatory letter from Lord Kelvin to Roentgen

However, also in 1896, the then President of the British Association for the Advancement of Science, Sir Joseph Lister spoke in Liverpool - his address was "The Interdependence of Science and the Healing Art". Before his address he had his hand X-rayed (photographed). He spoke on Roentgen's Rays and pronounced the following prophetic words "if the skin is long exposed to their action it becomes very much irritated, affected with a sort of aggravated sun burning" – much more was to be revealed as the years followed![14]

In the meantime the use of the new X-rays (Roentgen Rays) became widespread, not only for medical purposes, but also for amusement with mobile apparatus developed for fairgrounds. The apparatus became increasing sophisticated and early protection was developed to protect the users' hands from 'dermatitis' as knowledge of physics grew[7,8]. By May 1896, in New England, Professor Frank Austin used a portable X-ray machine to photograph children's hands for amusement at his daughter's birthday party![15] (*fig 4*)

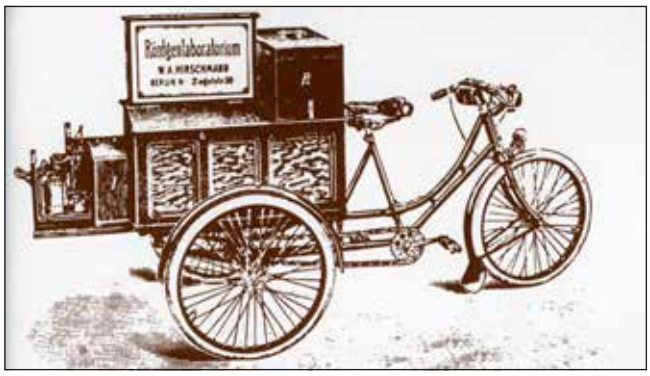


Fig 4. Portable X-ray machine – 19th Century

The spread of the news of Roentgen's Rays reached the USA within days with newspaper accounts[16] and Nature on 23rd January 1896 published a translated copy of his paper[17,18]. On 25th January 1896 Scientific American published a news section 'Professor Roentgen's Wonderful Discovery' with the account having come from Europe by cable. The article contained the sentence 'when the details reach us, the process will probably prove to be of scientific rather than practical interest'[19].

By the end of 1896 Dr James Third in Canada had acquired his own X-ray apparatus for Kingston General Hospital and published in 1902 a comprehensive review of diagnostic uses of X-rays[20]. In May 1896 Dr Williams of Boston had an 'X-ray run' in the basement of the library of Boston City Hospital and during the next 19 years he examined 150,000 patients. By the summer of 1896 X-ray apparatus was installed in several London Hospitals. However, by 1903 use of X-rays had increased and the King had opened a new outpatient department with an 'electrical division' containing X-ray apparatus[21].

The X-ray department was often hidden away in the country hospitals of the time – 'if you look for the darkest, steepest and most awkward stair below ground, you will generally find that it takes you to the X-ray department'[21].

The early years of the 20th century led to increasing understanding of the new X-rays with development of apparatus[22] and the awareness of side effects as we will discuss later. To X-ray a hand for bone – exposure would take initially up to 30 minutes, to X-ray a skull or pelvis may take 2-3 hours of exposure[21].

Barium overtook bismuth in 1910 to demonstrate the gastrointestinal tract (because barium was cheaper); the first radiology journal – Archives of Clinical Skiagraphy – was produced in England, and by 1897 X-rays were admissible as medico-legal evidence.

RADIOGRAPHY IN ULSTER

So how did radiology develop in Ulster? From Roentgen in 1895 discovering the X-ray, winning the Nobel Prize of Physics (1901), to Hounsfield's work on CT computed tomography in the EMI labs at Hounslow[23] (also awarded the Nobel Prize) it has been a remarkable 100 years of X-ray use[24].

So to Ireland and in particular Ulster -

The early national journals of the 20th century were full of discussion of the use of X-rays[25] and likewise the Dublin Journal of Medicine[26]. In the meetings of the Ulster Medical Society in 1912, there were frequent discussions of the use of radiology to solve various clinical difficult cases.

So what of X-rays in Ulster – two excellent reviews by DC Porter in 1962[27] and FS Grebell in 1987[28] tell the story – both published in the Ulster Medical Journal a quarter of a century apart.

Porter (1962) describes the giants who before Roentgen also set the building blocks for this discovery – William Gilbert – physician to Queen Elizabeth in the 16th century – was the father of electric and magnetic science. Galileo in the University of Pisa evolved the principle of the air pump. Sir Humphrey Davy (who devised the miners' safety lamp) used electric current to decompose gases. Humphrey Davy's successor as Professor of Chemistry at the Royal Institution, was Michael Faraday who later discovered electro-magnetic induction[27].

Sir William Crookes in 1870 developed cathode ray tubes and indeed, as alluded earlier, may well have stumbled on X-rays but did not recognise, or publish their nature.

Porter describes the rapid advances in X-rays in medicine in the first 15 years of the new century – highlighting the exposure times – in 1896 a chest X-ray of a girl of 10 years had an exposure time of 30 minutes, a wrist - 20 minutes, hip X-ray exposure of one hour, skull X-ray - 45 minutes – leading to loss of hair in 10 days.

In Ulster – the importance of X-rays was quickly realised on 9th July 1896 (only 6 months after Roentgen's announcement) at a medical staff meeting in the Old Belfast Royal Hospital in Frederick Street. Doctors Mitchell and Caldwell were directed to investigate the apparatus for the new X-rays. The first X-rays (photographs) were taken by John Clarke & Co, then in Corporation Street, who dealt with all cases for £1 per month.

During the first year – 50 radiographs had been produced. The work then passed to Lizars of Wellington Place under the auspices of Mr JC Carson, who also provided in his jaunting car, a domiciliary X-ray service at 10 shillings a time! In 1899 Mr John Campbell Rankin was appointed pupil to the hospital and later physician with an interest in 'electrical medicine' – in diagnosis and treatment, and also in sexual transmitted diseases. He learned 'electrical therapy' in Copenhagen and in 1903 he was appointed 'electrician'. He did many X-rays in his home in Mount Charles and in 1911 had a formal darkroom and new X-ray equipment in the hospital. The work expanded during the war and in 1919 Dr Maitland Beath was assistant to Dr Rankin and became an outstanding radiologist and one of the first Presidents of the Faculty of Radiologists[27].

Dr Grebell (1987) in his address at the Annual Oration to the students at the Royal Victoria Hospital continued the story of development in radiology. Mass tuberculosis screening in the UK using chest radiography was introduced by Bentley and Leitner in 1940[29].

Following the discovery of isotopes (Bequerel, the father of nuclear chemistry – Nobel Prize for Physics in 1903), came Lord Rutherford who discovered γ, and β – particles (Nobel Prize for Chemistry in 1908).

CT was invented by Godfrey Hounsfield in 1972 – and many suggest this is the greatest discovery in radiology since Roentgen's X-rays[28]; Hounsfield received a Knighthood and Nobel Prize for his work. The Royal Victoria Hospital got its first CT scanner in 1977.

The principles of MRI (magnetic resonance imaging) go back to Bloch of Standford and Purcell of Harvard, for which they received the Nobel Prize in 1952. Following the introduction of MRI to the RVH in 1993 – today all major hospitals have multi-slice CT scanners and MRI scanners – all with great ability for diagnostics in a wide variety of patients, in particular in cases of trauma (CT) and cancer (CT and MRI).

ADVERSE EFFECTS OF THE ROENTGEN RAYS

The adverse effects of the Roentgen rays became known quickly – even if the long term consequence was not initially clear. Professor John Daniel of Vanderbilt University wrote in March 1896 of a laboratory incident. In his attempt to X-ray his colleague's skull – he placed the X-ray tube 0.5 inch away from his skull and activated the beam for 1 hour – 3 weeks later the hair came out over a space of 2 inches and 'we were both at a loss to account for it, as we had no previous intimation of any effect whatever', Daniel said[30].

Later in the summer of 1896 Mr Herbert Hawks (Assistant to Dr Michael Pupion of Columbia) was demonstrating X-rays in Bloomingdales store and describes, probably for the first time, the severe 'burn' – 'like bad sunburn' on his hands

which caused him to cease work for 3 weeks[30].

The first fatality due to X-ray exposure may have been Clarence Daly – Chief Assistant to Edison – who had many 'radiation burns' on face, hands and fingers. By 1902 he had developed cancer of the skin – he had amputations of both arms but died in 1904.

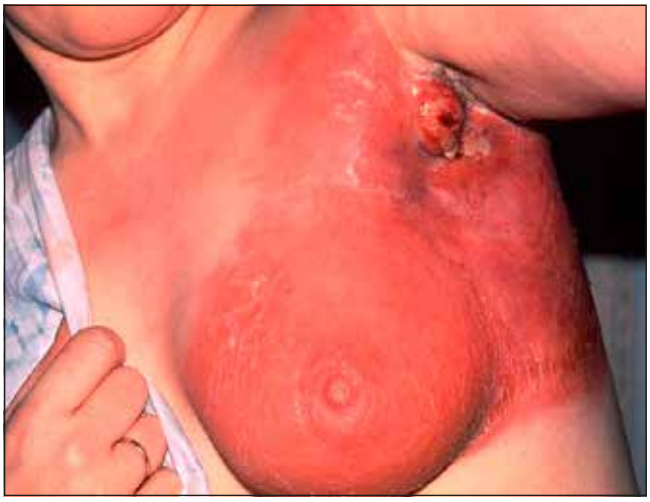


Fig 5. Acute radiation burn – during radiotherapy for breast cancer

Ironically Roentgen constructed a box lined with lead in which he stood when doing his experiments and X-rays only entered through a small aperture. This 'box' was for the purpose of light control and Roentgen's protection from the X-rays was serendipitous – as we have no information that in the early years Roentgen was aware of their carcinogenic potential. In England Dr Hall-Edwards – the physician responsible for the first 'X-ray' photograph in Britain in 1896 later developed cancer of his hands[9].

Later in 1896 the great Sir Joseph Lister postulated 'the transmission of the rays through humans today may not be altogether a matter of indifference to internal organs'[31]. Cancer of the hands was a common adverse effect to the early pioneers[11]. The therapeutic use of X-rays followed quickly from the discovery and a lady with cancer of the breast was treated in 1896[32]. (*fig 5*) Advances followed rapidly – Marie and Pierre Curie identified radium – discovered in 1896 and published in 1898. Eventually Marie was to die from a radiation - induced cancer and yet radiation for cancer was to become a cornerstone of cancer therapies over the ensuing decades. (*fig 6*)

Lentle, the previous Head of Radiology in the University of British Columbia, Vancouver has distinguished the reception of some Victorians to the new X-ray compared to radium discovered only a few years later. The Victorians were apprehensive of the ability of the X-ray to 'see through' the voluminous clothing of the era - an invasion of privacy, discovered by a rather stern man of 'Germanic extraction'. Whereas radium was well accepted as a 'cure all' having been discovered only a few years later by the petite 'feminine' Marie Curie![33] Gradually the early pioneers using radiation in patients realised the harm done could be long lasting.

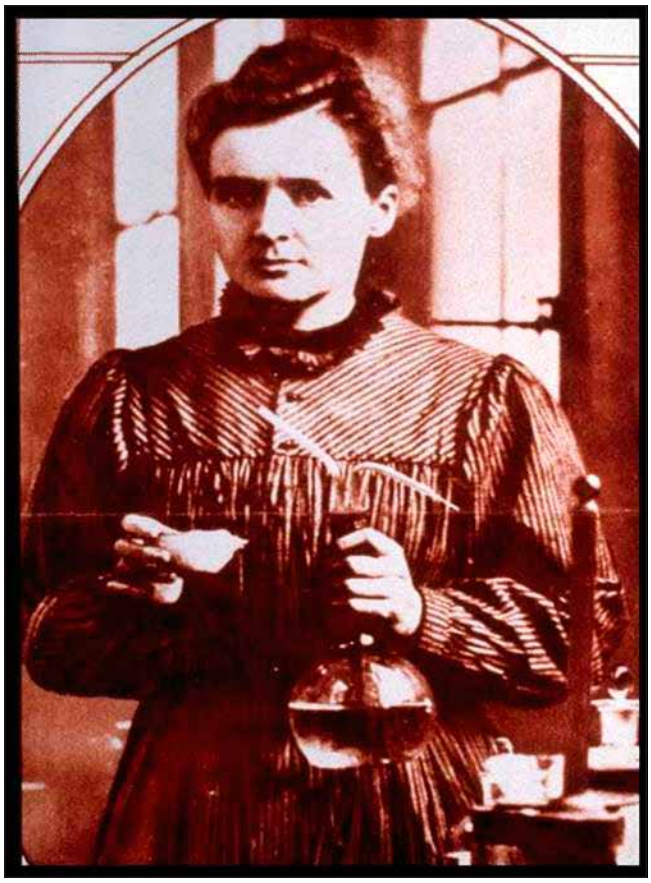


Fig 6. Marie Curie, 1867 – 1934

Dr Walter Cannon, who performed remarkable work on gastrointestinal physiology using radiology, beginning as a medical student in Hanover in 1896, noticed a red rash on his chest and limbs, when he was 59 years of age in 1931 (23 years after he stopped exposure to X-rays). A biopsy in 1932 diagnosed mycosis fungoides[34].

In a well written article DiSantis, in1991, describes the so-called 'wrong turns' in radiology's progress. Despite the early recognition in 1896 of adverse effects of radiology – the lay public would form long lines waiting at public exhibitions for fluoroscopy for amusement[35]. Even Thomas Edison, in 1896, introduced a recreational home fluoroscopy unit – it was Clarence Daly (Edison's Assistant) who became the first American radiological casualty. Training for X-ray physicians was cursory and a study in 1948 showed radiation damage in the hands in 48%[36]. In the USA, in 1920, X-ray units were used in beauty parlours to remove unwanted facial and body hair. (500 rad) (5Gy) for epilation. Perhaps 1000s of women developed skin cancer as a consequence. In the 1950s, in the USA, shops used fluoroscopy as part of shoe fitting- often in children with inadequate shielding with scattered rays affecting children (as high as the pelvis), the assistants and other customers.

Marie Curie's discovery of radium in 1898 sparked 'ray mania' - this new mysterious element discovered by a woman! The new element was incorporated into everything from chocolate to contraceptive jelly – it was perceived as a

panacea! The journal 'Radium' declared in 1916 – 'radium has no toxic effects! It was perceived as a cure of every disease, by 1904, including 'health giving' water impregnated by radium, radium toothpaste, radium roulette, radioactive china and radium beverages were fashionable in the 1920s. Radium paint, which fluoresced, was everywhere! However, the same workers who painted radium paint developed a mysterious and profound anaemia and osteonecrosis. To 'point' their brushes they used their tongues and they could light a fluorescent screen with their breath! Their deaths mounted and the first 'shadow' appeared on the new radium 'cure all'![35] Marie Curie, herself died from radiation induced aplastic anaemia.

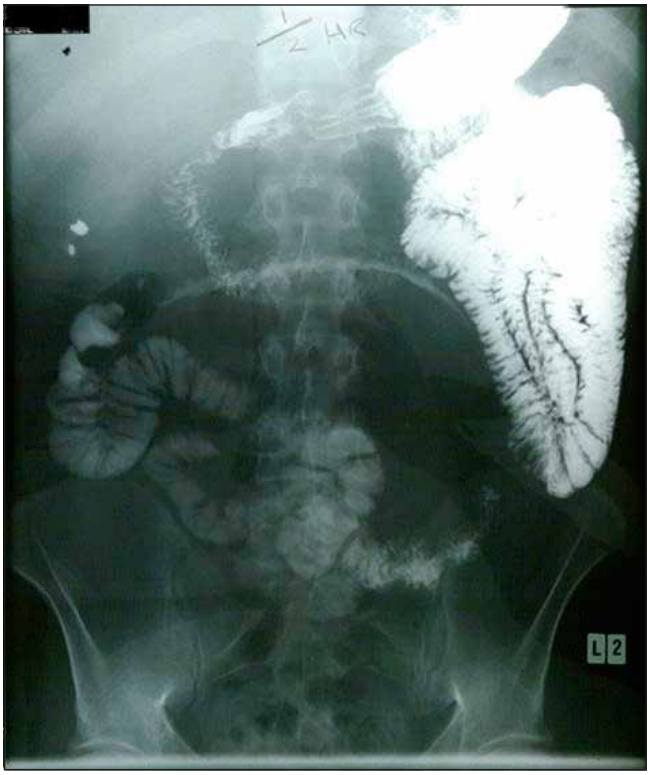


Fig 7. Radiation stricture to small bowel

The American physicist, Thorson, first found the direct relationship between exposure to X-rays and side effects – he deliberately exposed his left index finger to an X-ray tube for 30 minutes per day, for 3 days, developing swelling, erythema and pain[37]. Rollins in 1901 reported radiation could kill animals on prolonged exposure and advised X-ray users to wear radio-opaque glasses[38]. Rollins was the true pioneer in radiation protection[39] but it was not until 1921 that the British X-ray and Radium Protection Committee (1921) issued their report on radiation protection measures[40]. In the USA the United States Advisory Committee on X-ray and Radium Protection came into being in 1929[41] and, henceforth, protection measures became rigorous in, at least, the developed world.

THERAPEUTIC USE OF RADIATION

Marie Curie discovered and reported radioactivity of polonium in July 1898 and radium in December 1898[42,43] and the use of radium seeds and rod implants were greatly advanced by Patterson and Parker at the Christie hospital in Manchester[44]. Over the subsequent decades a large number of radionuclides were used for brachytherapy[45], the delivery of which optimised since the development of sophisticated computers in the 1970s.

External radiation was developed in the two decades before World War II and the earliest super-voltage unit (IMV) was placed in St Bart's Hospital London in 1937. The first medical accelerator (8MV) was installed in Hammersmith Hospital, in London in 1953. A quarter of a century later multi-dimensional computerised 3D planning was described in 1979[46].

With these, and other advances in radiation therapy it is now estimated that two-thirds of the 1.5 million new cancer cases diagnosed annually in USA – will undergo some form of radiation therapy[47]. Despite careful planning, including the use of radio-sensitisers, radio-protectants, non-cancerous cells are affected resulting in many clinical side effects – from fatigue, and depression[48], to secondary malignancy such as breast cancer in women who have had mantle radiotherapy for lymphoma when young[49].

The side effects are both early and late and can affect all major systems *(fig 7)* – from skin - dermatitis, radiation recall[50], cardiovascular disease after radiation for lymphoma[49,51], pneumonitis[52] mucositis, oesophagitis[53] enteritis[54], proctitis[55], cystitis[56], erectile dysfunction[57], and infertility[58].

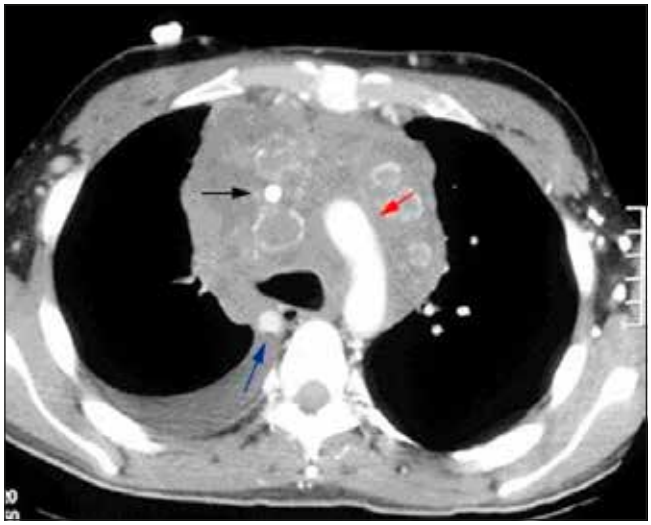


Fig 8. Hodgkin's disease requiring mantle radiotherapy

Most of these side effects are well recognised by physician and patient and for some complications, such as breast cancer after radiotherapy for Hodgkin's disease have guidelines for surveillance. (*fig 8*)

These adverse effects of radiation may lead to problems distinguishing side effects from recurrence or de novo cancer[59] but undoubtedly radiation therapy has produced improvement in survival in many cancers over recent years[60]. The mechanism of damage to cancer cells (and normal cells) is increasingly well defined with breaks in the DNA double

helix being the main method of cell damage[61]. While the management of the adverse effects of radiation therapy is not ideal, many treatment strategies are in practice[62].

Therefore, with the huge amount of literature both published and on the internet including the standard oncology text books such as DeVita[63] , there is great awareness in the public, the press and medical profession of the benefits and side effects of radiation therapy in the 21st century.

DIAGNOSTIC RADIOLOGY IN THE 21ST CENTURY – CT SCANNING - ? A PANACEA

Let us now turn to the remarkable changes in diagnostic imaging especially that of CT – with the huge benefits in non-operative management of trauma eg the conservative management of gunshot wounds, liver and splenic injuries including the use of CT in endovascular aneurysm repair and follow-up –as we now approach 120 years since Roentgen's remarkable discovery.

CT scanning is a remarkable advance for diagnosis - it has huge value in the assessment of medical and surgical patients; diagnosis of a myriad of conditions especially trauma and cancer and follow up after treatment of such patients. (*Fig 9*)

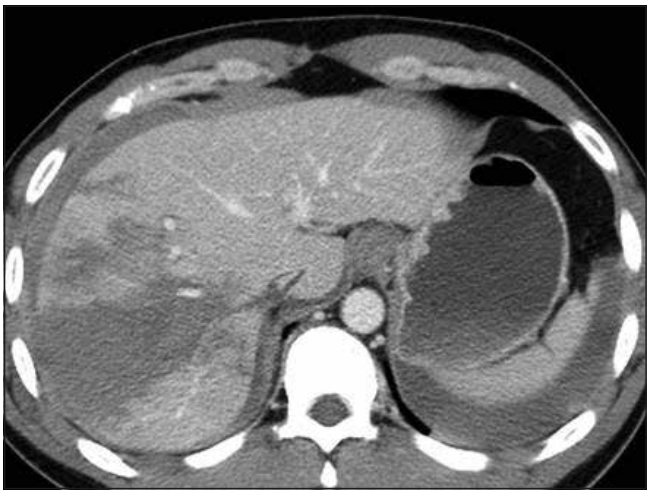


Fig 9. CT scan of liver trauma (reproduced with kind permission of Dr Barry Kelly)

In many surgical and medical emergencies CT scanning is invaluable as evidenced by any recent text book on surgical emergencies[64]. It is central to the conservative management of splenic trauma[65] and the recent suggestion of the non-operative management of gunshot wounds[66]. *But has the pendulum of imaging, particularly CT scanning swung too far to the detriment of clinical acumen? Has a fear of litigation pushed the clinician to over-investigate with imaging, especially CT?*

A Dutch paper in 2014 looked at the role of CT and MRI in the differentiation of simple appendicitis and perforated appendicitis![67] (*fig 10*) Furthermore, the quality of modern CT scanning picks up incidental lesions such as adrenal nodules and small pulmonary nodules – previously undetected in patients free from symptoms. Since the development and widespread use of helical CT in the 1990s; the detection of lung nodules as small as 1-2mm in diameter is common. It is now recognised that the majority of smokers undergoing thin section CT have small (usually <7mm) lung nodules – the majority of which are benign[68,69]. (*fig 11*) They have been increasingly found in studies of CT screening for lung cancer[70].

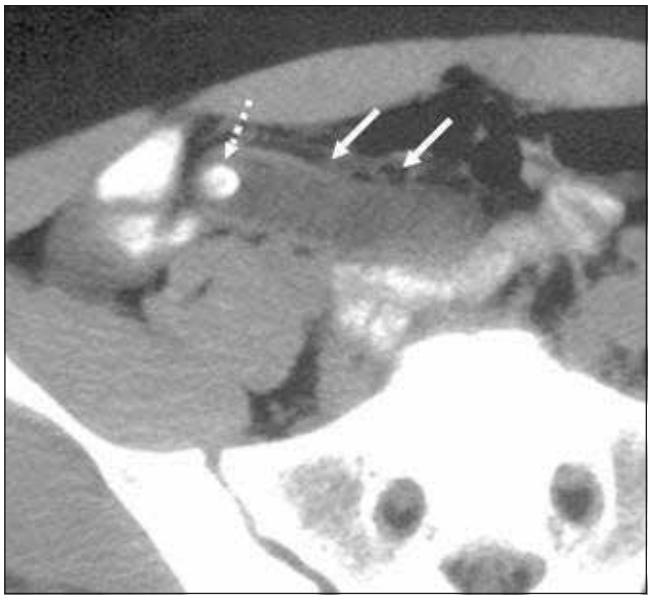


Fig 10. CT scan of acute appendicitis (reproduced with kind permission of Mr Stephen Badger)

The current guidelines in the literature are from the Fleischner Society and follow up depends on the size of the nodule and whether the patient is high or low risk. Unless the nodule is less than 4mm in size, in a low risk patient then all require CT follow-up – for example a nodule over 8mm would need repeat CT at 3, 6, 9 and 24 months[68].

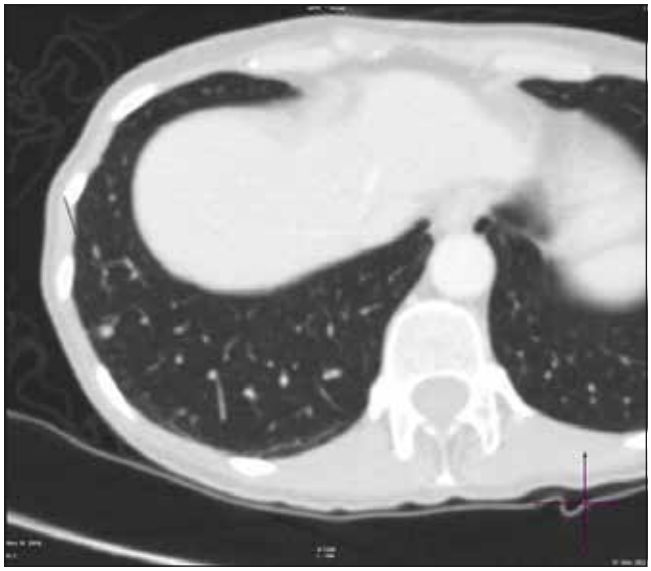


Fig 11. CT scan of an incidental benign lung nodule (reproduced with kind permission of Dr Barry Kelly)

While the benefit of such follow-up is that a small number will be early cancers, the majority are benign – and the

'downside' of this approach includes the possibility of morbidity/mortality for surgery for benign nodules, costs, patient anxiety and increased radiation to patients having repeated CT scans[71].

Such nodules are exceptionally common in CT lung cancer screening trials. The Mayo Clinic Lung Cancer Screening Trial was reported by Swensen in 2003[72] - After 3 annual CT scans in 1520 smokers (>50 years old) -at 2 years 2832 non-calcified pulmonary nodules were identified in 1049 subjects (69% of participants), 36 lung cancers were diagnosed by CT (2.6% of participants, 1% of nodules). Only one cancer was diagnosed in a nodule smaller than 5mm. Midthun has calculated that less than 1% of nodules less than 5mm were malignant. Cancer risk in a nodule <3mm was 0.2%; 0.9% for 4-7mm; 18% for 8-20mm, and 50% for nodules larger than 20mm[73].

With the current risk of malpractice in UK and USA it is difficult for the radiologist and clinician not to follow-up, as per these guidelines, these small indeterminate nodules – even though the risk for malignancy for the very small nodule is small[74] ~ nonetheless most of these patients are subjected to a series of at least three CT scans over a period of 24 months with the ensuing radiation dose and possible consequences. However, to improve lung cancer survival early diagnosis is essential[75] and we await the outcome of national lung cancer screening trials.

Lung cancer CT screening has been well reviewed by Bach and colleagues who have reviewed 8 randomised trials and 13 cohort studies[76]. The most impressive results come from the National Lung Screening Trial (53,454 participants), with 3 annual rounds of CT screening – resulted in a 20% relative decrease in deaths from lung cancer[77] but data from other studies were less clear[76].

RADIATION EXPOSURE IN PRACTICE

The overview paper described the radiation dangers of these repeated CT exposures in lung cancer trials[76]. The effective radiation dose in one of the trials was calculated to be 1.5 mSv per examination compared to a diagnostic CT of chest (8mSv)[78] or 14mSv in PET – CT scan[77]. The effective dose of radiation in a chest X-ray is 0.02mSv and a diagnostic CT of chest is equivalent to 400 chest X-rays. There are now clear data on the cancer risks of radiation based on medical imaging and the atomic bomb explosions[79,80,81].

Modelling predicts that in lung cancer screening cancer death is caused by radiation from CT per 2550 persons screened[76]. This risk becomes manifest 10-20 years later. For older patients the benefit of lung cancer screening may lie with those screened and found to have early cancer, but it is questionable for younger persons – ie the potential risks of lung cancer CT screening in non-smokers and those aged under 42 years outweighs any benefit[82]. In recent years the issue of the investigations of the solitary lung nodule, even outwith the context of lung cancer screening trials, has concerned the literature of the impact of radiation from CT in diagnosis and follow-up[83]. At the moment the Fleischner Society guidelines with subsequent (usually up to 3) sequential CTs are used as practical guidance[68,84]. A good editorial by O'Connor and Hatabu has again emphasised the risks of CT radiation – cancer induction in lung cancer screening[85].

CT SCANNING AND CANCER

A major study (from 15 countries) has shown that somewhere between 0.6% to 3.2% of cancers below age 75 years may be attributable to diagnostic imaging, especially CT[86]. There has been a huge increase in the use of CT in UK, Europe and USA. In a study of USA HMO's; the use of CT increased from 52 per 1000 clients in 1996 to 119 per 1000 in 2010 – an annual increase of 8% - leading to a doubling of the mean per capita radiation in each year[87].

Brenner has studied radiation risks associated with full body CT screening[88]. Especially in USA, there is interest in full body CT screening for healthy adults[89], with uncertain benefit[90,91] Brenner has calculated radiation doses in full body CT scanning includes 16mGy to lung, 14mGy to digestive organs and 10mGy to bone marrow. The average organ dose is 12 mSv[88]. To put these figures in perspective we need to look at studies of long term atomic bomb survivors[92,93]. Those survivors who were exposed to a dose from 5 to100mSv (mean 29mSv) had a significant increase of cancer risk. Even a dose of radiation exposure as low as 5-50mSv has a small increased cancer mortality risk. Brenner has calculated that a single full body CT scan in a 45 year old adult would result in a lifetime cancer mortality risk of 0.08% - if the 45 year old continued annual CT full body scans until age 75 years these 30 CTs would produce a 1.9% life-time cancer mortality risk[88]. CT full body screening in the USA has increased in popularity (less so in UK) to detect lung cancer, coronary artery disease and colon cancer[94], - nonetheless our patients should be advised of the radiation exposure and subsequent cancer risk?

The comprehensive Lancet paper of De Gonzalez from a decade ago looking at 15 countries (including UK) estimated cumulative cancer risk due to diagnostic X-rays[88]. Previously, in 1981, Doll and Peto, in1981 estimated that 0.5% of cancer deaths in the USA were due to diagnostic radiology[95]. The Lancet study (2004) estimated in the UK 0.6% of the cumulative cancer risk to age 75 years to be due to diagnostic radiation. In the UK this would be equivalent to 700 cases per year. In another 13 countries the risk was 0.6% to 1.8% - such as Australia (1.3%), Canada (1.1%), USA (0.9%), Norway (1.2%); in Japan the risk was 3.2%[88].

In men bladder cancer, colon cancer and leukaemia were the highest number of radiation induced cancers and in females colon, lung and breast cancers made the major contribution. Most cases arose after age 40 years (56% of cases occurred between 65-74 years of age). Of the diagnostic X-rays the largest number of cases were caused by CT, followed by barium enemas, hip and pelvis X-rays. Current evidence is that there is no lower threshold below which radiation does

not cause cancer[96]. Brenner has estimated that the cumulative risk of cancer mortality for CT in USA is 800 radiation - induced cancers in children under age 15 years[97].

A recent study from Australia looked specifically at CT scans in children and adolescents up to age 19 years. 680,211 patients who had a CT scan were studied and compared in a linkage study to 11 million unexposed individuals. Overall cancer incidence was 24% higher for exposed, compared to unexposed, individuals. There was a dose response association with each additional CT scan[98].

A measured editorial in the British Medical Journal in 2013, which accompanied this article put this in the context of numbers ie one excess cancer per 4000 head CTs at the modern CT dose of 2mSv[99]. Sodickson emphasises a balanced measured approach to the need of CT scans and risk benefit in a context where CT is indispensable in trauma, cancer diagnosis and follow up[99].

ENDOVASCULAR TECHNIQUES – RADIATION RISK

Since the publication of the EVAR I & II trials in the Lancet in 2005[100,101] and The Dream Group publication in The New England Journal of Medicine in 2004[102], and the subsequent longer term data published in 2010 by the EVAR Group[103,104], endovascular stenting for aortic aneurysm has become widely used. (*fig 12*)

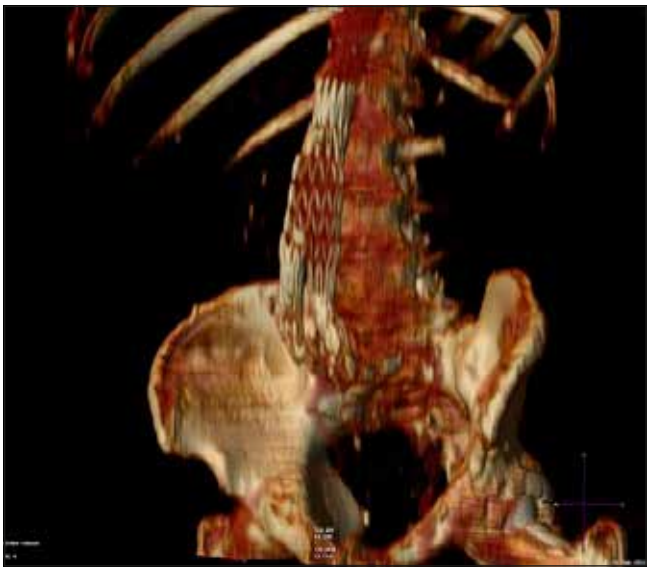


Fig 12. CT scan with endovascular stent in situ (reproduced with kind permission of Mr Stephen Badger)

Preoperative CT is essential for the placement of the stent, to determine the vascular anatomy[105]. After the procedure stenting CT was performed, in earlier series, at 1, 3 and 12 months postoperatively and annually thereafter (EVAR I, II, 2005). The patient is, therefore, exposed to significant CT radiation[106]. One series from Belfast of 320 elective patients undergoing EVAR found a mean screening time of 29.4 mins ± 23.3 minutes and a radiation dose during the procedure of 13.4 ± 8.6 mSv. During the first postoperative year follow-up CT scans exposed the patients to 24.0mSv, and then 8.0mSv in subsequent years. Abdominal X-rays added a further 1.8mSv per year. This adds up to substantial radiation with subsequent long term carcinogenic risks[107]. (*fig 13*) Of course many of these patients are elderly, but younger patients with aortic aneurysm are not uncommon and this radiation dose may be clinically relevant in these patients in years to come. The dose of radiation during EVAR procedures may be close to that during coronary angiography which is highest of all (16.0mSv – equivalent to 800 chest X-rays[108]. (*fig 14*)

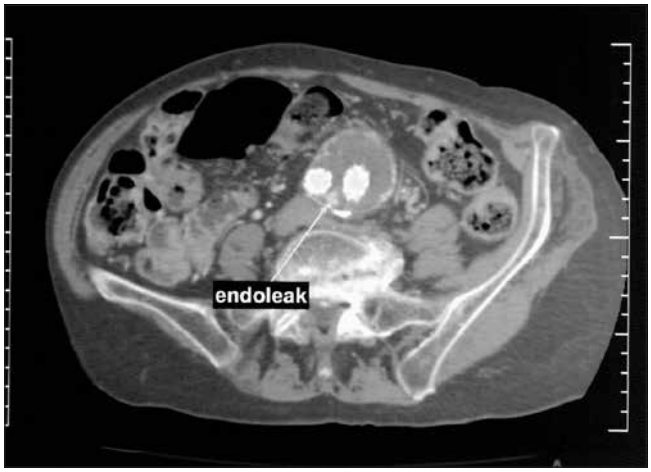


Fig 13. Scan showing endoleak post EVAR detected at follow-up CT (reproduced with kind permission of Mr Stephen Badger)

Similar data have been shown in USA[109] and Europe[110]. In an effort to decrease this CT radiation load recent data from the USA and Europe have indicated that the frequency of postoperative CT may be reduced[111] and some imaging may be replaced with ultrasound[112]. Similar data using colour Doppler duplex ultrasound are now emerging from UK[113,114] and Europe[115]. Clearly radiation exposure to the surgeons

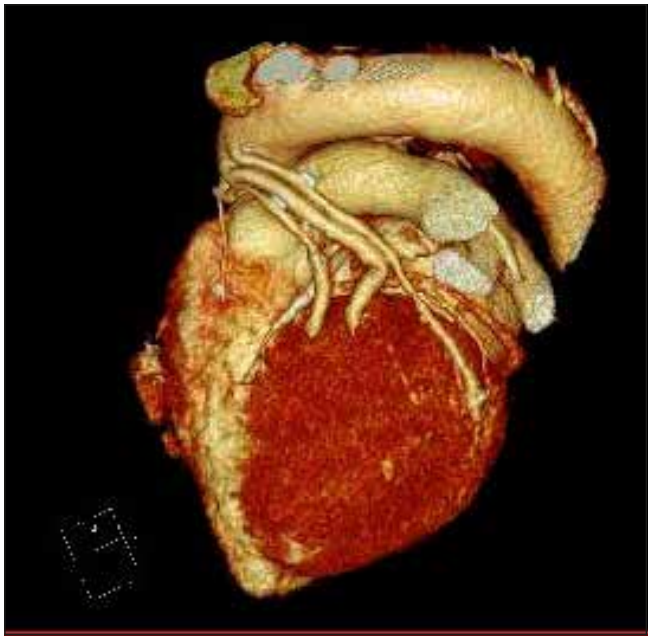


Fig 14. CT coronary angiogram (of the author!) following cardiac bypass

and radiologists performing EVAR procedures need careful monitoring[116].

THE FUTURE

The growth in radiological skill and advances in technology are remarkable from my early days as a student of medicine in 1971. Undoubtedly the advances from the discovery of X-rays by Roentgen in 1895 over the past centuary have had massive benefits for patients both as a diagnostic and therapeutic tool.

The demand for imaging and CT, in particular, has increased exponentially as a diagnostic tool in trauma and cancer, as a follow-up to gauge response in many diseases, but especially in cancer. It has a major role in endovascular procedures and may have a future role in cancer screening such as lung.

However, while the risks of radiation have been known for over a century and, of course, are well known to radiologists it is only recently that clinicians, the press and patients are becoming more aware. Even so the knowledge of clinicians and patients of the risks of imaging are not known in any depth. Only interventional radiological procedures require a consent form to be signed and routine CT does **not** require written consent. Only in the past decade have the cancer risks of CT been discussed widely in the general literature[71,88,98,108]. In 30 years there has been a 20 fold increase in CT scans in USA annually, in the UK similarly CT numbers have doubled in the last decade[108].

Only recently has Queen's University taught radiology as a formal subject in 4th year and few of today's clinicians really understand the various units used in radiation exposure in imaging. The biological effect is best measure in millisiverts (mSv) (the product of the absorbed dose (Grays, Gy) and a quality factor (Q) (which depends on the organ irradiated, the radiation type and regime).

However, in discussion with our patients, students and other clinicians, perhaps the equivalent radiation of an investigation such as CT, is best explained in terms of numbers of chest X-rays. This may be the best communication for comparison (and easiest to understand for patient and clinician) (eg CT chest = 350 chest X-rays, CT abdomen = 400 chest X-rays), CT coronary angiogram = 800 chest X-rays - as well laid out in Davies 2011, British Medical Journal article[108]. The annual background radiation (such as radon) gives each person 2.4mSv exposure per year.

While carcinogenic effects are the major radiation concern[82], other effects include disabilities in children of mothers exposed to radiation in pregnancy, cataracts, skin damage and increased cardiovascular disease. In the USA 6-11% of all CT scans are performed in children and it remains to be seen, with the prolonged lag phase, what future numbers of radiation - induced cancers will emerge[78].

Patients already have IPAD 'apps' to calculate radiation doses of their investigations[108]. In the UK there is reasonable adherence to College of Radiologists Guidance (2007) for investigation, for example head injury scans are guided by NICE guidelines. Recent debate centres around – 'what should patients be told'[108,118]. Informed consent is not required in the UK for routine imaging, outwith interventional radiology, but should patients be told of the potential benefits of a particular scan (versus adverse effects). Patients who request 'full body CT scans' – for a check-up (more common in USA) should be advised of its limited benefit and that the finding of incidental nodules such as in adrenal or lung in the long term – will usually lead to repeat CT scans. Those patients entering lung cancer screening trials will need detailed counselling, about possible adverse effects.

The risk of any one CT scan in an adult is low but those needing repeat CT for cancer (usually benefits exceed the risks) or after endovascular surgery (less frequent CT may now be appropriate) need more detailed advice/counselling. Risks need to be put into lay man's terms for example – the additional risk of death from cancer is 'minimal' at a dose of 1mSv – (X-ray abdomen), 'very low' – 10mSv – CT brain/chest/abdomen; over >100mSv – risk is 'moderate' ie repeat CT scans.

Minimal risk is 10^{-5}, very low risk is 10^{-4} and moderate risk is 10^{-2}. To help explain in lay terms - risk of death during a flight of 4500 miles is 'minimal', risk of death in a car accident in a drive of 2000 miles is in the 'very low' category[118].

For those children/adolescents having repeated CT scans for lymphoma/leukaemia follow-up records (dose/frequency) should be meticulous. The recent literature has revealed an increasing interest and understanding of radiation risk of imaging especially in paediatrics[119].

In the future patients may keep their own radiological imaging history on a smart phone!

CONCLUSION

It is well over a century since Roentgen discovered X-rays and the remarkable advances since 1895 are incredible. Without doubt of all the advances in medicine it must rate at the top, alongside the discovery of antibiotics and anaesthesia.

Notwithstanding the consequence of the atomic bomb, in Japan, and the disaster of Chernobyl (1986)[120] and Fukushima (2011)[121] (*fig 15*) overall radiation has been mostly a 'friend' as opposed to a 'foe'. However, with the advances in imaging and CT in particular, and the exponential increase in use, we must remain conscious of the possible long term adverse effects such as cancer. Maybe we are now at the stage of better information for patients (with modern technology – such as smart phones) and clinicians.

I applaud the early pioneers from Roentgen in 1895 (by all accounts a quiet modest man), I remain amazed at the spread of knowledge of his discovery being known worldwide within days, long before modern media.

Finally, I stand in awe of my colleagues in radiology who have transformed the care of our patients, preventing us

doing unnecessary surgery in our cancer patients, and their remarkable diagnostic accuracy in trauma and cancer. I remain in huge respect of my colleagues in interventional radiology, with their catheters embolising even tiny vessels in the cerebral circulation and dealing so well with the 'bleeding patient' who nowadays, much less frequently requires surgery.

Fig 15. Chernobyl, 1986

ACKNOWLEDGEMENTS

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Medical History

Surgical Travellers: Tapestry to Bayeux

John Hedley-Whyte, Debra R. Milamed

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SUMMARY

The planning for surgery in war was revisited in 1937 when Ian Fraser was elected a member of the Surgical Travellers. At their 1938 Surgical Travellers meeting in Vienna, Ian and Eleanor Fraser were evicted from their hotel room by the Nazis. The 1939 meeting in Belfast discussed the organization of surgery and the conduct of Emergency Medical Service Hospitals in the United Kingdom; the vast majority were to be under civilian government and military control.

From 1943 lengthy and informative organizational meetings were held at least monthly under the chairmanship of Sir Alexander Hood, KBE, Head of the RAMC. Surgical Consultants, now Major Generals, Brigadiers or Full Colonels in the British and U.S. Armies stationed in the UK, prepared for the invasion of Europe. The allocation of medical, surgical, nursing and auxiliary responsibilities was delineated. Liaison with the RAF and US Army Air Force was close as it was with the proposed leaders, Ulstermen Brooke and Montgomery. Montgomery chose Arthur Porritt as Surgeon in Chief to Supreme Headquarters Allied Expeditionary Force (SHAEF), and Eisenhower, General Albert W. Kenner.

Just after D-Day, Porritt met Ian Fraser, who had waded in on Arromanches Beach. The triage and evacuation plans for Allied casualties had been controversial, particularly as regards Landing Ship Tanks (LSTs), with the dispute with the Hood-selected surgeons on one side, against medical and surgical deployment of LSTs, and Admiral Ernest King and Winston Churchill on the other, favouring LST use for surgery and evacuation. King and Churchill were correct but total Allied air superiority allowed wide use of many of the Allies' Dakotas; 10,000 DC-3s were eventually in service. Supported by forty Allied combat planes to each Luftwaffe, the dispute about Landing Ship Tank use in about a fortnight became moot. The multifaceted role of the Princess Royal in the Emergency Medical Services of the United Kingdom and her close liaison with the Consultant Surgeons was of great value to the Allies.

INTRODUCTION

The planning of surgical response to Nazi aggression began in 1938 both in the Royal College of Surgeons of England and in the Surgical Travellers Club[1-3] . In 1938, the year of Chamberlain's "Peace in our time" speech, the Army Blood

Fig 1. Sir Ian Fraser (1901-1999), oil on linen, 91.5 x 76.2 cm, by Carol Graham, 1994. Reproduced with permission of Queen's University, Belfast, solely for this Medical History. Sir Ian's father, Dr. Robert Fraser, was a single-handed General Practitioner in Belfast. Ian's mother, Margaret, died in 1903. Ian won a scholarship to his father's old school Inst in 1913. Ian began his medical career as a student at Queen's in 1918; for the next eighty years he led a full and distinguished life. He was created D.S.O. in January 1944 for his legendary war surgery and for his penicillin work with Lord Florey and Dr. Norman Heatley[5-7]. An Oxford DSc followed, as did heroic surgery near Bayeux. The three months after D-Day the Second Battalion of The Royal Ulster Rifles were just to Fraser's east. From the Normandy beaches to the capture of nearby Caen, this combat cost the Second Battalion 400 killed or seriously wounded [8].
By the end of July 1944 and the Ste. Lô breakout, the First Battalion of the Royal Ulster Rifles had suffered 488 casualties. On D-Day 864 men of the First Battalion had landed by parachute glider or boat[8].

David S. Sheridan Professorship in Anaesthesia and Respiratory Therapy Harvard University, 1400 VFW Parkway, Boston, MA 02132-4927 USA

Correspondence to Prof. Hedley-Whyte

john_hedley-whyte@hms.harvard.edu

Transfusion Service was established under the direction of Lionel Whitby[1-4]. During the March 1938 visit of the Surgical Travellers to Vienna at the start of Anschluss, Ian and Eleanor Fraser were moved, despite their protests, out of the Hotel Bristol, as von Papen had taken over the entire hotel (Fig.1). From Vienna, the Frasers bussed down to Budapest. Here the displaced Travellers agreed to meet on Tuesday, 7 March and Wednesday, 8 March 1939 in Dublin, followed by three days of meetings and dinners in Belfast, before leaving from Ulster on the morning of Sunday, 12 March 1939[9]. Ian Fraser was to be host and the fifteen consultant surgeons would plan for the inevitable war[3].

Heneage Ogilvie was leader and founder in 1927 of the Surgical Travellers[2,10]. According to Sir Ian Fraser, members were chosen to "be amiable, enthusiastic, interested, interesting, intelligent, and above all, friendly and clubbable with a sense of humour." Spouses likewise[3].

WORLD WAR II

Howard Florey decided, on the suggestion of Hugh Cairns, that Ian Fraser should test penicillin "in the forward area on war casualties"[6,7]. Heneage Ogilvie was at the same time, in 1942 and early 1943 in North Africa, Sicily and Italy, testing regimens for sulfonamides[1]. Fraser caught diphtheria at the Salerno landings and was flown to Catania to be cured by Max Rosenheim[5]. Ogilvie, promoted to Major General, was recalled to the UK to be the consultant surgeon for the Eastern Command, while my father[1], having left Musgrave Park in July 1942, was from September 1942 consultant surgeon in the adjacent Northern Command[9]. From Friday, 5 March 1943 my father had been meeting with General Paul Hawley and Colonel Professor Elliott Cutler at the U.S. Army Medical Corps European Headquarters in Cheltenham. Sir Alexander Hood, DGMS, RAMC agreed that Ian Fraser should be Ogilvie's understudy in Eastern Command and at the War Office. Hood also arranged that Ogilvie and Fraser should meet together with General Paul Hawley and Cutler of the U.S. Army Medical Service, Vice-Admiral Gordon Gordon-Taylor of the Royal Navy (Fig.2), and Brigadier Arthur Porritt, Chief Surgeon designate to Supreme Headquarters Allied Expeditionary Forces, together with Northern command's Angus Hedley-Whyte (Fig. 3). Meetings of the group were held at 10:00 a.m. during April to December 1943 and on Thursday 13 January 1944, Wednesday, 9 February, Thursday, 13 April and Thursday, 11 May 1944 and Monday, 15 May 1944. Topics discussed included D-Day's General Plan of Operation for Allied Medical Units and their supply[9].

The plans for evacuation of wounded and sick led to delineation of Army and Navy responsibility in LSTs, other Allied vessels and on the beaches and harbours on both sides of the Channel and the Irish Sea. The roles and availability of motors, aircraft and Hospital Trains were discussed and priorities assigned[15]. The transfer of wounded to RAMC, US Army, US Navy and Royal Navy Hospitals was planned. In general, the Navies would be responsible for their own wounded and the Armies for both soldiers and airmen and wounded Prisoners of War. Standards for potable water and milk, their testing and procurements in Normandy were

Fig 2. Portrait of Sir Gordon Gordon-Taylor (1882-1960) in naval uniform, photograph. Wellcome Library, London, Iconographic Collections, image no. M0017976.

Educated at Robert Gordon College in Aberdeen, Gordon-Taylor won the Aberdeen Gold Medal for Classical Studies. In 1898 he entered the Middlesex Hospital Medical School as an Entrance Scholar, winning in 1901 the Gold Medal in Anatomy. For the rest of his career he was associated with the Middlesex. World War I saw Gordon-Taylor at the Battle of the Somme where he amputated the leg of machine gunner Lionel Whitby. Passchendaele followed and Gordon Gordon-Taylor became Acting Consulting Surgeon to the 4th Army, where his surgical distinction made him a legend. He was promoted to Major and was awarded a Military OBE. In 1932 Gordon-Taylor was elected to the Council of the Royal College of Surgeons of England. In 1934, he visited Australia to examine in the Anatomy Section of the Primary Fellowship. On the outbreak of World War II he was appointed Consultant Surgeon to the Royal Navy. He assiduously visited the Naval Hospitals and the Emergency Medical Service Hospitals and ships. There were also visits to Canada, and the United States, where as Visiting Professor of Surgery at Harvard, he took Elliott Cutler's place. Further World War II visits to the U.S. led to his heading an Anglo-American visit to Russia in 1943. Created KBE, he became a Commander of the Legion of Merit of the USA. When his former amputee patient Sir Lionel Whitby was Vice-Chancellor of Cambridge, Whitby arranged an honorary Cambridge Sc.D. Over thirty of Gordon Gordon-Taylor's more than 135 publications concern war surgery[11,12].

1 "My" or "I" denotes first author.

enacted. Plans for treatment of tuberculosis and gas gangrene and the deployment of penicillin and sulfonamides and above all blood and plasma were delineated. "Whole blood will be an item of medical supply and will be distributed through medical supply channels. It will be given the highest priority in transportation"[9]. A ten-day supply of blank forms and stationery were to be stocked in advance dumps and a month's supply in Base Depots.

Fig 3. Baron Porritt of Wanganui and Hampstead, GCMG, GCVO, CBE (1900-1994)[13]. Portrait, oil on canvas, 128 x 93 cm,1964-65, by Sir James Gunn, RA. Reproduced with permission of the Hunterian Museum, Royal College of Surgeons of England, solely for this Medical History. Arthur Espie Porritt was born in Wanganui; his father was a surgeon as was his maternal grandfather. His commendable academic and athletic performances led to a Rhodes to Magdalen, Oxford. At the 1924 Paris Olympics he took a bronze in the 100 meters. Although a knee problem prevented further competition, he served as captain of New Zealand's Olympic Team in Amsterdam in 1928, the year he qualified BM from Oxford. Through house jobs at Mary's and after being Assistant Director of the Professorial Unit, he became surgeon to Mary's and then Surgeon-in-Ordinary to the Duke of York, later HM King George VI. Placed by Hood in the BEF2, he became known to Ulstermen Brooke, Alexander and Montgomery. In North Africa with Montgomery he was chosen as Surgeon in Chief Designate to SHAEF to help Montgomery and Eisenhower[14].

Always cheerful, optimistic and supremely practical he liaised well after D-Day with Americans, Canadians, French, Poles and the Allied Air Forces. His Presidency of the Royal College of Surgeons of England from 1960-1963 was rewarded with a Baronetcy. In 1967 he was appointed Governor-General of New Zealand. He and Lady Porritt, a former Sister in QAIMNS, were extremely popular and successful for their five-year term in the land of Porritt's birth. His death at their home in St. John's Wood, London was on New Year's Day; he had been fully active until Christmas[14].

The Allied Invasion of Normandy was to involve 8,000 doctors, six hundred thousand doses of penicillin, 50 tons of sulpha drugs, sixteen hundred pallets of medical equipment each weighing half a ton. Each rifleman, the surgeons decreed, should carry ashore or be dropped with equipment and supplies weighing not more than 43 pounds. The armies, navies and air forces edged this up to 68.4 pounds by D-Day with disastrous results from drowning upon disembarkation[16].

On May 15, 1944, thirty-nine-year-old Pete Quesada was asked to explain the D-Day and Normandy tactical air plan. Major General J. Lawton Collins, known as "Lightning Joe Collins" asked "Pete, how are you going to keep the German Air Force from preventing our landing?" "There is not going to be any German Air Force there," replied Quesada. Winston Churchill's skeptical response was: "Ahhh, young man, how can you be so sure?" He replied, "Mr. Prime Minister, because we won't let them be there. I am sure of it. There will be no German Air Force over the Normandy invasion area" [17]. But there were barely enough LSTs[18]. On April 28, German E boats were to sink 3 LSTs off Slapton Sands, Devon, and drown over 700 Allied personnel. Each LST carried two physicians and 20 navy corpsmen from either the Royal Navy or US Navy[19].

HOOD AND WAR CABINET

During the Thursday, 13 January 1944 conference in Hood's office, the consulting surgeons could not agree on the partial conversion of Allied LSTs to be casualty evacuation vessels from Normandy. They were flat-bottomed and unsuitable sites for surgical operations. Essentially all Allied Hospital Ships had been deployed to the Pacific or Africa or sunk by German bombing despite their Red Cross marking. The War Cabinet summoned Hood and the Fighter Command leader of the U.S. Army Air Force and asked to predict the Allied air coverage for the LSTs' landing and evacuation roles. They opined that four British Hospital Ships should be lent for the U.S. Navy to operate on D-Day and the following month[20].

1944 INSPECTIONS

On Sunday, 9 January, Brigadier Angus Hedley-Whyte took the train from York to Cambridge, the base of Major General Heneage Ogilvie, to discuss the inspections they would carry out from Middlesex to Scotland. Dinner was with Basil Hume, later Anthony Eden's surgeon. On Wednesday, 12 January, all Consulting Surgeons had meetings in London in preparation for their meeting at 10:00 a.m. next day with Lieutenant General Hood. On Monday, 17 January, I went to London. Next day, I was returned to the Dragon School at Oxford and my father went to see the Princess Royal[2] at Harewood House. Father's first meeting had been Tuesday, February 9 to Friday, February 12, 1943[9]. From Harewood,

2 Princess Royal, HRH Princess (Victoria Alexandra Alice) Mary, CI, GCVO, GBE, RRC, TD, CD April 25, 1897-March 28, 1965), was the only daughter of King George V and Queen Mary [21].

my father went to 103 Field Ambulance near Leeds. According to Ian Fraser, the Consulting Surgeons' job "was to visit all the various hospitals on the east coast to advise them that they must make a plan to evacuate their hospital when "D" day came, so leaving adequate empty beds for the wounded evacuated from France. The government would supply them with the necessary blood afterwards"[3]. The job from 1940 to 1945 of the Princess Royal was to facilitate the taking over of suitable stately homes for bed expansion. The Princess was to follow, with the Army Consultants, standards of care.

On Sunday, 23 January to 25 January, my father and DADMS Gwynne-Evans visited medical facilities of 2nd corps., Alan Brooke's Corps with the BEF in France in 1940. Menthorpe Gate, Malton and Cottingham, Yorkshire, Askham House, Northumberland and Hutton- in- the-Forest, Penrith, were evaluated. Reports were made late on 25 January to the Royal College of Surgeons of England Council and next day to the Hospitals Committee of the BMA at Tavistock House. That evening, my father dined with Brigadier, later Lord Porritt, Surgeon in Ordinary to King George VI and to Ulsterman Bernard Montgomery, Allied Ground Commander (Fig.3). Ian Fraser and Molly Porritt joined them at the Berkeley Grill[9].

On Tuesday, February 1, a conference with 'Ford at Reg 2' discussed potential EMS hospital expansions. On Thursday, February 3, the Medical Facilities of 77 Division were inspected together with Brigadier Arnold Stott[22] and Major General Philip Mitchiner[23] Stott's wife Kay joined them for dinner. On Friday, 4 February, Arthur Porritt acting for General Montgomery conducted Hedley-Whyte and Stott on a two-day inspection of 2nd Corps. On the evening of 5 February, the three inspectors were joined by Lord Webb-Johnson and Norman Heatley at the York Club. Sunday, 6 February was spent on penicillin matters at Stannington on the Ridley Estate at Blagdon, Northumberland. Porritt got the night train back to London; Heatley spent the night at Moorfield, our house near the Royal Victoria Infirmary, Newcastle-upon-Tyne. Heatley caught the 9:20 a.m. train to Oxford and my father took the sleeper to London with Durham Medical School Dean R.B. Green[6,7]. On Wednesday, 9 February, they reported to DGMS Hood and dined with Max Rosenheim[5,24]. My father attended meetings in London until luncheon on Thursday, 10 February at the Royal College in Lincoln's Inn Fields. He then traveled again to Harewood House. On Sunday, 13 February, my father received reports of progress in site expansions for the EMS. On Tuesday, 15 February, my father reported to Balme at the Ministry of Health in London. For the next fortnight my father lectured mostly in Northern and Eastern commands on "Types of Bombs and their wounds". On Wednesday 12 April, father met with senior RAF and US Army Air Force surgeons to describe future plans for air-crew casualties. Air transport of casualties with head, face and hand injuries was assigned to specialists at Oxford (Hugh Cairns and Cecil Calvert) and to East Grinstead Plastic Surgeons, New Zealanders Sir Harold Delf Gillies and Sir Archibald McIndoe. Sir Alexander Hood was briefed on Thursday, 13 April. On 8-10 May, a 'final' three-day briefing for most surgeons involved in D-Day was held in Lincoln's Inn Fields. On Thursday, 11 May, both U.S. and British Consultant Surgeons met with Sir Alexander Hood. Both Professor Cutler and General Paul Hawley speaking for the United States and Sir Gordon Gordon-Taylor speaking for the Royal Navy and responding to Ian Fraser's pleas, begged for a dozen pints of blood or more on each of the LSTs going to the Invasion. The Whitbys agreed to top up American donations. On Friday and Saturday, 12 and 13 May 1944, my father had to attend to the UK Tax Authorities in Leeds who did not wish to grant tax abatement for stately home transfer to being an EMS hospital[9].

D-DAY SHIPS

Ian Fraser wrote of wading ashore at Arromanches, "Water up to my nipples… was not strafed"[3]. Indeed, on the beach he met Montgomery's surgeon Arthur Porritt and was given dry clothes and marched to the site of British Army Hospital 108 near Bayeux[3,5]. Fraser when in Yorkshire in Northern Command had planned the layout of 108 on photographs provided by RAF reconnaissance. My father, with his record of 1940 Normandy War surgery was a courtesy ex officio advisor. Senior Surgeon Fraser and Matron arranged camouflage over the objections of the Norman Baroness landowner. "Colonel Fraser was causing more damage than the Wehrmacht had in four years"[3]. Fraser claims he was able to adapt French telegraph pole bore diggers to make almost instantaneous hospital latrines[25].

In the three months from mid-June to mid-September 1944, surgery on Allied and POW casualties was almost continuous. Casualties from British attack Epsom (26 June to 1 July), cost 4,020 men killed or wounded[26]. Charnwood 7 July: after the RAF had dropped 3,500 tons of bombs on Caen, led to 3rd British Division including the 1st and 2nd Battalions of the Royal Ulster Rifles' taking Caen[8]. The Norman capitol was due to have fallen on D-Day. Operation Goodwood began on 18 July, but failed to take Boarguébus ridge[27]. On D-Day + 43, 20 July, Goodwood fighting finally sputtered out[28]. On 25 July four American infantry and two armoured divisions attacked just west of St. Lô. They, as VII Corps, were commanded by 'Lightning Joe Collins'[26,29].

BREAKOUT

Collins's Corps VII broke through German defenses in late July 1944. Meanwhile, Montgomery renewed British attacks in operations Bluecoat on 2 August and Totalize on 7 August. As August 1944's heat wave continued, Fraser operated eight hours on eight hours off. Fraser, stripped to the waist, treated the wounds of Ulstermen, Canadians, Poles and German POWs, as well as UK and American Casualties[3]. In late August there was no longer the constant passage overhead of naval support gunfire of 7 battleships, 2 monitors, 23 cruisers and 104 destroyers [25,27]. Three of the battleships, the *Arkansas, Texas and Nevada*, had come from Ulster to support the Allies for June. They stayed off Normandy until required

for the French Riviera landings[30]. The *Nevada* had been beached at Pearl Harbor and there repaired. The fourteen and sixteen-inch guns were accurate up to 25 miles inland: the front south of Bayeux and Hospital 108 was well within the range of Naval gunfire[31].

EVACUATION OF WOUNDED

On 16 December 1943 the U.S. Ninth Air Force made the inaugural flight of the UK evacuation system[32]. Initially these flights were generally between Meghaberry Aerodrome near Lisburn and RAF Station Pershore, Worcestershire and took two hours. From December 1943 through May 1944, a total of 2,786 ambulatory and litter patients were flown from Ulster to England; many of whom were American casualties of training mishaps[19,33,34,35]. In the spring of 1944 an increasing number of patients were flown to Prestwick and thence to the United States. There were 446 in May 1944. Also in May, Membury, Devon, and Ramsbury, Wiltshire Airfields were designated as the main reception air fields; field hospital and ambulance detachments were stationed at these two aerodromes[33]. A temporary airstrip near Bayeux was established on 8 June and on 10 June a C-47 evacuated thirteen patients. Patients were also evacuated to RAF Merrifield, Somerset, and RAF Rednall, Shropshire. Allied Air Evacuation Liaison officers were deployed to the Office of the Chief Surgeon, Advance Echelon, Communications Zone, the offices of the Chief Surgeon of the First and Third U.S. Armies, and to the Advance headquarters of the Ninth Air Force. These liaison officers were scheduled to land in France on D-Day and to arrange for airfields, holding stations and medical evacuation planes[33,36,37]. A week after Fraser's arrival 600 patients a day were being flown to the UK. By the end of June 1944, 8000 patients had been evacuated to the UK from Normandy. During July 1944 only two of the 19,490 casualties air evacuated from Normandy died in flight[33]. Heavily loaded transports could land at Querqueville, unload, then 'hop' to Binniville and Colleville or to a combat airstrip to pick up casualties. The only crash was a C-47 not from Normandy near Prestwick killing 13 patients and two crew[33]. "Evacuation by air is the only means available at present for the proper evacuation of casualties from the Armies", wrote General Hawley on 30 August 1944[33]. "Where there is no supply by air, there is no evacuation by air"[19,38]. The spring planning at Hood's meetings of the Allied Consultant surgeons and Pete Quesada's promise had been vindicated. During September 1944, partly because of the failure of Arnhem, 26,126 casualties had to be flown back to the UK—an explanation of the sadness and fatigue of the RAF who flew Ian Fraser to the UK and thence to India[3] (Table 1).

NORMANDY WOUNDS

About 85% of the battle casualties on which Fraser operated occurred in infantry riflemen; over half were caused by German shells and over half needed surgery of the extremities. Ten percent of casualties required thoracic surgery and five percent laparotomies[19] (Fig.4).

Porritt's SHAEF colleague, General Kenner stated, "Men wounded in the morning are often on the operating table of a general hospital in the UK within 10 hours"[19]. The use of LST Tank ships for evacuation dwindled and the four hospital ships were generally not full. The death rate of Fraser's 108 hospital ranged from 11 to 14 percent of surgical admissions. He and his staff treated "exsanguinations, eviscerations, cardiorespiratory difficulties, and deep shock"[3,19,25]. On average, 108 hospital staff performed 100 major operations every twenty-four hours. The surgical nursing care was superb but Fraser noted that brunettes went grey-haired[5], a change that my father said happened in his BEF2 hospital in Normandy four years earlier. Fraser was not short of donated blood. Of the men treated by Hospital 108, less than one percent died after reaching the UK. Kenner and Porritt attributed this to "the echeloning of skilled surgical care throughout the evacuation chain." Professor Cutler concluded after his inspections of the Allied hospitals in Normandy in the first month after D-Day, "The level of professional care is very high…low incidence of serious infection"[19].

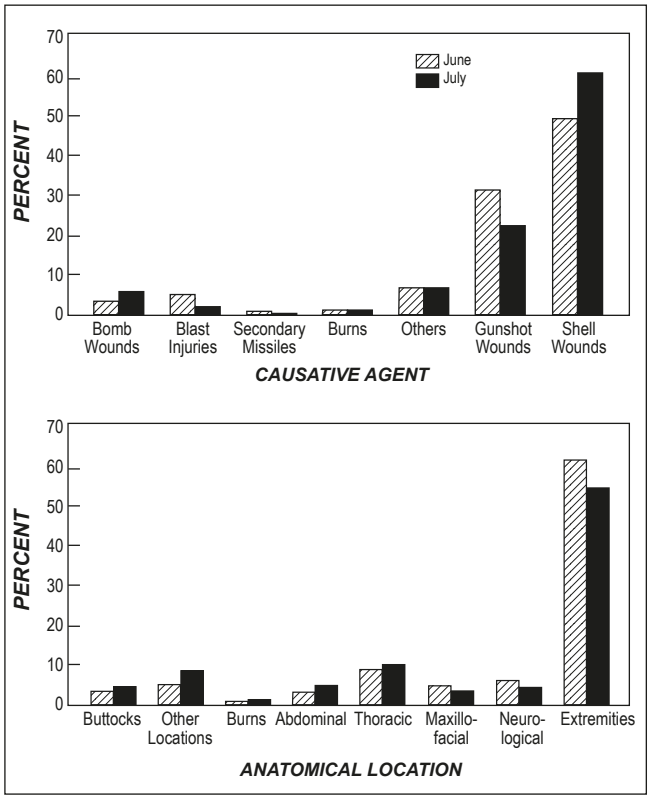

Fig 4. Causes and Locations of Wounds, Battle of Normandy, June-July 1944, Cosmas and Cowdrey, *Medical Service in the European Theater of Operations*[19].

"A prolonged diet of C- and K-rations produced, after D-Day, vitamin deficiency"[19]. The U.S. had not yet implemented the results of the 1942 Musgrave Park research[39]. 'We were vindicated,' Rycroft told Duke-Elder as well as Rycroft's own patients, including the Winston Churchills.

EMS REARRANGEMENTS

With the start in June 1944 of the V1 doodlebug and V2 rocket attacks, a further need for expansion of EMS beds

was mooted. After D-Day, EMS hospitals in Northern Ireland took "a steady stream of service casualties from overseas"[40,41]. In response to demands on the EMS it was decided by the Northern Ireland Ministry of Health and Local government to appoint as consultant advisors the Professors of Medicine and Surgery at Queen's, W.W.D. Thomson and P.T. Crymble. These appointments, as effectively Allied Consultants, regularized their previous and existing service and their extensive contributions in both World Wars[40]. Both Brigadiers Ian Fraser DSO, and Angus Hedley-Whyte DSO were demobbed after VJ Day. Fraser wrote my father's Lancet obituary[42].

Montgomery wrote in his memoirs:

"I learnt during the 1939-45 war that four things contributed to the saving of life:

1. Blood transfusion.
2. Surgical teams operating well forward in the battle area, so that badly wounded could be dealt with at once without having to be moved by road to a hospital.
3. Air evacuation direct to a Base hospital many hundreds of miles in rear, thus saving bumpy journeys by road or rail.
4. Nursing sisters working well forward in the battle area. When I joined the Eighth Army in 1942, nursing sisters were not allowed in the forward battle area. I cancelled the order. Their presence comforted and calmed the nerves of many seriously wounded men, who then knew they would be properly nursed. No male nursing orderly can nurse like a woman, though many think they can"[43].

The plans of Porritt, Ogilvie, the Surgical Travellers and Eisenhower's Generals and Admirals, led to organized execution of Montgomery's four precepts for the saving of life[43].

ACKNOWLEDGEMENTS

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Letters

GLOMUS TUMOUR OF THE ELBOW: AN UNUSUAL CAUSE OF INTESTINAL PERFORATION

Key Words – Glomus tumour; stercoral perforation

Editor,

A 72 year-old-female presented to the Emergency Department with a twelve hour history of sudden onset generalised abdominal pain and distension. On examination she was systemically unwell and had a rigid abdomen with four-quadrant peritonism. On further questioning, she reported a 10 month history of an exquisitely tender swelling over the posterior aspect of her left elbow, which had been treated as bursitis, causing her to take excessive amounts of codeine-based analgesia.

An abdominal radiograph demonstrated faecal loading and a small pocket of free air in the left upper quadrant suggestive of pneumoperitoneum (Figure 1).

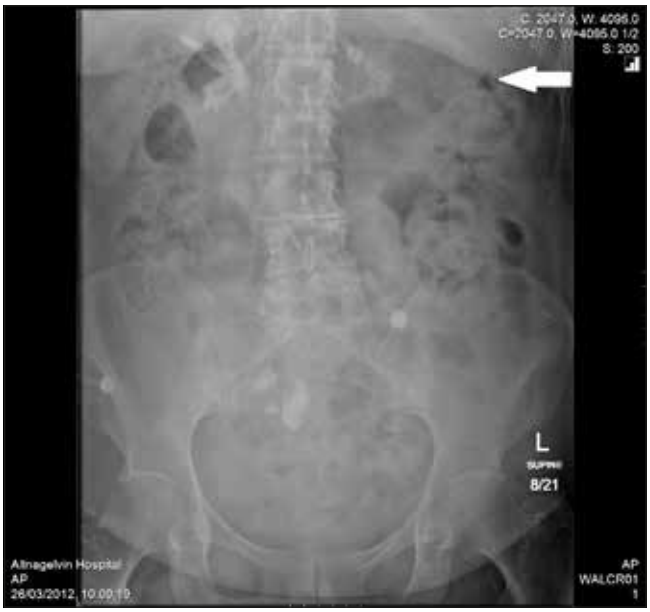

Fig 1. Supine anteroposterior abdominal radiograph showing faecal loading of the colon. A small triangular pocket of free air is evident in the right upper quadrant suggestive of pneumoperitoneum (arrowed).

An emergency laparotomy revealed a stercoral perforation of the sigmoid colon with gross faecal contamination of the peritoneal cavity. A Hartmanns procedure was performed and 38mm of colon was resected. There was no histopathological evidence of malignancy or diverticular disease in the resected specimen. Postoperatively an orthopaedic opinion was requested in relation to her left elbow swelling. An ultrasound scan revealed a 14x12x7mm localised subcutaneous lesion with increased vascularity (Figure 2).

Once fully recovered, an elective excisional biopsy of the left elbow swelling was performed under local anaesthesia. Histological analysis demonstrated morphological and immunohistochemical features in keeping with a glomus tumour (Figure 3). At review six weeks post-operatively her pain had completely resolved.

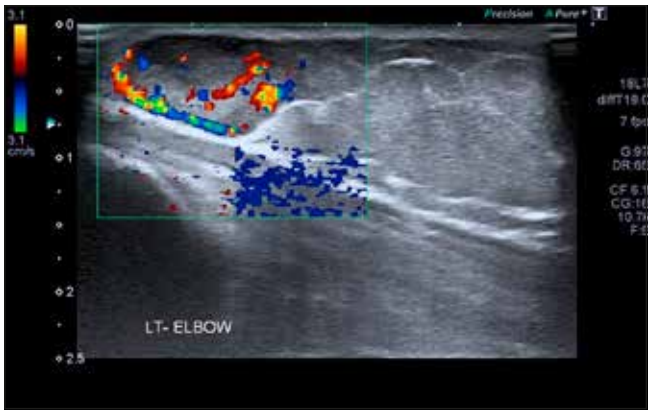

Fig 2. Doppler ultrasound image of the area of maximal point tenderness showing a well circumscribed subcutaneous lesion measuring 14x12x7mm with increased vascularity

The glomus body is a specialised arteriovenous anastomosis located in the stratum reticularis of the dermis governing flow in the cutaneous microvasculature in response to temperature. Glomus tumours are uncommon neoplasms of the glomus body consisting of glomus cells, vascular structures, smooth muscle and nerve fibres containing immunoreactive substance P [1]. They are typically benign although cases of local invasion have been reported. Metastases are exceedingly rare [2]. They are most abundant at the tips of the digits, particularly the subungual area [1]. Extra-digital cutaneous sites and extra-cutaneous sites have also been reported [3].

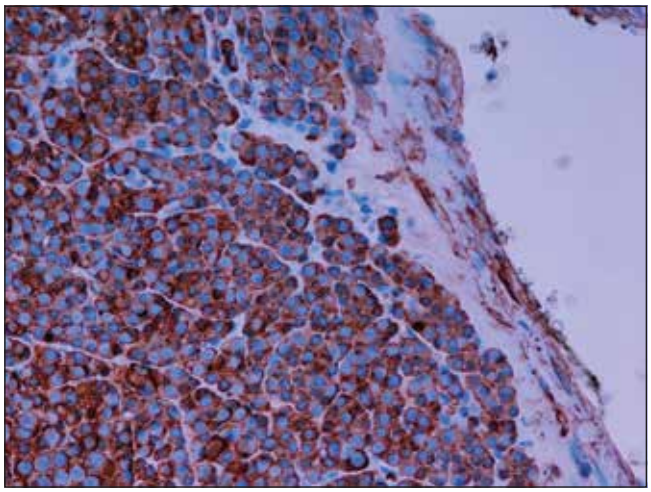

Fig 3. Histological slide showing glomus cells staining positively with smooth muscle actin (X40 magnification) in keeping with modified smooth muscle cells.

Clinically, cutaneous glomus tumours appear as solitary, small bluish subcutaneous lesions with the classic triad of point tenderness, severe pain and cold intolerance. Clinical suspicion should be increased by a positive Love test where

severe pain is elicited by applying localised pressure with a blunted point. Reduced pain when this test is repeated after the induction of transient ischaemia via a tourniquet aids the diagnosis (Hildreth's test). Duplex ultrasonography showing a well-circumscribed lesion with high vascularity and point tenderness provides good evidence towards the diagnosis. However, magnetic resonance imaging (MRI) has been deemed more sensitive for the detection of glomus tumours [4]. Treatment is by local excision.

Delayed diagnosis of glomus tumours can prolong unnecessary pain resulting in the excessive use of analgesia which may result in significant morbidity. Stercoral perforation is a rare cause of intestinal perforation with a high mortality. The association of stercoral perforation and analgesic use has previously been documented [5].

Although rare, we recommend that the diagnosis of a glomus tumour is considered in cases that present with a cutaneous swelling associated with severe pain and exquisite point tenderness. Analgesics must be prescribed with caution.

Mr Kevin J Donnelly[a]

Mr Neville W Thompson[a]

Dr Diarmaid O'Longain[b]

Dr Iain Cameron[c]

a Department of Trauma and Orthopaedic Surgery, Altnagelvin Hospital, Glenshane Road Derry, Northern Ireland BT47 6SB

b Department of Radiology, Altnagelvin Hospital, Glenshane Road Derry, Northern Ireland BT47 6SB

c Department of Pathology, Altnagelvin Hospital, Glenshane Road Derry, Northern Ireland BT47 6SB

Correspondence to: Mr Kevin Donnelly

Email: kevdonnelly@hotmail.com

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THE MOBILE PHONE AS A TOOL IN THE ASSESSMENT OF NONSPECIFIC ABDOMINAL PAIN

Editor

Nonspecific abdominal pain (NSAP) continues to provide a diagnostic dilemma for the general surgeon. Hospitalisation is often accompanied by a series of negative investigations and prolonged inpatient stay. In an era of intense scrutiny, clinicians are perhaps increasingly reliant upon radiology and other investigations to assist in clinical judgment and decision-making. Clinical acumen, however, remains essential in the assessment of the patient. We decided to observe particular characteristics and behaviors of patients admitted with NSAP and identified the use of a mobile phone as one marker of patient well-being. We hypothesized that patients found to have a significant underlying diagnosis were not likely to be actively using their mobile phone during consultant-led consultation.

100 patients (40 male and 60 female with age range 20 – 90 years) admitted as an emergency over a 3 week period with abdominal pain were included and observations taken during the post-take consultant-led ward round. 51 patients were in possession of a mobile phone at their bedside. 13 patients (all females < 35 years) were actively using their phone during the consultation, none of whom had a cause for their pain identified that required surgical intervention despite appropriate and timely investigation. In the other 49 patients, diagnoses included cholecystitis, diverticulitis, pancreatitis, flare of inflammatory bowel disease and bowel obstruction. Patients not using a phone were more likely to require intervention (appendicectomy, laparotomy, hernia repair, abscess drainage, endoscopic retrograde cholangiopancreatography or radiologically-guided drainage). Interestingly, all of the male patients admitted had a diagnosis on discharge to explain their symptoms. Patients using their mobile phones during consultation also tended to accumulate an array of magazines at their bedside within a short period of time from admission. Older female patients and male patients tended not to have a mobile phone at their bedside. Those patients who had a serious diagnosis causing risk to life and/or requiring urgent surgical intervention did not have a mobile phone or magazine at their bedside during the study period.

Acute nonspecific abdominal pain (NSAP) is generally defined as acute abdominal pain of less than 7 days duration for which there is no diagnosis after examination and baseline investigations.[1] Hospitalization followed by active clinical observation has been the traditional approach and the most widely accepted management of patients with non-specific symptoms. The predictive value of clinical diagnosis can vary depending on the underlying cause and reaches 68% - 92%.[1] Methods used to improve diagnostic yield have included questionnaires, abdominal ultrasound, CT scanning and laparoscopy but have been relatively unsuccessful.[1] We found that young females admitted with non-specific abdominal pain and actively using their mobile phones during consultant-led ward rounds were not likely to have any significant underlying pathology requiring surgical intervention. Clinical expertise remains paramount in the assessment of a patient and in a profession where aptitude is critical, observation can tell you a lot about a patient.

McBrearty A, Porter D, Moorehead RJ

Ulster Hospital, Upper Newtownards Road, Dundonald, Northern Ireland BT16 1RH

Correspondence to: Mr Anthony McBrearty

Email: anthonymcbrearty@doctors.org.uk

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"PAEDIATRIC DNA CODING: CAN'T ATTEND, WON'T ATTEND."

Editor

Patients failing to attend for their outpatient clinic appointment is common and occurs for a variety of reasons which are frequently multi-factorial and complex. This may range from simple forgetfulness to more complicated financial and employment related issues with an average appointment costing patients £15 in lost earnings and travel costs[1]. Not only is it frustrating for clinicians attempting to efficiently run their clinics but it is estimated to take 21 minutes of a clinicians time, even when the patient does not attend[2]. Approximately 6 million appointments are missed each year in the NHS and is estimated to cost the public in excess of £700m/year[3]. Several systems have been used to improve patient attendance at clinics with varying success rates including the use of SMS reminders and appointment provision at times to suit the patient. Current practice in the NHS is for patients to be discharged back to their referrer following a failure to attend the outpatient clinic.

While this may be acceptable practice in adult medicine the authors feel that in paediatric medicine a different perspective and approach should be considered. Often the reasons for non attendance at paediatric clinics are similar to those for adults, however it is important for the clinician to be aware, that in the majority of cases the child does not make this decision. Therefore not being brought to outpatient appointments potentially puts children at risk of avoidable ill health. Recent studies have shown hospital paediatric outpatient Did Not Attend (DNA) rates of 15% occur[4].

With these figures and recent major child protection cases fresh in everyone's mind (e.g. Daniel Pelka, Baby Peter) all clinicians treating children in any outpatient setting must be alert to the possibility that a failure for children to attend their appointment may go deeper than just forgetfulness, and in fact may be a child protection issue. GMC guidance would recommend that all medical practitioners caring for children (0-18years) must safeguard and protect the health and well-being of the child[5]. It is imperative that clinicians consider the paediatric "DNA" differently, and that a system is in place to allow them to flag this up to the appropriate teams and to ensure adequate and safe follow up for each child.

The authors therefore recommend that all children are offered two appointments as standard (rather than Discharge after first DNA). But after any DNA a letter goes to the referrer stating

"Your patient was not brought to the appointment by their caregiver and no telephone call was received, one further appointment has been offered. Please review the case to ensure there are no other concerns." This provides a simple mechanism for all specialists to highlight potential child protection issues in an otherwise busy outpatient setting.

We hope that this not only will offer the caregivers of children the greatest opportunity to avail of healthcare services, but that this may also initiate a culture whereby safeguarding concerns are noted and acted upon.

The authors have no conflict of interest.

Christine M McFeely

Philip R Bell

Robin A Adair

Department of Otorhinolaryngology, Department of Paediatrics, Ulster Hospital, Southeastern Health and Care Trust, Upper Newtownards Road, Dundonald, Belfast BT16 1RH. Northern Ireland

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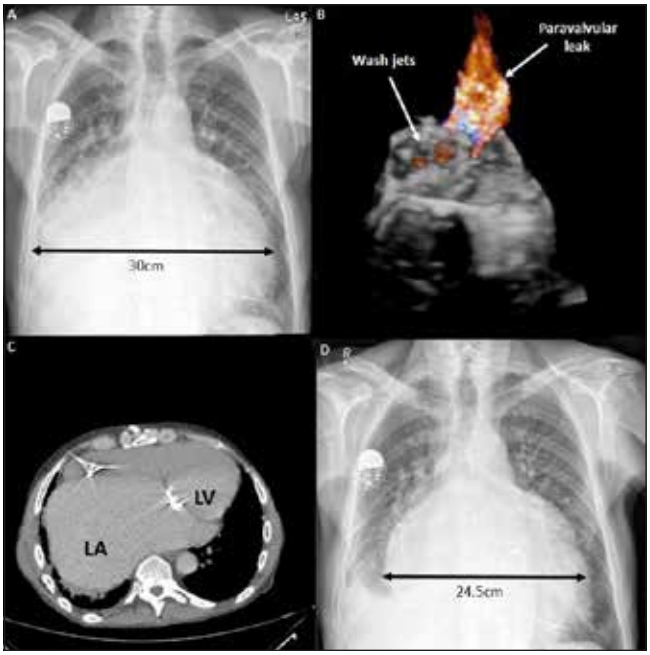
GIGANTIC LEFT ATRIUM- CAN SURGERY REVERSE THE DOWNWARD SPIRAL OF CARDIAC CACHEXIA?

Editor,

A 72 year-old male with a history of mechanical mitral valve replacement (MVR) 16 years previously, presented with cardiac cachexia, heart failure symptoms and anaemia. Chest x-ray (CXR) demonstrated a giant globular heart (Figure A) whilst transoesophageal echocardiogram found severe paravalvular leak (PVL) along ¼ of the mitral circumference (Figure B). The previous MVR utilised a continuous technique with 4 x 2/0 Prolene to secure the valve. Elevated plasma lactate dehydrogenase and lowered reticulocyte count supported the diagnosis of haemolytic anaemia from the paravalvular leak. A computed tomography (CT) scan demonstrated a gigantic left atrium, measuring 14 x 18 cm (Figure C), with no evidence of occult malignancy. Echocardiography and blood cultures were negative for endocarditis. Pulmonary function test demonstrated significant restrictive lung defect. With normal lung

parenchyma on CT chest, this was most likely due to the mass effect of the left atrium.

At surgery, the left atrium occupied the entire right basal portion of the chest, making visualisation of the mitral prosthesis difficult. The valve was excised and a size 29 St Jude mechanical prosthesis inserted using interrupted 2/0 Ethibond pledgeted sutures. One third of the left atrium was excised with the remaining portion plicated to reduce its volume, taking care not to injure the oesophagus posteriorly. The patient made a slow but uneventful post-operative recovery and was discharged at 2 weeks following surgery.



Figures showing (Figure A) preoperative CXR, (Figure B) TOE, (Figure C) CT scan and (Figure D)post-operative CXR.

At 3 months review he is gaining weight and haemoglobin remains stable. CXR demonstrated a significant reduction in heart shadow compared to previously (Figure D). This case highlights the role of concomitant left atrial reduction in addition to MVR to reduce the stagnant blood volume, improve forward flow, while also reducing the mass effect of the left atrium on the lungs.

R Beattie[1], P Johnston[2], R Jeganathan[1]

Departments of [1]Cardiac Surgery and [2]Cardiology, Royal Victoria Hospital, Belfast, Northern Ireland, UK BT12 6BA

Corresponding author: Rory Beattie

rory.beattie@doctors.org.uk

PLEOMORPHIC ADENOMA OF THE SOFT PALATE; AN IMPORTANT BENIGN DISEASE IN AN UNUSUAL LOCATION

Editor,

Pleomorphic adenomas are benign tumours of the salivary glands, most commonly seen in patients between the ages of forty and sixty.[1] Approximately four fifths occur in the parotid gland, and around 5% in the minor salivary glands, which includes the palate.[1] Pleomorphic adenomas are treated by surgical resection as they have the ability to become malignant and metastasise, within and beyond the head and neck regions.[1]

An 80 year old lady was referred to the ENT clinic for investigation of catarrh. General ENT examination revealed an incidental finding of an asymmetric firmness on the right side of her soft palate. The patient was unaware of such swelling and had no difficulty with speech or swallowing. Past medical history included essential thrombocythaemia, and atrial fibrillation requiring warfarinisation. This lady never smoked and did not consume alcohol beyond the recommended guidelines.

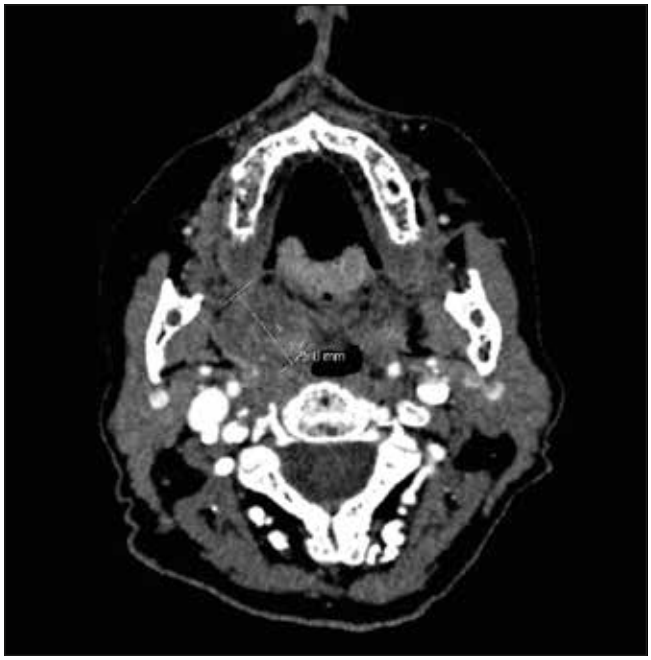


Fig 1.

CT neck with contrast was performed which revealed 2.5cm x 2.5cm x 2.6cm rounded pharyngeal soft tissue mass within the soft palate (fig 1). Biopsies were taken which revealed various cellular components. An epithelial component forming anastomosing cords and strands was identified, along with hyalinised fibrous tissue and myxoid areas within the stroma. (fig 2) These are the histopathological findings of a pleomorphic adenoma.

Although definitive treatment is surgical resection, a conservative approach was adopted given our patient's age, co-morbidities and localisation of the tumour.

Differential diagnoses for this case range from benign pathology, including odontogenic cysts, palatal abscess and mucocele, to malignant soft tissue tumours.[1]

CT and MRI are both useful radiological modalities. CT is superior in assessing erosion of tumour into nearby structures.[1,2] MRI provides enhanced delineation of tumour

extension and degree of encapsulation.[2]

Histologically cellular components of pleomorphic adenomas vary.[3] The presence of chrondromyxoid matrix is a very diagnostic finding of pleomorphic adenomas.[3] Three main groups have been recognised: myxoid (80% stroma), cellular (myoepithelial predominant) and mixed (classic) type.[1]

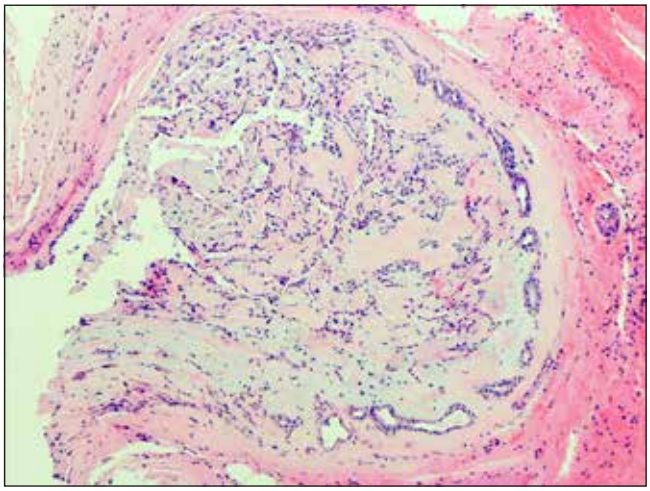


Fig 2.

Although pleomorphic adenomas are benign, they have the potential to metastasise. The time interval to metastasis from diagnosis varies; Bae et al state it ranges from three years to twenty-two years.[4] Pleomorphic adenomas can metastasise to cervical lymph nodes, within the head and neck, bone and lung.[4]

Pleomorphic adenomas can recur so adequate margins of normal tissue on resected specimens are necessary.[3] Vicente et al report between 5-30% of patients have recurrence which is usually due to inadequate margins.[5] It is recommended that patients are followed up for 10-20 years to identify recurrence.[3]

This case represents the importance of a full ENT examination for all patients, as significant pathology may be missed otherwise. Full history taking and examination have been indoctrinated from our early days of medical school. However, with time constraints and pressures of busy clinics, we must be reminded that comprehensive history taking and examinations are essential.

To the best of our knowledge, pleomorphic adenoma of the soft palate in Northern Ireland has not been previously reported.

The authors have no conflict of interests.

Donna McCartan, [1] Tom Delap [1]

Department of ENT, Antrim Area Hospital [1]

Correspondence to Donna McCartan (dmccartan@doctors.org.uk)

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MESENTERIC CASTLEMAN DISEASE

Editor,

We present a previously well 27-year-old female with three-month history of fatigue and weight loss. Investigation showed iron deficiency anaemia. HIV, hepatitis virology and liver specific antibodies were all negative.

Endoscopy was normal and CT scan showed a rounded mass measuring 5.5cm in the left side of abdomen (Figure 1). At laparotomy a smooth walled lesion measuring 6.5 x 5.5 x 4 cm was resected from the proximal small bowel mesentery.

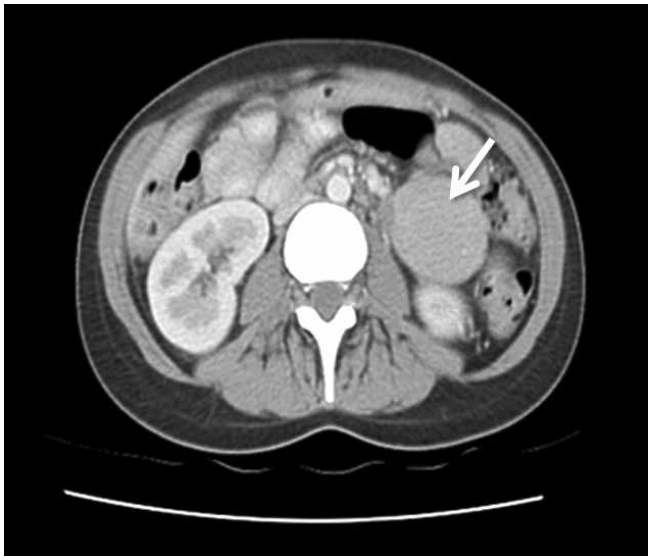

Fig 1.

Histology revealed lymphatic tissue with effacement of the normal follicular architecture and replacement by multiple atypical germinal centres. These were surrounded by concentric rings of small lymphocytes in an 'onionskin' pattern with an enlarged mantle zone. Some of these follicles had more than one germinal centre containing increased numbers of follicular dendritic cells. Others had a prominent hyalinised vasculature with a 'lollipop' configuration. Testing for Epstein Barr Virus (EBV) and Human Herpes Virus 8 (HHV8) was negative. A diagnosis of mesenteric Castleman disease was made.

Castleman disease (CD) is a rare nonclonal lymphoproliferative disorder of unknown aetiology. It has attracted attention due

to its association with HIV and HHV-8 (Human Herpes Virus) as it demonstrates a link between viral disease and malignant transformation [1]. Awareness of CD is important because the disease is potentially life threatening, is exceptionally rare and incompletely understood [2].

It is broadly classified into unicentric (e.g. single lymph node station) or multicentric and histologically into hyaline vascular (HV) variant or plasma-cell (PC) variant.

Patients with unicentric CD are mostly HIV negative, have HV pathology and do not have systemic symptoms or laboratory abnormalities [2,3]. They usually present as an incidental finding or signs and symptoms relating to site and mass effect. A study of 315 cases of unicentric CD by Testa *et al.,* found that 65% were in mediastinum, 16% in neck, 12% in abdomen, 3% in axilla and 4% in diverse locations[4]. Mesenteric Castleman disease is a very rare event with 42 cases in total reported in the English literature [5].

Approximately 10% of patients with unicentric CD have mixed HV and PC morphology. This can rarely be associated with systemic upset and laboratory findings such as anaemia, hypergammaglobulinaemias and raised inflammatory markers.

Multicentric disease patients can present with generalised lymphadenopathy, organomegaly and systemic upset such as fever, night sweats, fatigue, anorexia and weight loss [2].

The pro-inflammatory response syndrome produced in CD is caused by excess interleukin-6 (IL-6) production by B cells in the effected lymph node mantle zone. Local elaboration of IL-6 and consequent vascular endothelial growth factor (VEGF) production leads to the characteristic B-cell proliferation and vascularisation in CD [2].

This condition is very poorly characterised in the literature but should be considered when a mesenteric mass is noted on imaging. Surgical resection is curative in 95% of unicentric CD with resolution of systemic symptoms and in general the long-term prognosis in the HIV negative patient is excellent [2].

Computed tomogram demonstration a homogenous soft tissue lesion located between the tail of pancreas and the left kidney (arrowed).

Michael Warnock MB, ChB

William Campbell BSc, PhD, FRCS

Graeme Macauley MB, ChB, MRCS

P. Declan Carey MD, FRCS, FRCSI

Department of Surgery, Belfast City Hospital, 51 Lisburn Road, Belfast, BT9 7AB, Northern Ireland

Keywords: castleman disease, mesentery

Correspondence to: michael.warnock@doctors.org.uk

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COMPLIANCE WITH NICE HEAD INJURY MANAGEMENT GUIDELINES IN A BUSY DISTRICT GENERAL HOSPITAL – IS IT ASKING TOO MUCH?

Editor,

Traumatic brain injury (TBI) is a frequent presentation to emergency departments (ED) with over one million attendances in the United Kingdom per annum, 20% requiring admission. [1]

NICE developed guidelines for the triage, assessment and management of head injuries (CG-56, 2007).[2]

The literature is sparse on the feasibility of CG-56 in a busy District General Hospital (DGH).

This retrospective review was conducted on consecutive adult patients admitted with TBI to a DGH [Daisy Hill Hospital] in Northern Ireland over a one-year period.

We assessed the initial management of these patients with reference to CG-56 guidelines i.e. frequency and "completeness" of central nervous system (CNS) observations and "timeliness" of CT brain.

Demographics; time of arrival to assessment; indication for admission; risk stratification to determine if CT was required; details of CT including urgency and abnormalities; recording CNS observations and details of patient transfer to regional neurosurgery unit were retrieved.

RESULTS:

216 patients (median age 50 years) were admitted to Daisy Hill Hospital during this period (81% male). 171 (79.2%) patients were admitted out-of-hours.

Eighty-six (41.3%) patients had recent alcohol consumption. Sixty (28.6%) were admitted due to worrying clinical signs (e.g. confusion).

821 out of 2613 sets of observations (31.4%) were complete. Almost 15% had incorrect/missing GCS scores, while SaO_2, temperature, pulse rate, pupillary response and limb movement were not recorded in 19%, 37%, 11%, 14% and 11%, respectively.

150 (69.4%) underwent a CT brain, thirty-three (22.0%) of which had abnormalities.

Sixty-four (53%) with "low probability" of TBI had a CT brain, of whom seven (10%) had an abnormality. Sixty-two (90%) patients with "high probability" of TBI had a CT, of whom 16 (25.8%) had abnormalities.

Of the initial CTs performed for 62 high risk patients, only 12 (19.4%) had their scan reported within one hour of request (CG-56 guideline).

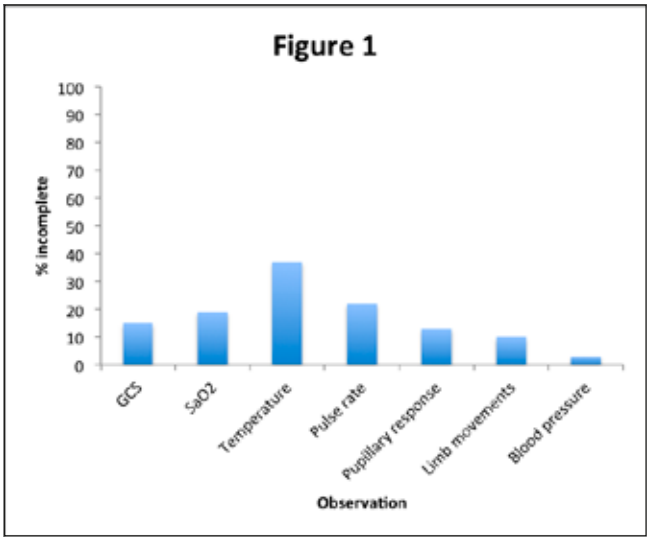

Fig 1.

DISCUSSION:

Although the CG-56 guidelines are a frame-work for professionals, there is paucity of data of their implementation at the "coalface".

Data have shown morbidity and mortality increase out-of-hours – 79% of our head injury admissions attended out-of-hours.

The accurate recording of CNS observations is considered essential for good patient care, with hypothermia, hypoxia, abnormal pupillary reaction and decreased GCS predictors of poor outcome.[3] Our study demonstrates poor compliance with CG-56 guidelines. Possible causes includes staffing pressures in the ED.

Our series has shown problems with compliance of clinical observation in a busy DGH. However, in our centre the poor compliance did *not* adversely influence patient outcome (review of data by neurosurgeon [TF]).

An extra £15,000 per 100 head injuries was spent annually in a London hospital due to increased imaging.[4] Other studies have shown increasing use of CT in the ED aids decision-making and reduces admissions, offsetting the cost of imaging.[5]

The guidelines are useful but should be re-evaluated. We suggest rigid adherence to all the GCS variables may be difficult in a busy unit with different observers leading to inter-observer variation. Selection of patients who need less frequent observations may be the way forward.

Andrew Spence[1], Sean Finnegan[1], John Harty[1], Tom Flannery[2]

[1]Department of Medicine, Daisy Hill Hospital, Newry, Northern Ireland

[2]Department of Neurosurgery, Royal Victoria Hospital, Belfast, Northern Ireland

Correspondence to: Dr Andrew Spence

7 Downshire Crescent, Hillsborough, Northern Ireland, BT26 6DD

Email: andy.spence@gmail.com

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ERRATUM

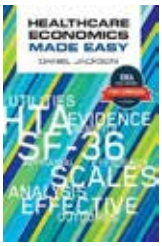
The editor has been informed that there is an error in the authorship of the following paper:

Evaluation of a Final Year Work-shadowing Attachment.
Peter Kavanagh, Mairead Boohan, Maurice Savage, David McCluskey, Pascal McKeown.
Ulster Med J 2012; 81(2): 83-88.

The first author should read: Peter McKavanagh. We apologise for any inconvenience caused.

Book Review

HEALTHCARE ECONOMICS MADE EASY BY DANIEL JACKSON.



ISBN: 1904842941 Scion Publishing, First Edition, 29th February 2012. RRP: £16.50

This is a clearly written and accessible introduction to health economics. With all the key concepts worked through in just over a 100 pages. In the preface, the author indicated that the book is designed for healthcare professionals and managers who need a basic understanding of the world of health economics. The book introduces the key concepts and definitions upon which health economics is based and upon which many of the decisions which effect clinical practice in Northern Ireland are made, explaining for example; cost effectiveness, health related quality of life and the much used quality adjusted life year or QALY.

This book should prove useful to all those responsible for planning and delivering health service. It is a quick read but also a useful reference for the desk. Tools such as health technology assessments, as used by NICE and the Scottish Medicine Consortium, are playing an increasing part in determining the treatment options available to our patients, yet we have very limited resource and expertise in health economics within Northern Ireland's healthcare system. For this reason I would commend this book as a means by which people working in our system can better understand both the impact of their own practice on our health economy and also appreciate the methods that are being adopted to determine clinical practice at a regional and super-regional level.

Dr Tony Stevens, Medical Director, Belfast Trust

Ulster Med J 2014;**83(3):**186-199

Abstracts

17th Meeting of the Irish Society of Human Genetics, Friday 5th September 2014.

Trinity Centre for Health Sciences, St James's Hospital, Dublin.

PROGRAMME:

10.00 – 10.55	Registration / Tea and Coffee.
10.55 – 11.00	Welcome.
11.00 – 12.15	Oral Presentations. Plenary I: clinical research.
12.15 – 13.15	**Keynote address:** *"Marfan syndrome and related disorders: from gene to therapy"* Prof. Bart Loeys, University of Ghent, Belgium.
13.15 – 14.15	Lunch (Provided) and Poster viewing.
14.00 – 14.15	Council Meeting
14.15 – 15.30	Oral presentations. Plenary II: Basic research.
15.30 – 16.00	Tea and coffee / Poster viewing.
16.00 – 16.15	ISHG AGM.
16.15 – 17.15	**Keynote address**: *"Clinical Genomics: Merging Human Genetics and Genomics"* Prof. James R. Lupski, Neurogenetics, Baylor College of Medicine, USA
17.15 – 18.00	Wine reception / Presentation of Prizes / Meeting close.

SPOKEN PAPERS:

S01. Malformation risks of antiepileptic drug monotherapies in pregnancy

PJ Morrison[1], E Campbell[1], F Kennedy[1], A Russell[1], WH Smithson[3], L Parsons[3], B Liggan[2], B Irwin[1], N Delanty[2], SJ Hunt[1], J Craig[1], J Morrow[1]

[1]Departments of Medical Genetics and Neurology, Belfast Health and Social Care Trust, Belfast, [2]Department of Neurology, Beaumont Hospital, Dublin, [3]AED Pregnancy register, UK and Ireland

Antiepileptic drug (AED) exposure during pregnancy increases the risk of major congenital malformations (MCMs). The risk magnitude varies by AED exposure. We provide results from the UK and Ireland Epilepsy and Pregnancy Registers, of the risk of MCMs after monotherapy exposure to valproate, carbamazepine and lamotrigine.

Fifteen-year prospective observational study (1996 – 2012). The main outcome measure is the MCM rate. Informative outcomes were available for 5206 cases. 1290 women were exposed to valproate monotherapy, 1718 to carbamazepine monotherapy and 2198 to lamotrigine monotherapy. The MCM risk with valproate monotherapy exposure in utero was 6.7% (95% CI 5.5% to 8.3%) compared with 2.6% with carbamazepine (95% CI 1.9% to 3.5%) and 2.3% with lamotrigine (95% CI 1.8% to 3.1%). A significant dose effect was seen with valproate (p=0.0006) and carbamazepine (p=0.03) exposed pregnancies. A non-significant trend towards higher MCM rate with increasing dose was found with lamotrigine. MCM rate for high-dose lamotrigine (>400 mg daily) was lower than the MCM rate for pregnancies exposed to <600 mg daily of valproate, but this was not significant (3.4% vs. 5.0%, p=0.31).

In-utero exposure to valproate carries a significantly higher MCM risk than lamotrigine (p=0.0001) and carbamazepine (p=0.0001) monotherapy. High-dose lamotrigine was associated with fewer MCMs than all doses of valproate. While lamotrigine has a favourable profile compared with valproate for adverse pregnancy outcomes, the requirements for seizure control should not be overlooked. These risks should help in the genetic counselling of mothers with epilepsy considering a pregnancy.

S02. Pre-Implantation Genetic Diagnosis (PGD) in Ireland – from validation to introduction of a clinical service

T Dineen[1], X Zhang[1], J Flanagan[1], A Kovacs[1], R Mihart[1], J O'Callaghan[1], J Culligan[1], N Daly[1], J Waterstone[1]

Fertility Centre, Fernhurst House, College Road, Cork

Pre-implantation Genetic Diagnosis PGD was first described in 1990. Until recently Irish couples opting for PGD had to travel abroad for treatment. With the first reported clinical pregnancy following embryo biopsy in an Irish fertility centre, pursuing IVF treatment with PGD in Ireland is now a reality. In 2012, the Irish Medicines Board (IMB) licensed two Irish fertility clinics to carry out embryo biopsy for PGD. To validate the PGD process, Cork Fertility Centre (CFC) biopsied non-viable oocytes and embryos and transferred the biopsied material to Reprogenetics, UK for genetic diagnosis. The gene amplification rate and the contamination rate were recorded to assess the biopsy and sampling procedures. Embryo integrity following biopsy, together with the proportion of biopsy cells remaining intact after removal were used to evaluate embryo biopsy skill. The results of all validation measures were evaluated according to internationally recognised guidelines. Having been licensed for embryo biopsy, the first clinical case of PGD at CFC involved a couple where the male was affected by Cystic Fibrosis (CF) and the female was a CF carrier. A number of Assisted Reproductive Technology (ART) techniques were involved for this couple, including testicular biopsy, IntraCytoplasmic Sperm Injection (ICSI), embryo biopsy and embryo vitrification. The couple are currently 33 weeks pregnant. Increasing awareness of genetic risk is inevitable and where Irish couples are burdened with difficult reproductive choices, the availability of PGD in Ireland is a welcome development.

S03. Cerebral Cavernous Malformations: four families illustrating phenotypic diversity with implications for counselling and management.

AC Magee[1], FJ Stewart[1], TA Dabir[1], M McConachie[2]

[1.]Genetic Medicine, A Floor, Belfast City Hospital BT9 7AB [2.] Molecular genetics, Ninewells hospital, Dundee, DD1 9SY

Cavernous cerebral malformations (CCMs) are characterised by abnormally large and leaky capillaries arranged in mulberry-like structures with no clear flow pattern, occurring in 0.5% of the population. CCMs can remain neurologically silent, or predispose to seizures, neurological deficits and haemorrhage. Three CCM loci have been identified; the phenotype includes cutaneous vascular malformations (CVM). We present 5 families: 4 with mutations in KRIT1 (CCM1 locus) and 1 in MGC4607 (CCM2 locus). Including the probands, 16 gene carriers were identified. All carriers had either CCM (13), CVM (12) or both (9). Four had only CCMs, and another 3 only CVMs. Seven are asymptomatic (age range 3y-71y). All 7 have CVMs, 4 have both CCMs and CVMs. Nine gene carriers are symptomatic. Five presented with cerebral haemorrhage (age 6m-66years, 2 with spinal symptoms (age 33 and 45), and 2 with seizures (age 2and 43). One obligate gene carrier, asymptomatic at age 71,declined investigation. This series supports previous reports suggesting that around 50% of gene carriers remain symptom free. It also illustrates an extremely wide range of age at onset and phenotypic expression. These findings raise many issues for families, in particular the genetic testing of children who may be at risk. Surgical intervention for asymptomatic CCMs is rarely indicated. There is no agreed screening protocol for carriers. However, future therapeutic strategies including antioxidant compounds, statins, and antiangiogenesis agents will provide families and individuals with possible therapeutic options.

S04. A retrospective review of Hereditary Paraganglioma/ Phaeochromocytoma referrals to the Northern Ireland Regional Genetics Service

A McCoubrey [1], VPM McConnell [2]

[1.] University of Glasgow, Glasgow, G12 8QQ [2.] Dept. of Genetics, Belfast City Hospital, Belfast Health and Social Care Trust

Hereditary Paraganglioma (PGL)/ Phaeochromocytoma (PCC) Syndrome (HPPS), an autosomal dominant inherited condition falls within the differential diagnosis for paragangliomas and phaeochromocytomas which are currently estimated to have a genetic predisposition in up to one third of cases. There is no universally agreed consensus for diagnostic investigation of these individuals which has been compounded with the advent of multi-gene testing panels. A retrospective review of clinical details including age, gender, tumour site(s), malignancy, family history, gene mutation frequencies and characteristics and referral source were obtained from chart reviews of referrals for HPPS. Patients with three cancer predisposition syndromes associated with the development of Paraganglioma/ Phaeochromocytoma – Von Hippel-Lindau, multiple endocrine neoplasia type 2 (MEN2) and neurofibromatosis type 1 (NF1) were excluded. Endocrinologists and vascular surgeons had the highest referral rates. The majority of patients presented with carotid body tumours or phaeochromocytomas with an age range of 8-81 years for first tumour diagnosis. 74 individuals from 20 pedigrees tested positive for a familial SDH gene mutation of which 30 had an SDHD mutation and 44 an SDHB mutation. Two possible founder SDH gene mutations and 12 tumours were identified on screening. The importance of identifying the genetic aetiology of PGL/PCC which facilitates identification of gene mutation carriers and appropriate genetic counselling and screening recommendations is supported by this review. Education of health professionals and the use of multi-gene testing panels may result in a higher mutation detection rate, more complete genetic counselling and improved understanding of clinical phenotypes of these predisposition syndromes.

S05. Identification of MLL4-GPS2 Fusion as an oncogenic driver of Undifferentiated Sarcoma in a Child

D Stack[1], E O'Meara[1], S Phelan[1], N McDonagh[1], L Kelly[1], R Sciot[2], M Debiec-Rychter[3], T Morris[4], D Cochrane[5], P Sorensen[6] & MJ O'Sullivan[1,7]

[1.] National Children's Research Centre, Crumlin. [2.]Dept. of Imaging and Pathology, KU. Leuven, Belgium. [3.]Dept. Of Genetics, KU. Leuven, Belgium. [4.]National Centre for Medical Genetics, Crumlin. [5.]Division of Neurosurgery, British Columbia's Children's Hospital, Canada. [6.]Dept. of Molecular Oncology, British Columbia's Children's Hospital, Canada. [7.]Dept. of Pathology, Our Lady's Children's Hospital, Crumlin.

Undifferentiated sarcoma is a poorly understood, therapy-resistant cancer, lacking both diagnostic and prognostic markers. Our index case was a spindle cell undifferentiated sarcoma, which arose as an intracranial, extra-axial mass in a 12-year old girl. Karyotypic analysis revealed a balanced, non-constitutional chromosomal translocation t(17;19)(p13;q13) as the sole aberration. By FISH analysis using increasingly proximate BAC pairs, followed by paired fosmid probes, we narrowed the chromosomal breakpoint regions to loci containing the MLL4 and GPS2 genes. With 3'RACE, RT-PCR and Sanger sequencing, we confirmed an in-frame fusion of MLL4 and GPS2 containing the first 2 and partial 3rd exons of MLL4 fused to GPS2 partial 5'UTR and entire coding sequence. MLL4 belongs to the MLL family, with MLL1 frequently rearranged in infant leukaemia. GPS2 is a potent suppressor of Ras-Mapk signalling. The fusion sequence and wild-type GPS2 were PCR-amplified and inserted into vectors phrGFPIIN and pcDNA3HA. These were then transiently and stably transfected into HEK293 and NIH3T3 cells, facilitating study of the cell biologic dysregulation resulting from expression of the transcript. Transient transfection of the MLL4-GPS2 fusion in HEK293 and NIH3T3 cells caused re-localisation of the fusion protein to the nucleus, whereas wild-type GPS2 is predominantly cytoplasmic. Importantly, stable transfection of the MLL4-GPS2 fusion produced significantly greater anchorage-independent growth compared to controls, as assessed by colony formation in soft agar assays. This study has identified a novel t(17;19)(p13;q13) translocation in undifferentiated sarcoma generating the fusion gene MLL4-GPS2, the expression of which promotes anchorage-independent growth, a classic in-vitro feature of malignant behaviour.

S06. Incidence of fragile X syndrome in Ireland an all-Ireland study

JJ O'Byrne[1], M Sweeney[1], D Donnelly[2], D Lambert[1,3], D Beattie[2], C Gervin[2], CA Graham[2], DE Barton[1], SA Lynch[1]

[1.] National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin, Dublin 12. [2.] Northern Ireland Regional Genetics Centre, Belfast Health and Social Care Trust /City Hospital, Belfast, Northern Ireland. [3.] The Children's University Hospital, Temple Street, Dublin 1.

Although Fragile X syndrome (FXS) is one of the most common causes of inherited developmental delay/intellectual disability with an estimated of 1:4000 males and 1:8000 females worldwide, the observed incidence in Ireland is unknown. Ireland has a unique situation with two health systems testing for FXS from the same population base which allows interesting comparisons to be drawn between incidences in the Republic of Ireland (ROI) and Northern Ireland (NI). To determine the observed incidence of FXS in the ROI and NI separately and combined. To compare these observed incidences to estimated worldwide incidences of FXS. A retrospective clinical and lab database review of positive fragile X

cases, born between years 2000-2009 inclusive, in both ROI and in NI was carried out.

Inclusion criteria: i) Birth place: ROI/NI, ii) Birth year: 2000-2009, iii) FXS confirmed on clinical examination iv) Full mutation allele (>200 CGG repeats) v) molecular test performed 2000-2014. Note: patients with intermediate or premutation alleles were excluded. The observed incidence of FXS in all Ireland is approximately 2.5 - 3 times less than the estimated worldwide incidence. Our study, along with other recent published studies, suggests that either the world wide incidence is over estimated or there is large frequency variability between different populations. As both ROI and NI cohorts had similar incidences we are confident that these figures are due to population incidence rather than poor ascertainment, inadequate testing or inappropriate referrals.

S07. Investigating polygenic contributions of common hippocampal variants to epilepsy predisposition

CD Whelan[1], DP Hibar[2], JL Stein[2], D Speed[3], The ILAE Consortium on Genetics of Complex Epilepsies, S Sisodiya[4], M Ohnson[5], D Goldstein[6], N Delanty[1,7], SE Medland[8], B Ranke[9], PM Thompson[2], G Cavalleri[1]

[1.]Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, [2.]Imaging Genetics Center, Keck School of Medicine, University of Southern California, [3.]UCL Genetics Institute, University College London, [4.]Institute of Neurology, University College London, [5.]Division of Brain Sciences, Imperial College London , [6.]Duke Centre for Human Genetic Variation, North Carolina, [7.]Division of Neurology, Beaumont Hospital, Dublin 9 , [8.]Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia, [9.]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Hippocampal sclerosis (HS) is a common feature of localisation-related epilepsies (LREs), present in 50-75% of all surgical resections in the disorder. However, the underlying cause of HS is debated. Animal models and post-mortem cell counts suggest that HS can result from recurrent epileptogenesis, but some MRI investigations have highlighted a familial component to HS and concomitant neuronal loss within hippocampal regions. Recently, the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium identified genome-wide significant signals correlating with hippocampal volume in a study of 29,037 individuals. We tested the hypothesis that variants predisposing en masse to changes in hippocampal volume may, in turn, contribute to epilepsy predisposition. To test this, we summarised variation across nominally-associated ENIGMA SNPs into quantitative 'risk' scores, weighted for local linkage disequilibrium and effect size, and related these scores to disease state in (i) a phenotypically mixed sample of epilepsy patients (n=2,502), (ii) four epilepsy 'subtypes', including LREs (n=1,801), lesional epilepsies (n=280), non lesional epilepsies (n=614) and idiopathic generalised epilepsies (IGEs; n=194) and (iii) an independent sample of healthy controls (n=5,191). Results did not reveal a significant association between disease state and risk score: observed scores only explained a small fraction (0-0.2%) of total variance in our risk model. Our findings suggest that being genetically predisposed to having smaller hippocampal volume may not be a risk factor for epilepsy. However, further analyses in additional epilepsy patients and healthy control cohorts are required to confirm or reject this position.

S08. Contribution of common polygenic variation captured by the Immunochip to coeliac disease heritability in an independent Irish population

C Coleman[1], EM Quinn[1], AW Ryan[1], RJL Anney[2], V Trimble[1], DW Morris[2], G Donohoe[2], J Conroy[3], G Trynka[4], C Wijmenga[5], S Ennis[3], R McManus[1]

[1]Department of Medicine, Institute of Molecular Medicine, Trinity College Dublin, St. James's Hospital, Dublin 8, Ireland, [2]Department of Psychiatry, Trinity College Dublin, Dublin, Ireland , [3]Conway Institute, University College Dublin, Ireland, [4]Genetics Department, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [5]Genetics Department, University Medical Center and University of Groningen, The Netherlands

Coeliac disease (CD) is a chronic immune-mediated disease with a prevalence of ~1% in European populations. Following the large Immunochip study of Trynka *et al* (2011) the HLA and 39 other CD susceptiblity loci are known. In an independent Irish CD case-control study we examined whether reported risk alleles were similar in direction of effect and whether a weighted burden of risk alleles (polygenic risk score) could be used to distinguish case status.

Following stringent quality control we analysed 143,074 markers genotyped on Immunochip in 425 cases and 453 controls. To examine concordance in the observed direction of effect in our sample, we performed a binomial sign-test for LD independent markers identified as genome-wide significant by Trynka *et al*. Secondly, for LD independent markers we calculated the polygenic risk score for each individual in our study. Regression was performed for disease status adjusting for marker-count-per-score (missingness), gender and population covariates. Binomial sign test indicated there was significant concordance in direction of effect between studies. 83% (122/147) of genome-wide significant SNPs show effect in the same direction (Pr (K>=122) = 7.9×10^{-17}). When restricted to non-HLA markers 10/11 (91%) show effect in the same direction (Pr (K>=10) = 0.0059). The polygene analysis showed that polygenic risk scores were significantly associated with coeliac case-control status across a range of p threshold values. Including the HLA markers up to 36% of the variance was explained by the polygenic score (SNPs P< 0.0001; P = 7.86×10^{-67}). We have replicated the findings of a large CD association study in an independent Irish population. Polygenic scores explained a significant proportion of the variance in coeliac disease confirming the contribution of common SNPs to CD susceptibility.

S09. AncestryMapper: Displaying and Calculating Genetic Distance Between and Within Populations At a Large Scale

ET O'Halloran, TR Magalhães, S Ennis

UCD Academic Centre on Rare Diseases, School of Medicine and Medical Science, University College Dublin

In recent years next generation sequencing has made it feasible to analyse individuals and populations genetic relatedness on a whole genome basis, advancing on the work previously done with Y chromosome and mitochondrial analysis. This has made it possible to trace ancestral human migrations and admixture events. It has also allowed for investigation into genetic diseases and predispositions specific or acute amongst specific populations. These methods are also useful for analysing internal population stratification of particular disease states. Traditional methods of illustrating this have relied on 2 dimensional methods. In the case of PCA and Admixture analysis, being context-sensitive to the input data. PCA analysis in particular is undermined by the limitations of plotting only two or sometimes three components at once. Ancestry Mapper provides a suite of software to plot multiple principal components at once, as well as display Admixture results in a more accurate and graded manner. It also can calculate genetic distance directly between populations that gives each individual an index related to a set of comparison populations. Our method produces numbers that are biological meaningful and easy to interpret. Ancestry Mapper also displays Admixture results in a more accurate and graded manner. Our initial dataset used the HGDP and HapMap data as a reference comprising 56 populations. We have now expanded

our method to over 170 human populations which provides better coverage and detail. Here we present the method applied to several admixed populations and demonstrated that the results concur with previous investigations and anthropological assumptions.

S10. The Genetic Ancestry of the Sherpa

A Cole[1],S Cox[2], C Jeong[3], D Witonsky[3], P Robbins[4],H Montgomery[2], M Ota[5],M Hanaoka[6], Y Droma[6], CM Beall[7], A Di Rienzo[3], G Cavalleri[1]

[1.]Department of Molecular and Cellular Therapeutics, The Royal College of Surgeons in Ireland. [2.]Institute for Human Health and Performance, University College London. [3.]Department of Human Genetics, University of Chicago. [4.]Department of Physiology, Anatomy and Genetics, University of Oxford. [5.]Department of Legal Medicine, Shinshu University School of Medicine, Matsumoto, Japan, [6.]First Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan.[7.]Anthropology Department, Case Western Reserve University, Cleveland, Ohio.

The Sherpa are an indigenous ethnic group of the Himalayas that display a remarkable ability to function at high altitude. It is thought that the Sherpa have migrated from Eastern Tibet to the Solu-Khumbu region of Nepal approximately 500 years ago.

We set out to shed further light on the history of the Sherpa and other indigenous high altitude populations through genetics. We aim to determine the genetic ancestry of the Nepalese-Sherpa in the context of their neighbouring populations that represent the ancestral genepool of indigenous Himalayan populations. We had access to Genome-wide genotyping data on 189 samples of Tibetan and Nepalese-Sherpa ancestry. We complemented this dataset with further additional data from the HGDP for Pakistan and Chinese populations, and the 1000 Genomes for Indian populations. We are performing a number of analytical tests to quantify and visualise population structure including Fst and Principal Component Analysis (PCA) as well as maximum likelihood tests of individual ancestries (using ADMIXTURE). PCA identified population substructure between two Sherpa villages in Nepal, namely Khumjung and Thame. Using ADMIXTURE we identified the ancestral 'high altitude component in the Nepalese-Sherpa, this was also present in Tibetans, believed to be admixed descendants of the Sherpa. Information about the nature and distribution of genetic variation in indigenous populations of the Himalayas can illustrate gene flow that might account for adaptive genetic and physiological traits of high altitude natives.

S11. In the era of the exome, how deep should we dig?

J Casey[1,2], P McGettigan[2,3], E Crushell[4], J Hughes[4], S Ennis[2,5], SA Lynch[1,2,5]

[1.] Dept. of Genetics, Temple Street Children's University Hospital, [2.]Academic Centre on Rare Diseases, School of Biomolecular and Biomedical Science, University College Dublin, [3.]University College Dublin, [4.]National Centre for Inherited Metabolic Diseases, Temple Street Children's University Hospital, [5.]National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin.

Our research aims to identify the genetic cause of recessive disorders in the consanguineous Irish Traveller population using exome sequencing. Through our studies, we have encountered two important issues with implications for both researchers and clinicians; (a) clinical variability and (b) incidental findings. We have noted inter- and intra-familial variability in patients with the same disease mutation. This may be due to simple clinical heterogeneity whereby the same mutation can give rise to slightly different phenotypes. However, in consanguineous families, there is the possibility of more than one recessive disorder, distorting the phenotype. When faced with phenotypic variability, we found it useful to analyse each patient exome individually and have identified patients with up to three recessive disorders using this approach. But how extensively do we need to analyse genomic data in search of a potential secondary disorder?

Recent studies have reported a rate of incidental findings of 1-5% when the entire exome is analysed. The risk of incidental findings is minimised in our studies by limiting the search for causative variants to linkage regions identified in a mapping study. However, despite this approach, we have made incidental findings in two families. In family A, we identified a previously reported homozygous variant causative of glycogen storage disease type 5. In family B, we identified a novel homozygous variant in a gene associated with catecholaminergic polymorphic ventricular tachycardia. Does the benefit of these incidental findings outweigh any potential harm? Our findings support the need for specific thought processes and customised population-tailored approaches to exome sequencing in families from consanguineous populations.

S12. Methylation in Chronic Kidney Disease and its association with microRNAs: Analysis via Microarray, Sanger and Next Generation Sequencing

LJ Smyth[1], JK Kilner[1], KA Benson[1], AP Maxwell[1,2], AJ McKnight[1]

[1.]Nephrology, Centre for Public Health, Queen's University of Belfast, United Kingdom. [2.]Regional Nephrology Unit, Belfast City Hospital, United Kingdom

This study was designed to identify differential methylation affecting microRNAs (miRNAs) in patients with chronic kidney disease (CKD). Comparative analyses between traditional Sanger and next generation sequencing techniques were then conducted. DNA samples from 255 patients with CKD (cases) were compared to 152 individuals without renal disease (controls) for differences in quantitative DNA methylation levels. Following stringent quality control procedures and correction for multiple testing, data was analysed from the HumanMethylation450K BeadChip array (Illumina) which assessed 485,577 sites. Extracting miRNA genes revealed 2,249 methylation sites within miRNAs, and five miRNAs associated with CKD (MIR940, MIR34A, MIR429, MIR141, and MIR329-2) were prioritised for follow-up.These results were supportedby replication analysis of an independent cohort of CKD cases and controls (n=400) using the 450K platform. Bidirectional Sanger sequencing was completed using carefully designed fragments for both genomic and bisulphite treated DNA flanking each miRNA. This approach determined 36 methylated CpG sites and 13 known SNPs, in the 23 cases and 23 controls analysed, but did not provide validation of methylation levels. Next generation sequencing, using the Ion Chef, OneTouch2, and Torrent® Personal Genome Machine™ (Life Technologies®) was employed for fine-mapping of SNPs and methylated sites in the target region, providing qualitative validation of 450K results. Forty-six individuals with both blood-derived and cell-line derived DNA were resequenced for approximately 500bp surrounding each miRNA. We have developed an effective technical protocol for validation and replication of EWAS studies, additionally confirming blood and cell-line may be useful sources of derived DNA for epigenetic studies.

POSTER PRESENTATIONS

P01. Neurofibromatosis type 2 – Review of patients in Northern Ireland & Patient Satisfaction with Multidisciplinary Clinic

DE Donnelly, L Jeffers, PJ Morrison, S Hampton, N Baillie, S Cooke.

Belfast Health & Social Care Trust

There are 18 families with Neurofibromatosis type 2 currently

being followed up in Northern Ireland. These patients attend a variety of specialists including Genetics, ENT, Neurosurgery, and hearing support workers, but have not always attended well. We have found that 40% of our patients have mental health issues, including depression, anxiety and anorexia, which has negatively impacted on their medical care. In order to address this we began a multidisciplinary team clinic in Sept 2012. We have recently completed an audit of patient satisfaction with this clinic and now present the results.

P02. An infant with a novel Kir6.2 mutation causing neonatal diabetes and unexplained lack of response to sulphonylurea

SM O'Connell[1], A McDonald [1], N O'Toole[1], A Bradfield[1], M Bradley[1], A Hattersley[2], S Ellard[2], P Proks[3], KK Mattis[3], F Ashcroft[3], SMP O'Riordan[1]

[1.]Department of Paediatrics and Child Health, Cork University Hospital, Ireland. [2.]Royal Devon and Exeter Foundation Trust, UK, [3.]Department of Physiology Anatomy & Genetics Parks Road, Oxford, UK

Neonatal diabetes (NDM) is defined as diabetes developing before 6 months of age, affecting 1 in 100,000 live births. Permanent NDM is diagnosed in the first six months of life with no remission. The majority have a mutation in the ATP-sensitive potassium (K_{ATP}) channel, the majority of whom respond to sulphonylureas. We describe the response to sulphonylurea in an infant with NDM, heterozygous for a novel Kir6.2 subunit KCNJ11 missense de novo mutation (W68G). A female born at 37 weeks by Caesarean section for intrauterine growth retardation (birth weight 1.95kg <0.4th centile) was hyperglycaemic from day one of life. Initially stabilised with intravenous insulin she was treated with subcutaneous basal insulin with erratic glucose control. Glibenclamide was commenced slowly (0.05mg/kg/day) from day 20 of life up to a maximum dose of 1mg/kg/day over two months according to the Exeter transfer protocol. At age 2 months insulin pump therapy was commenced resulting in tighter glycaemic control and weight gain. Transfer off insulin was unsuccessful. In vitro testing of the mutant channels indicates she should respond to glibenclamide. Low levels of glibenclamide on pharmacokinetic studies suggest this patient may be excreting more rapidly than normal. This infant with a novel Kir6.2 mutation failed to respond to glibenclamide despite a sustained period on a recognised effective dose and clear in vitro response. As an unusually rapid rate of sulphonylurea metabolism is suggested by ongoing pharmacokinetic studies, a higher dose of glibenclamide has been commenced.

P03. The population incidence of childhood Gonadoblastoma over fifteen years in the Republic of Ireland

SM O'Connell[1], SA Lynch[2], D Coyle[3], M McDermott[4], M O'Sullivan[4,6], E Roche[5], F Quinn[3], D Cody[7]

[1.]Department of Paediatrics and Child Health, Cork University Hospital, [2.]National Centre for Medical Genetics, [3.]Departments of Paediatric Surgery and [4.]Histopathology, Our Lady's Hospital Crumlin, Dublin, [5.]The National Children's Hospital, Tallaght, Dublin, [6.]University of Dublin, Trinity College, Dublin, [7.]Department of Paediatric Endocrinology, Our Lady's Hospital Crumlin, Dublin

Gonadoblastoma is a rare tumour of the gonads presenting in childhood or adolescence. It is associated with disorders of sex development (DSD), most commonly Turner mosaic syndrome with Y chromosome material (TMSY), and 46XY gonadal dysgenesis (GD). Little is known about the incidence of this rare tumour. A retrospective review of children and adolescents with a diagnosis of gonadoblastoma presenting before age 16 years in the Irish Republic (RoI) from 1999-2013 inclusive was undertaken using the records of the National Cancer Registry Ireland (NCRI) and the Departments of Endocrinology, Pathology and Surgery at the main children's hospitals. Clinical notes and histopathological findings were reviewed. Eight cases of gonadoblastoma were identified over the period. All were phenotypically female. Five cases had TMSY (age range gonadoblastoma diagnosis 6 months – 14 years), bilateral in two cases. Three cases of 46 XY GD were aged 4 months, 8 and 9 years at diagnosis of gonadoblastoma (unilateral). In one case of 46 XY GD with SRY deletion, clinical symptoms (age 8) prompted gonadectomy. Histology showed unilateral dysgerminoma and contralateral gonadoblastoma. In all other cases gonadoblastoma was diagnosed on elective gonadectomy. The incidence of gonadoblastoma in RoI over the past 15 years is 8, giving a population incidence of 0.08 per 10,000 births. To our knowledge this is the first population incidence rate of GB in children reported. Due to the low age of gonadoblastoma cases observed in this cases series, the recommendation for elective gonadectomy in high risk conditions is supported.

P04. Early Occurrence of Gonadoblastoma found at Elective Gonadectomy in Turner Syndrome mosaic for Y Chromosome

JM MacMahon[1], R Morrissey[1], M McDermott[2], MO'Sullivan[2], F Quinn[3], A Green[4], SA Lynch[4], SM O'Connell[1]

[1.]Department of Paediatrics and Child Health, Cork University Hospital, [2.]Departments of Histopathology and [3.]Paediatric Surgery, Our Lady's Hospital Crumlin, Dublin. [4.]National Centre for Medical Genetics, Our Lady's Hospital Crumlin, Dublin.

Turner Syndrome (TS)is a common genetic disorder and occurs in phenotypic females who are missing all or part of one sex chromosome. The most common mosaic forms are 45X/46XXand 45X/46Xiq, however mosaicism for cells containing Y chromosome material (TSMY) is well documented. This is associated with increased risk of gonadoblastoma (GB) and elective gonadectomy is recommended following diagnosis. A review of TS patients attending the Paediatric Endocrinology clinic (n=9) identified three cases with TSMY. All underwent elective gonadectomy. Case 1 was diagnosed at 2 years. Peripheral blood karyotype showed mosaicism for 45X (25 cells) and an isodicentric Y chromosome made of Yp and proximal Yq material (25 cells). Gonadectomy at 6 years revealed extensive unilateral GB. Interphase FISH of the tissue showed isodicentric Y chromosome in 43% of GB cells. Case 2 presented with dysmorphic features at birth. G banded karyotype and interphase FISH of blood showed 45X in 95% and 47XY+18 (Edwards syndrome) in 5% of cells analysed. Interphase FISH of buccal cells showed 45X only. Gonadectomy at 13 months revealed bilateral GB, interphase FISH was similar to blood: 45X(86%), 47XY,+18(14%). Case 3 presented with severe neonatal aortic stenosis. Peripheral blood karyotype showed 45X (29 cells) and a pseudoisocentric Y chromosome with breakpoint at Yq11.23 (6 cells), confirmed on buccal and skin karyotyping. Gonadectomy revealed unilateral GB, karyotype pending. This case series highlights early age of occurrence of GB despite low mosaicism for SRY cell lines and supports a recommendation for early surgery in such cases.

P05. A Child with Clinical and Cytogenetic Features of Male Edwards Syndrome and Turner Syndrome with Bilateral Gonadoblastoma in Infancy

JM MacMahon[1], R Morrissey[1], M McDermott[2], F Quinn[3], A Green[4], SM O'Connell[1]

[1.]Dept of Paediatrics and Child Health, Cork University Hospital. [2.]Depts of Histopathology and [3.]Paediatric Surgery, Our Lady's Hospital Crumlin, Dublin. [4.]National Centre for Medical Genetics, Our Lady's Hospital Crumlin, Dublin.

Mosaic Turner Syndrome (TSM) commonly occurs in the form of 45X/46XX and 45X/46Xiq, although mosaicism including the presence of a Y chromosome is well documented. It is associated

with increased risk of gonadoblastoma (GB). To date, there are only 6 reported cases of TSM with a trisomy 18 karyotype (Edwards Syndrome), of which only 2 were phenotypically female with 45X, 47XY+18 karyotype. We present the case of an infant born with dysmorphic features (webbed neck, low set ears and broad chest). G banded karyotype and interphase FISH of blood showed 45X in 95% and 47XY+18 in 5% of cells analysed. However, interphase FISH of buccal cells showed only 45X. Antenatal ultrasound at 13 weeks gestation showed increased nuchal fluid, suggestive of Edwards Syndrome, but had resolved on follow-up scan at 15 weeks. Due to presence of SRY, an elective gonadectomy was performed at 13 months, which showed bilateral streak ovaries with early evidence of GB bilaterally, rudimentary uterus and bilateral fallopian tubes with unilateral ectopic adrenal tissue. Interphase FISH of the gonadal tissue was similar to the blood findings with 45X in 86% of cells and 47XY+18 in 14% of cells analysed. This case highlights a rare karyotype of TSM and Edwards Syndrome in the same patient. Current investigations are ongoing into the possible causes for this unusual finding. This case was also associated with a finding of bilateral gonadoblastoma. To the authors' knowledge this is the only reported case with the above karyotype and finding of gonadoblastoma.

P06. One SHOX after another: Two interesting patients with vice versa derivative X chromosomes identified by array comparative genomic hybridisation (aCGH)

AR Thompson[1], A Kulkarni[1], KJ Marks[1], K Snape[2], R Taylor[1], L Bradley[2]

[1]SW Thames Regional Genetics Laboratory. [2]SW Thames Regional Clinical Genetics Service, St George's NHS Healthcare Trust, London Oratory.

Two independent patients with derivative X chromosomes were identified using aCGH. Case 1: A 16 year old female was referred with suspected Marfan syndrome due to a history of tall stature, mild scoliosis and hyperflexibility. Development and intellectual ability were normal. She had a past history of anxiety and shyness and was noted to have very long legs. Karyotype was requested for suspected Triple X syndrome. However, G-banded analysis identified additional material of unknown origin on the long arm of one X chromosome in all cells. Further investigation by FISH and aCGH identified this derivative X chromosome to be der(X)(pter→q28::p22.12→pter), confirming this patient has functional trisomy of PAR1 (pseudoautosomal region), including SHOX, and functional monosomy of PAR2. Parental studies suggested that this rearrangement arose de novo. Case 2: A 32 year old male referred with primary infertility, short stature and mild to moderate learning disabilities. The proband's brother has epilepsy and severe learning disabilities. Both the proband's brother and mother are of short stature. Array CGH and FISH investigations identified an X chromosome rearrangement: der(X)(qter→p22.33::q28→qter), confirming this patient has functional monosomy of PAR1, including SHOX, and functional trisomy of PAR2. Inheritance studies identified this derivative X chromosome in both the proband's mother and brother

Genetic mechanisms for these two cases with conversely rearranged X chromosomes are suggested and genotypic and phenotypic features are explored.

P07. Watch out – mosaicism about! - Prenatal diagnosis of mosaic partial duplication of 3q

S Ramachandrappa, A Kulkarni, CF Pinto, L Bradley

South West Thames Regional Genetics Service, St George's Hospital, London

Array-Comparative Genomic Hybridisation (a-CGH) is becoming the first line investigation for prenatal samples where an underlying genetic pathology is suspected. Here we describe an instructive case where older techniques would have missed an important genetic abnormality. A genetic opinion was sought on a 14 week old female infant admitted with apnoeic episodes secondary to gastroesophageal reflux. She was the second child of non-consanguineous parents. She had previously presented elsewhere for routine second trimester anomaly scan and was found to be small for gestational age with short (<3rd centile) long bones. Third trimester scanning found bilateral renal hydronephrosis and an oedematous extra postaxial left digit. She was born at 38 weeks in good condition.

On examination at 14 weeks, length and weight were <0.4th centile and head circumference was between the 0.4th – 2nd centile. Dysmorphic features included prominent forehead, hypertelorism, long bushy eyebrows, a broad nasal bridge, long fingers with bilateral clinodactyly and short limbs. Comparison with reported cases is presented. An aCGH performed on amniotic fluid indicated mosaicism for partial duplication of the long arm of chromosome 3q (93,630,075-197,766,791) which was confirmed by MLPA analysis. Karyotype analysis of cultured cells from the same sample did not detect any abnormalities. Notably, aCGH on a postnatal blood sample did not reveal any areas of copy number variation. This case illustrates the superiority of new molecular cytogenetic technologies being applied to prenatal diagnosis over more traditional approaches, particularly with reference to the diagnosis of mosaicism.

P08. BRCA1/2 testing in individuals who do not meet the Manchester Score

L Jeffers, T Dabir, P Logan

Northern Ireland Regional Genetics Service, Belfast City Hospital

With demand for BRCA tests increasing genetic departments need to ensure testing is offered to appropriate patients to avoid blockages and delays in their systems. While a significant family history of breast and/or ovarian cancer and certain pathologies may warrant BRCA testing there are other risk factors for genetic cancers that lead to referrals and requests for testing. We carried out an audit to ascertain prevalence of pathological BRCA1/2 mutations in particular groups of affected individuals without significant family history of relevant cancers. An audit of three groups of patients who do not meet the Manchester score (>10/10 or combined score >15) was carried out; 1. Women diagnosed with breast cancer under the age of 40 years without a family history, 2. Women with bilateral breast cancer without a family history, 3. male breast cancer without a family history. 294 chart searches yielded 10 individuals who met audit criteria: 4 women diagnosed under age of 40 years, 2 women diagnosed with bilateral breast cancer, 4 male breast cancers. No pathogenic mutations were identified in BRCA1/2 in any of the 3 groups. Prevalence of pathogenic mutations is too low in specific groups not meeting Manchester score to offer high cost testing on NHS. Although our numbers are small, Manchester score of >10/10 or combined score >15 seems to be a good criterion to offer BRCA testing to breast cancer families for better yield and resources utilization.

P09. TP53 mutation analysis in breast cancer: What is the evidence?

S.Liew[1], T Dabir[2]

[1]. Queen's University, Belfast [2]. Medical Genetics Department, Belfast City Hospital.

Hereditary breast cancers account for around 5-10% cases and are predominantly due to BRCA1/2 genes and less commonly due to other high penetrant (TP53, STK11,PTEN) and less penetrant

(CHEK2, ATM, PALB2, BRIP1) genes, Premenopausal breast cancer is part of Li-Fraumeni syndrome (LFS) related cancer spectrum. TP53 mutation is found in 0-8% young breast cancers (<30 years) without family history of LFS while BRCA1/2 mutations are found in 8-12% unselected young breast cancer cases. Unlike TP53 gene testing BRCA1/2 mutation analysis is not routinely offered in young breast cancer cases alone unless the testing criterion is met (Manchester score, triple negative receptor status etc.) at our centre. We analysed our data of past six years (2008-2013) of TP53 gene testing in women with breast cancer. Information was obtained regarding family history of cancers, age of onset, receptor pathology and BRCA1/2 testing. No TP53 mutation was found in our young breast cancer alone cohort (0%). The solitary mutation was found in a woman with family history suggestive of LFS (10 %). TP53 gene mutation detection in breast cancer is likely to be better when supported by family history of LFS tumours and should be considered along with receptor pathology for better resources utilization. Our observation is similar to previously published studies and support revised Chompret criteria for better TP53 mutation detection rate. NGS panel testing for breast cancer genes would be cost effective and useful for understanding the genetic epidemiology of breast cancer genes.

P10. Epidemiology, clinical features and genetics of Multiple Endocrine Neoplasia type 2B (MEN 2B) in a complete population

A Znaczko[1], DE Donnelly[1], PJ Morrison[1,2]

[1]Department of Genetic medicine[1], Belfast HSC Trust, Lisburn Road, Belfast. BT9 7AB. UK [2]Centre for Cancer Research and Cell Biology, Queens University of Belfast, 97 Lisburn Road, Belfast BT9 7AE

Multiple endocrine neoplasia (MEN2B) or the mucosal neuroma syndrome is an autosomal dominant hamartoneoplastic syndrome. Features include multiple mucosal neuromas, phaeochromocytoma, medullary thyroid carcinoma, and Marfanoid body habitus. MEN2B is thought to be relatively rare, but the prevalence has not previously been reported.

Objective: To assess the prevalence of MEN2B in a complete population, and delineate the clinical features. Methods: Prospective study of all cases of MEN2B since 1988. Results: The prevalence of MEN2B ranges from 0.178 – 0.219x10^{-5}. Conclusions: The minimum prevalence of MEN 2B in a complete population (Northern Ireland) is low. MEN2B is a rare disorder.

P11. Array CGH demonstrates multiple loss events in a de novo t(2;7) translocation in child with craniosynostosis

H. Ryan

National Centre for Medical Genetics, Crumlin, Dublin

Chromosomal abnormalities are a frequently underlying reason for congenital malformations. We report a child that presented with craniosynostosis, bilateral epicanthic folds and small fingers and toes. A karyotype was performed on an amniocentesis that had indicated an apparently balanced de novo t(2;7)(q32.1;p15.3) translocation. At 9 months of age peripheral blood from the child was referred for array CGH analysis with the question of whether there were any imbalances associated with the translocation. Array CGH demonstrated multiple loss events around the apparent breakpoints in the form of a 2.3Mb loss within 2q32.1, and separate 493kb and 280kb losses within 7p21.3. These small loss events would also explain the interpretation discrepancy between the indicated 7p breakpoint by G-band that indicated by array. Investigations of online databases demonstrated a previous case report in a child with craniosynostosis and with a de novo translocation involving 7p21.3, potentially suggesting that the chromosome 7 events are related to this aspect of the proband's phenotype. To date there is no defined phenotypic association with the 2q32.1 region of loss. This case illustrates a number of aspects; the importance of array analysis in instances of an individual with an apparently balanced translocation but with phenotypic abnormalities, and the challenges faced in determining the consequence of rare chromosomal abnormalities that are not directly associated with a well-defined syndrome.

P12. Implementation of a Hereditary Breast/Ovarian Cancer Predictive Testing Service

T McDevitt[1], M Higgins[1],A Crowley[1],M Rogers[1], DE Barton[1]

National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin, Dublin 12

We describe the introduction of a new service for the predictive testing of hereditary breast/ovarian cancer genes: BRCA1 and BRCA2. When a BRCA 1 or BRCA2 mutation is identified in family, following mutation screening of both genes in an individual with breast/ovarian cancer and a family history of the same; predictive testing can then be offered to unaffected members of the family. Prior to implementation in September 2012, predictive testing for a known familial BRCA1 or BRCA2 pathogenic mutation had only been available to family members via an external laboratory in the UK. Approximately 90-95% of pathogenic mutations in BRCA1 and BRCA2 are detectable by Sanger sequencing analysis; therefore this was the method of choice for the new predictive service, together with Mutation Surveyor (SoftGenetics®) data analysis. For the verification, we re-analysed 86 samples that had been previously tested and reported by an independent external laboratory over a 6 month period. Following this analysis, we were able to show concordance with previous results and to obtain data on sensitivity and specificity. In addition, we describe the systems employed to ensure an efficient workflow system and the policies and procedures devised to minimise the risk of a false normal result. Following subsequent implementation in 2012, a hereditary breast/ovarian cancer predictive testing service is now available through family cancer clinics for those individuals at risk of inheriting a BRCA1 or BRCA2 mutation.

P13. Parental gonadal mosaicism for a BRAF mutation in Cardiofaciocutaneous syndrome

S Geoghegan[1], R Morrissey[1], J Shorto[2], S Ramsden[2],MP O'Riordan[1], A Green[3], SM O'Connell[1]

[1.]Department of paediatric and Child health, Cork University Hospital. [2.]Genetic medicine, St Mary's Hospital, Manchester. [3.]National centre for medical genetics, Our Lady's Hospital Crumlin.

Cardiofaciocutaneous syndrome (CFCS) is a rare autosomal dominant (AD) condition characterized by cardiac abnormalities, a distinctive craniofacial appearance and short stature. CFCS is part of the RASopathy group including Noonan, LEOPARD and Costello syndromes. The four associated genes are BRAF (~75%), MAP2K1 and MAP2K2 (~25%), and KRAS (<2%). Most individuals represent new sporadic mutations. Two brothers presented for paediatric management of failure to thrive (FTT) and developmental delay. The parents are healthy, unrelated with one unaffected daughter. The first boy was born at term with a normal birth weight (50th centile). There was polyhydramnios, intrauterine growth restriction and right sided hydronephrosis noted on antenatal scans. The neonatal period was complicated by FTT and gastro-oesophageal reflux disease. A phenotype suggestive of Noonan syndrome with short stature, pulmonary stenosis, global developmental delay, and sensorineural hearing loss became apparent. His brother was born at term with a normal birth weight (50th centile). He has a similar phenotype. Mutation analysis of the PTPN11, MEK1 and MEK2 genes were normal. Mutation analysis of the BRAF gene showed heterozygosity for a pathogenic mutation

in BRAF c.770A>G (p.Gln257Arg) in both brothers. Neither healthy parent had the BRAF mutation in their blood DNA. The likely explanation for these findings is that one or other parent has mosaicism for the BRAF mutation at least in their gonadal tissue. There could be up to a 50% chance of the parents having another child affected by CFC. We describe the first reported family with cardiofaciocutaneous syndrome due to gonadal mosaicism for a pathogenic BRAF mutation

P14. Increasing testicular size due to bilateral Large Cell Calcifying Sertoli Cell tumours (LCCSTs) in a peri-pubertal child with Carney Complex.

S Geoghegan[1], R Morrissey[1], M Moore[2], M O'Sullivan[3], M Murphy[4], A Irvine[5], F Quinn[6], SM O'Connell[1]

[1.]Department of Paediatrics and Child Health, and [2.]Department of Radiology, Cork University Hospital, [3.]Department of Histopathology, Our Lady's Hospital Crumlin, Dublin, [4.]Department of Dermatology, South Infirmary Victoria University Hospital, Cork, [5.]Departments of Paediatric Dermatology, and [6.]Paediatric Surgery, Our Lady's Hospital Crumlin, Dublin, Ireland.

Carney Complex (CNC) is a rare multi endocrine neoplasia syndrome associated with endocrine and non-endocrine tumours. Three types of testicular tumour have been described; Large cell calcifying Sertoli Tumours (LCCST), Leydig cell tumours and testicular tumours of adrenal origin. LCCST is a rare benign stromal tumour, which has been observed in 41% of males affected with Carney Complex, It is generally benign although malignant transformation has been described. In pre-pubertal patients conservative management is preferred, with anti sex steroid therapy as needed, to manage secondary sexual characteristics. LCCST can cause replacement obstruction of seminiferous tubules leading to reduce fertility. CNC patients have morphologically reduced sperm and abnormal sperm number. An 11 year old boy diagnosed with Carney complex one year previously with multiple lentigines and blue naevi was referred for endocrine management. He was heterozygous for a known nonsense mutation of the PPKAR1A gene (p.R42). Height was < 2nd centile. Bone age was normal. Testicular volume was 4mls bilaterally. Six months later testicular volume had increased and appeared bulky. Height velocity was 5.6cm/yr (+0.8 SDS). Biochemical work up was consistent with a pre-pubertal boy. Ultrasound showed bilateral multiple small echogenic foci, not typical for microlithiasis, irregularly spread throughout testes. Histology confirmed LCCSTs. Assessment of boys with CNC in the peri-pubertal age group can be complex. The clinical evaluation of growth and puberty must be balanced with known complications of this multi-system condition, with a high index of suspicion for the associated endocrine features.

P15. Hyperferritinaemia with or without cataract

FJ Stewart

Northern Ireland Regional Genetics Service, Belfast City Hospital

Hyperferritinaemia Cataract syndrome is an autosomal dominant condition characterised by high serum ferritin and an increased risk of early cataract formation. There is no iron overload and the transferrin saturation is normal which distinguishes it from haemochromatosis type I and IV. It is caused by mutations in the L-ferritin gene (FTL). It is generally regarded as being extremely rare as opposed to haemochromatosis which is very common in the Irish population.

In the last 2 years we have tested 11 individuals for this condition. They appear to come from 4 families. 8 were mutation positive. The other 3 were predictive tests in at risk relatives .All have had the same c.-167C>T mutation. The age of onset of cataracts is very variable within families ranging from early childhood to old age and is not inevitable.

The raised ferritin appears only to cause cataracts in sharp contrast with haemochromatosis which can involve the major organs. One patient had been mistakenly diagnosed with haemochromatosis and had serial venepunctures leading to a haemoglobin of 4 g/dl. The diagnosis should be considered in all cases of raised ferritin with normal transferrin saturation or early onset of cataracts +/- a family history.

P16. Study of an extended 4 generation family with A143T Fabry mutation. Presentation of variable phenotypes including very mildly affected individuals

Anna Znaczko, A Wilson, F Stewart

Clinical Genetics, Northern Ireland Regional Genetic Services, Belfast City Hospital, Belfast Health Social Care Trust

Fabry disease results from deficient activity of the enzyme α-galactosidase (α-Gal A) and progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body. The classic form, occurring in males with less than 1% α-Gal A enzyme activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias), the appearance of vascular cutaneous lesions (angiokeratomas), sweating abnormalities (anhydrosis, hypohydosis, and rarely hyperhidrosis), characteristic corneal and lenticular opacities, and proteinuria.

Variant phenotypes with later onset presentation have now been recognised and are caused by mutation with some residual enzyme activity. One such mutation is Alanine to Threonine substitution at position 143 (A143T). The disease causing potential of the A143T mutation is currently debated. Studies linking the mutation to phenotypic presentation have varied conclusions. Some reports conclude that the A143T is non-pathogenic mutation, while others conclude it is a late onset variant taking primate manifestation in cardiac, renal or central nervous system without associated classic manifestations. Studies of 9 individuals with confirmed A143T mutation. We compared their phenotypes and researched their enzyme levels with regards to the typical clinical features. In this family, the A143T mutation is proven to be pathogenic, but majority of the affected individuals appear to be remarkably asymptomatic with only on relative requiring enzyme replacement therapy (ERT). We will continue regular and thorough follow-up and review the need for ERT in the affected individuals.

P17. Familial Hypercholesterolaemia cascade screening service in Northern Ireland

MH Cather[1], IS Young[2],DP Nicholls[2],M O'Kane[3], P Sharpe[4], E Hanna[5], PJ Hart[1], CA Graham[1]

[1.]Regional Genetics Laboratories, Belfast City Hospital, Belfast. [2.]Belfast HSC Trust Lipid Clinic, Royal Victoria Hospital, Belfast. [3.]Western HSC Trust Lipid Clinic, Altnagelvin Hospital, Londonderry. [4.]Southern HSC Trust Lipid Clinic, Craigavon Hospital, Portadown. [5.]Northern HSC Trust Lipid Clinic, Antrim Hospital, Antrim

Genetic diagnostic testing for familial hypercholesterolaemia (FH) has been available at the Belfast Trust Regional Genetics Laboratory since 1989.As NI has a population of 1.8m, and FH has a prevalence of 1 in 500, it is estimated that there are 3,680 people with the condition. Over 26% of the expected total has been identified. The Health Commissioning Board has set year-on-year targets increasing to 40% by March 2016. Currently there are 222 identified index FH patients, of these 171 families have had cascade screening, an average of eight relatives per family have been counselled and tested. Of the 1366 relatives screened 53% have the family mutation and are confirmed with FH. This demonstrates that a further 4.2 affected FH patients are identified per family from

the index case. The appointment of the first FH specialist nurse in Northern Ireland (NI) was in 2009, to commence cascade screening in index patients attending the Belfast Trust lipid clinic. This service was extended in 2013 to enable each Trust to have an FH Nurse and a Lead FH Nurse was appointed to co-ordinate the team. The FH Nurses have completed training and are now based in their own Trust arranging to see FH patients at Lipid Clinics, drawing family pedigrees and identifying relatives who could be contacted to offer genetic testing for the known family DNA mutation and cholesterol. We hope to establish a regional FH database within the next year.

P18. 17p13.2p13.1 microduplication – two new cases provide evidence that the reciprocal duplication of the 17p13.1 microdeletion syndrome critical region is the cause of intellectual disability

N Savage[1], MW Humphreys[2], T Dabir[2], C Shaw-Smith[3], D Osio[3], MN Collinson[1]

[1.]Wessex Regional Genetics Laboratory, Salisbury, UK. [2.]Northern Ireland Regional Genetics Centre, Belfast, UK. [3.]Peninsula Clinical Genetics Service, Exeter, UK

Although the 17p13.1 microdeletion syndrome is well defined, very few duplications of this region have been described. We present two new cases with a de novo duplication of 17p13.2p13.1 and compare their genotype and phenotype with two previously reported cases. All four patients exhibit intellectual disability and various dysmorphic features. There is a 260 kb minimal region of overlap (MRO) between the four duplications which encompasses the 148 kb minimal critical region described for the 17p13.1 microdeletion syndrome. The six candidate genes for intellectual disability (DLG4, GABARAP, CTDNEP1 (DULLARD), GPS2, NEURL4 and KCTD11) within the microdeletion syndrome critical region are, therefore, within the duplication MRO. Other genes involved in brain development (NLGN2, FXR2 and EFNB3), located outside of the MRO, are duplicated in some of the cases, which may be contributing to their intellectual disability. Several regions exist in the genome where deletion or duplication of the same dosage sensitive gene/s causes a specific phenotype; for example, the nearby 17p13.3 region. We propose that duplication of the 148 kb 17p13.1 microdeletion syndrome critical region causes a reciprocal microduplication syndrome with a phenotype that includes cognitive impairment and Dysmorphism.

P19. A prospective analysis of the diagnostic yield & cost benefit of array comparative genome hybridization (aCGH) in previously undiagnosed patient cohort

MW Humphreys[1], T Dabir[1], L Bradley[1], S McKee[1], S McNerlan[1]

Northern Ireland Regional Genetics Centre, Belfast, UK

Array CGH is now recognised to be the most appropriate front line test for children with developmental delay, dysmorphism or learning disability. Up until Nov 2011 The Northern Ireland Regional Genetics Centre had no revenue funding to provide a local array CGH service. In late 2011 funding was authorised for 500 send away aCGH tests during our local tender process. We carried out an audit to determine the diagnostic yield by array CGH within this cohort of 500 undiagnosed patients and to assess the cost benefit of array CGH and its possible impact on current practice of genetic investigations. The audit determined that the pick-up rate for new abnormalities by array CGH to be 18%, which compares very favourably with published data (8-17%). To assess the cost benefit of providing aCGH as a frontline test, 90 of the 500 patients analysed were reviewed. The estimated total prior test cost for these 90 patients was £42,676. The cost of the 90 array CGH tests was £29,250, indicating that ~£13,426 could have been saved for these 90 patients if a frontline array test had been available, thus confirming the cost benefit of this strategy. The results of this audit support this strategy to be good practice, as a significant proportion of patients showed a new abnormality, not detected by previous investigations. Array CGH is now offered as a frontline test in the NI Regional Genetics Centre for this patient cohort in line with other UK Genetics Centres.

P20. Integrating tertiary genetics practice with mainstream medicine

SA Lynch[1,2,3] C McGorrian[4], J Galvin[4], J O'Byrne[4], S Stewart[4], J Casey[1,2]

[1.]Dept. of Genetics, Temple Street Children's University Hospital, [2.]Academic Centre on Rare Diseases, School of Biomolecular and Biomedical Science, University College Dublin, Dublin, [3.]National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin. [4.]Mater Hospital Eccles Street

Governmental bodies have recognised the need to educate Health care professionals (HCPs) on developments in genetic health as genetic testing becomes mainstream. A lack of funding and infrastructure with front line HCPs is limiting the awareness of genetic services in the Republic of Ireland. Following our recent KEDs/HRB grant, where we commenced engagement with HCPs to enhance education of genetics in health care, we have now successfully secured additional funding from UCD to develop e-learning modules for both rare and non-rare genetic disorders. e-Learning modules are becoming a popular method by offering distance learning to busy HCPs who need to keep on top of their CPD requirements. e-learning offers a cheap alternative as CPD is now obligatory & conference attendance expensive, especially for GPs, who are self-employed and may need to pay locums to cover absences. Our plan is to develop our microsite (http://www.ucd.ie/medicine/rarediseases/), further by development of e-learning modules on cancer genetics, cardiac genetics, haemochromatosis, investigation of developmental delay and fetal medicine. Our microsite, which went live in Sept 2013 has already had 700 hits and our animation videos > 1000 views. Whilst there are e-learning genetic alternatives in other countries, there are specific disorders and infrastructure issues (referral guidelines etc.) which require local knowledge. HCPs will receive a CPD certificate upon completion of a module, with1 credit per 1 hour of online learning. The e-learning will be open to all HCPs and we would anticipate it will continue to be developed over time. Our proposal is timely with the recent EU recommendation of rare diseases.

P21. Development of a targeted Next Generation Sequencing gene panel for Heritable Connective Tissue Disorders

SV Heggarty, SP Hegarty, D Beattie, V McConnell, FJ Stewart, CA Graham

Regional Medical Genetics, Belfast Trust, Belfast City Hospital, Belfast

Connective Tissue Disorders (CTDs) are a heterogeneous range of disorders that affect the structural integrity of various tissues and organs. Heritable CTDs include Marfan, thoracic aortic aneurysm and dissection (TAAD), Loeys-Deitz and Ehlers-Danlos syndromes and although associated with definitive phenotypes these syndromes may have non-specific or atypical presentations. Patients may present with life-threatening complications due to defects in the heart and vascular system. Causative mutations have been identified in genes that are involved in the structure, production or processing of collagens as well as proteins that interact with collagens. A targeted next generation sequencing gene panel has been developed and validated for routine clinical diagnostic use. A Haloplex (Agilent) custom design kit and Ion Torrent PGM (Life Tech) were used to sequence the coding regions (+/- 20 bp) of 7 of the major genes associated with heritable CTDs (ACTA2, FBN1,

TGFBR1, TGFBR2, MYH11, SMAD3 and COL3A1) and the data analysed using the NextGENe Package (SoftGenetics). This method enables the detection of single nucleotide changes as well as small duplications and deletions in these genes. An initial validation of the heritable CTD panel was completed on 12 patients who carried mutations previously identified in the FBN1, ACTA2, MYH11 and COL3A1 genes. A further 53 patients have been analysed and novel likely-pathogenic variants identified and confirmed by Sanger sequencing in 9 additional patients. This method enables a more efficient and comprehensive diagnostic strategy for the analysis of heritable CTDs than the traditional single gene Sanger sequencing approach.

P22. Policy development for carrier testing in autosomal recessive genetic conditions

J Turner, A Ward, A Green, R Kelly

National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin, Dublin 12

Novel laboratory methods have led to an exponential increase in the number of genes being discovered for genetic disorders with mutation screening identifying causative genetic alterations in affected individuals. Many autosomal recessive conditions are rare but the arrival of an affected child inevitably leads to heightened anxiety among family members especially when considering a pregnancy. Increasingly relatives are requesting carrier testing for the family mutation in cases where the population carrier frequency is small and therefore the risk to a pregnancy is low. Often there is no straightforward carrier test for their unrelated partner. We were mindful that offering testing to relatives may unnecessarily raise anxiety. The clinical utility of this testing is questionable, in a climate where budgets are restricted and demand is great. We aim to offer our service in an equitable manner focusing our limited resources where need is greatest. Our current practice was reviewed, guidance was sought from other genetics units about their procedures and a policy document was developed. It was decided that if the prior risk to a couple of having an affected pregnancy is less than 1 in 400 carrier testing should be discussed with the clinical team. Criteria used to decide if cascade testing is indicated include seriousness of the condition, population carrier frequency and the presence of an effective carrier test due to common mutations. As no international guidelines addressing this issue exist we believe this represents a positive shift in our practice which could inform that of other genetic services.

P23. A case of atypical Angelman Syndrome

C Joyce[1], B ó hIcí[2], K Meaney[2], T Morris[2] and L Gibson[3]

[1.]Clinical Biochemistry, Cork University Hospital. [2.]National Centre for Medical Genetics, Dublin. [3.]Paediatrics Dept., Cork University Hospital.

An 8 year old boy presented with speech delay, tongue protrusion and an abnormal gait. He had major separation anxiety issues and was prone to sudden outbursts and disruptive behaviour. Although physically active he had excessive weight gain. As over-eating was part of his initial diagnosis, he was investigated for Prader Willi Syndrome. Methylation and copy number analysis of the Prader Willi/Angelman critical region using MS-MLPA showed normal copy number and 13% methylation. This result is compatible with a diagnosis of Angelman syndrome. There was no microdeletion or rearrangement observed by FISH analysis with the D15S10 probe (15q11.2-13). An imprinting centre deletion also seemed unlikely as there was normal MPLA copy number within the AS-SRO (smallest region of overlap). The possibility of paternal UPD was then investigated using chromosome 15 microsatellite markers which showed bi-parental inheritance. Therefore, AS in this patient is most likely caused by an imprinting centre defect. The recurrence risk for this defect in future pregnancies is low. Our patient belongs to a group of patients with a mosaic imprinting defect and an atypical phenotype who present with muscular hypotonia at birth and obesity.

P24. Overgrowth Syndromes - Ingeniously Heterogeneous

JJ O'Byrne[1], PM Kelly[2], C Costigan[3], R Gul[4], S Byrne[5], SA Lynch[1]

[1.]National Centre for Medical Genetics, [2.] Department of Paediatric Orthopaedics, and [3.]Department Of Paediatric Diabetes & Endocrinology, Our Lady's Children's Hospital, Crumlin, Dublin; [4.]Department of Paediatrics, Midland's Regional Hospital, Portlaoise, Co. Laois, [5.]Department of Paediatric Orthopaedics, Children's University Hospital, Temple street, Dublin.

Background: Overgrowth Syndromes can present in a myriad of ways and represent a set of disorders that pose categorisation, diagnostic, prognostic and management challenges to physicians. Aims: To highlight the heterogeneous presentations of overgrowth syndromes and difficulties in managing the conditions. Methods: Four distinct cases of overgrowth syndrome are presented. Results: Case 1 - Developmentally appropriate two year old boy with mild hypertrophy of left lower leg, macrodactyly of 4th and 5th toes and capillary malformation. Case 2 - Developmentally appropriate three month boy with right index finger macrodactyly present from birth. Case 3 - Mildly learning disabled sixteen year old girl with general overgrowth, hemihypertrophy and capillary malformation. Case 4 – Developmentally appropriate six week old boy with isolated overgrowth of right foot.

Conclusions: Disorders resulting in overgrowth are a rare heterogeneous group of conditions and represent a diagnostic and therapeutic challenge as an extensive list of differential diagnoses exists. Management often involves multiple specialities including plastic surgery, orthopaedic surgery, dermatology, oncology and clinical genetics. Attempts to develop an accurate molecular diagnosis for each condition are important as they guide management and may influence screening protocols for embryonal tumours which currently differ between and within countries. Married with detailed phenotyping, this genotyping will aid the development of future management protocols and tailored therapies. To this end, working with colleagues in the UK and USA, we hope to genotype the presented cases.

P25. Human DHFR and DHFRL1 both localise to the mitochondria of HEK293 cells.

L Hughes[1], M Ozaki[1.] F O'Sullivan[2], A Parle-McDermott[1]

[1.]School of Biotechnology, Dublin City University, Dublin 9, [2.]National Institute for Cellular Biotechnology, Dublin City University, Dublin 9

Dihydrofolate reductase is an essential enzyme in folate metabolism and considered to be exclusively cytoplasmic. In 2011 the formerly annotated pseudogene DHFRL1 was reported to be expressed and functional[1,2] as well as participating in de novo dTMP synthesis in mammalian mitochondria[2]. DHFRL1 has no mitochondrial targeting sequence so its localisation mechanism is unknown. Here we have used site directed mutagenesis to examine if altering the starting sequence of either protein affects their localisation.

Hek 293 cells cultured under standard conditions were transfected with pCMV6-ac-GFP vectors containing DHFR, DHFRL1, and mutated versions of both genes. Transfected cells were fixed and stained with Mitotracker™ red and localisation studies were performed by confocal microscopy and Western blotting of extracted mitochondrial proteins.

The first three amino acids of DHFR and DHFRL1 were successfully mutated, DHFR to DHFRL1 and DHFRL1 to DHFR. Localisation

of the wild type and mutated proteins was examined by Western blot and confocal microscopy. In both experiments all four proteins localised to the mitochondria. GFP from the transfected empty vector has a mitochondrial band on the Western blot but showed minimal localisation on confocal microscopy. Western blot analysis on mitochondrial extracts from untransfected Hek 293 cells showed the presence of an endogenous active reductase, specific activity 14.88 nmol/min/mg protein.

In conclusion, we have demonstrated that when coupled to GFP both DHFR and DHFRL1 localise to the mitochondria of HEK293 cells and that altering the first 3 amino acids of either protein does not affect localisation. We have also shown there is an endogenous active reductase present in the mitochondria of this non-cancerous cell line.

1. McEntee G, Minguzzi S, O'Brien K, Ben Larbi N, Loscher C, O'Fágáin C, Parle-McDermott A. The former annotated human pseudogene dihydrofolate reductase-like 1 (DHFRL1) is expressed and functional. *PNAS* 2011;**108(37):**15157-62. 2.Anderson DD, Quintero CM, Stover PJ. (2011) Identification of a de novo thymidylate biosynthesis pathway in mammalian mitochondria. *PNAS* 2011;**108(37):**15163-8.

P26. Exploration of Lacosamide Response

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

[1.] Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. [2.]Centre for Human Genome Variation, Duke University, North Carolina, USA. [3.] Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London, UK. [4.]Department of Neurology, Hôpital Erasme, Université Libre de Bruzelles, Brussels, Belgium. [5.]Division of Neurology, Beaumont Hospital, Dublin, Ireland.

Approximately 65 million people in the world have epilepsy. In up to 70% of patients, seizures are effectively controlled by anti-epileptic drugs (AEDs). Lacosamide (LCM) is an AED that was first approved in 2008 for the treatment of focal-onset seizures. We aimed to determine the clinical relevance of genetic variation in predicting LCM responsive and non-responsive patients. We also aimed to determine the clinical relevance of genetic variation in predicting optimal LCM dose and predicting adverse drug reactions to LCM. A total of 484 patients were recruited from four tertiary epilepsy referral centres: Dublin, Ireland; London, UK; Brussels, Belgium; North Carolina, USA. Response to LCM was determined into four categories; (i) seizure freedom, (ii) ≥75% reduction in seizure frequency, (iii) no response and (iv) seizures worsening. Overall, 3% of patients experienced seizure freedom, while 8% experienced an increase in seizures while on LCM. These figures are in line with expectation given that we ascertained for refractory patients. Seizure freedom was observed at lower doses compared to the other response categories. LCM response also varied depending on epilepsy diagnosis with the Genetic Generalised Epilepsies emerging as a potential target group for LCM treatment. Up to 40% of patients reported an adverse drug reaction (ADR), with variability across the four sites. Results will be presented from ongoing genetic analysis of this cohort.

P27. Investigation of Parent-of-Origin Effects in Autism Spectrum Disorders

S Connolly, EA Heron

Neuropsychiatric Genetics Research Group, Trinity College Dublin

The detection of parent-of-origin effects aims to identify whether or not the functionality of alleles, and in turn associated phenotypic traits, depends on the parental origin of the alleles. Genome-Wide Association Studies (GWAS) have had limited success in explaining the heritability of many complex disorders and traits but successful identification of parent-of-origin effects using trio (mother, father, offspring) GWAS may help shed light on this missing heritability. Autism Spectrum Disorders (ASDs) are considered to be heritable neurodevelopmental disorders and a number of trio GWAS datasets exist for examining this heritability. Here, we have investigated parent-of-origin effects in large trio GWAS datasets that have previously been analysed for parent-of-origin effects using statistical approaches that did not have the capacity to detect epigenetic effects such as maternal-offspring genetic effects and all assumptions of the approaches may not have been satisfied. Here the approach of Estimation of Maternal, Imprinting and Interaction Effects Using Multinomial Modelling (EMIM) is used to identify SNPs associated with ASD through a parent-of-origin mechanism which has the potential to aid in understanding more fully the genetic underpinnings of ASD.

P28. Examination of Pathways possibly involved in the Pathogenesis of Neovascular AMD

MAG Irvine, AE Hughes

Centre for Public Health, Queen's University, Belfast.

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly, affecting 10% of those aged over 65 years and 25% of those aged over 75 years. The neovascular subtype of AMD is less common than the dry form, but is ultimately more likely to lead to blindness. Our research examined loci associated with neovascular AMD to inform molecular pathways that may contribute to disease causation. Data from the large US MMAP study were examined and participants split into groups dependent on their genotypes carried at the two most strongly associated loci: CFH(rs10801555) or ARMS2(rs932275).Each of the groups created was analysed using PLINK, and for each SNP the odds ratios (OR) and p-values were compared between groups. SNPs were ranked according to the change in OR between the most harmful and most protective genotypes. The top 200 SNPs were loaded into the DAPPLE online programme which creates networks between genes where SNPs have been published as having associations with each other.

There were two interesting findings. Stratifying on CFH, GDF6 closely associated with ARMS2, which together are thought to lead to angiogenesis. Stratifying onARMS2, four of the associated SNPs were found in genes that form part of a glutaminergic pathway which is involved in neuronal apoptotic death and therefore may possibly affect the death of reticulocytes in the retina. Confirmation of our results will be required in additional genotyping datasets that should become available shortly.

P29. Genetic susceptibility to reflux nephropathy in vesicoureteric reflux patients

JM Darlow[1,2], R Darlay[3], M Hunziker[2,4], B Kutasy[1,5], AJ Green[1,6], H Cordell[3], P Puri[2], DE Barton[1]

[1.]National Centre for Medical Genetics, Dublin. [2.]National Children's Research Centre, Dublin. [3.]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne. [4.]National Children's Hospital, Tallaght, Dublin. [5.]Our Lady's Children's Hospital, Crumlin, Dublin. [6.]UCD School of Medicine and Medical Science, Dublin.

Vesicoureteric reflux (VUR), the reverse flow of urine from bladder to kidneys, due to a developmental defect of the vesicoureteric valve mechanism, occurs in about 3% of infants, but in many it resolves as the child grows. The principal cause of morbidity in VUR cases is reflux nephropathy (RN), an overall term for congenital

renal dysplasia and acquired renal damage due to hydronephrosis and pyelonephritis, and is the commonest cause of renal failure in children. VUR appears to be very genetically heterogeneous. One approach to the discovery of the factors that determine which children with VUR will have RN and which will not, is to perform a genome scan for VUR and then, when the genes and mutations responsible for the linkage and association peaks have been identified, to look for relationships between genotypes and phenotypes. Another approach is to perform a genome scan using RN as the phenotype in VUR patients to look for additional genes that affect whether RN will occur in the presence of a mutation that causes VUR. The SNP genotyping of individuals can be used for both types of analysis. We genotyped 500 VUR patients and 400 other family members and published a linkage and association genome scan for VUR (using genotypes of 850 controls from the IBTS-TCD BioBank) in January 2014, and are now preparing a scan for RN, for which we hope to present results. As of early June, we have classified 391 VUR cases as without RN and 129 with RN from 230 families.

P30. Investigation of cell signalling events induced by expression of YWHAE-NUTM2, a fusion protein resulting from t(10;17)(q22;p13) in Clear Cell Sarcoma of Kidney.

E O'Meara[1], N McDonagh[1] and MJ O'Sullivan[1,2]

[1]National Children's Research Centre, Our Lady's Hospital, Crumlin, Dublin 12. [2]Histology Laboratory, Our Lady's Children's Hospital, Crumlin, Dublin 12

Clear cell sarcoma of kidney [CCSK], the second commonest childhood renal cancer is diagnostically challenging, aggressive and therapy-resistant. Individual case reports of CCSKs with t(10;17)(q22;p13) prompted our characterization of the chromosomal translocation. This translocation results in rearrangement of YWHAE (encoding protein 14-3-3ε) on chromosome 17 and NUTM2 on chromosome 10, producing an in-frame fusion transcript YWHAE-NUTM2. To investigate the cell biological effects of the fusion protein, we developed cell lines allowing inducible expression of Ywhae-Nutm2 in HEK293 and NIH3T3 cells. We show that HA-Ywhae-Nutm2 is present in both nuclear and cytoplasmic compartments, while 14-3-3ε is localised primarily in the cytoplasm. Since 14-3-3ε can mediate signal transduction by phosphoprotein interactions, we reasoned that Ywhae-Nutm2, with its ability to enter the nucleus, could alter cell signalling events. Unfractionated, nuclear and cytoplasmic HEK293 cell lysates, induced to express HA-Ywhae-Nutm2 or mock-treated were applied to an antibody microarray encompassing 850 total and phospho-specific antibodies. Altered protein expression and phosphorylation events in response to HA-Ywhae-Nutm2 expression were identified by this screen. Of these, the levels of the anti-apoptotic proteins Mcl-1, Bcl-2 and Bcl-xL were shown to be increased in cytoplasmic fractions (Mcl-1), or decreased in nuclear fractions (Bcl-2 and Bcl-xL). Hsp60 has been identified by western blot as being increased following induction of HA-Ywhae-Nutm2 in unfractionated and both the nuclear and cytoplasmic fractions. Further validation of, and investigation into, the altered cell signalling events in response to Ywhae-Nutm2 expression will assist in identifying novel therapeutic targets for this treatment-resistant cancer.

P31. Next Generation Sequencing to interrogate Vitamin D related genes in patients with New Onset Diabetes after Transplantation (NODAT).

KA Benson[1], S Chand[2], LJ Smyth[1], JA McCaughan[1,3], S Shabir[2], W Chan[2], J Kilner, AP Maxwell[1,3], R Borrows[1], AJ McKnight[1]

[1.]Nephrology, Centre for Public Health, Queen's University of Belfast, United Kingdom, [2.] Renal Department, Queen Elizabeth Birmingham, [3.] Regional Nephrology Unit, Belfast City Hospital, United Kingdom

New Onset Diabetes after Transplantation (NODAT) is a serious complication for 5-40% of organ transplant recipients. NODAT increases the risk of cardiovascular complications, graft rejection, infection and premature death. Low vitamin D (VitD) levels, and SNPs in the VDR gene, have been associated with the development of NODAT. Individuals (n=96) with an oral glucose tolerance test performed at baseline, 7 days, 3 months and 12 months after kidney transplantation were recruited, alongside kidney transplant recipients with established NODAT (cases) and transplant recipients with no evidence of NODAT (controls) matched for age, gender and follow-up time (n=173). 25-OH VitD levels were available for 90 individuals.

Targeted next generation sequencing was used to investigate 43.8 kb across 38 high value SNPs associated with VitD levels, exons, splice sites, and untranslated regions for CYP2R1, CYP12B1, CYP24A1, CUBN, GC, NADSYN1, and VDR genes. This method permits a cost effective, accurate and efficient examination of customised genetic regions. AmpliSeq amplicons were designed in two pools (n=163, n=166) and sequenced on an Ion Torrent PGM. Libraries were prepared using Ampliseq kit 2.0 and processed on an Ion Chef, or OneTouch2+ES machine. Reads were aligned using TorrentSuite v4.0.3 and SNP genotypes called using Partek Genomics Suite v6.6. Maximum reads per sample were 120,000 and 317,000 for 318 and 316 chips respectively. SNPs were compared with 25-OH VitD levels and development of impaired glucose tolerance or NODAT. We have developed a novel screening assay and reveal important findings for SNPs associated with vitamin D levels and NODAT.

P32. Next generation sequencing of the mitochondrial genome to evaluate association with end stage renal disease

AP Douglas[1], AP Maxwell[1 2], AJ McKnight[1]

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

Introduction: Kidneys are highly aerobic organs, which are heavily dependent on the normal functioning of mitochondria - the cellular "power-plants". Mitochondria possess discrete DNA from the nuclear genome, mtDNA,which encodes important respiratory chain components. The uraemic state associated with end-stage renal disease (ESRD) may increase the risk of oxidative damage to mtDNA. Whole genome resequencingof mtDNA in a cohort of White kidney transplant donors and recipients was employed to identify mtDNA variants associated with ESRD. Methods: The mtDNA was amplified in two overlapping fragments with long range PCR, and size confirmed using 0.7% agarose gel electrophoresis. Both fragments were pooled for each sample, enzymatically fragmented, and each individual's DNA was barcoded before being pooled for library preparationand next-generation sequencing using the Ion Torrent Personal Genome Machine. Data was analysed using Partek Genomics Suite, HaploView, and PLINK. Results: DNA from 64 individuals (39 recipients, 25 donors) has been sequenced across the entire 16,569 bp (37 genes) mtDNA. This revealed 361 mtDNA variants, of which 89 had a minor allele frequency greater than five percent. Successful call rate exceeded 98% for all SNPs and samples. Seventeen SNPs were nominally associated with ESRD with $P<0.05$. The most significant result was 2706A>G, $P=0.0016$. Analysis of a further 127 individuals for replication is ongoing. Conclusion: Mitochondrial DNA variants are significantly associated with ESRD, though the importance of the association is still to be elucidated, and requires further analysis.

P33. A Northern Irish population study of renal disease in Tuberous Sclerosis Complex

T O'Neill, C Shepherd, R Hardy, D Donnelly, PJ Morrison

TS clinic, Northern Ireland Regional Genetics, Belfast City Hospital

Tuberous sclerosis (TSC) is an autosomal dominant disorder caused by mutations in TSC1 or TSC2. It is characterized by benign tumours particularly in the kidneys and brain. Renal angiomyolipomas (AML) affect ~80% of patients causing morbidity and mortality through haemorrhage and renal insufficiency. Current treatments include embolization, nephrectomy and mTOR inhibitors. There is a risk of renal carcinoma. Methods: We have a database of all TSC patients in Northern Ireland, and investigated the incidence of renal complications in all patients. Results: 98 patients were recorded on the database, giving an incidence of 1 in 18,000 (age range 1-78 years). 36 had no evidence of renal disease on USS.

Two patients had no AMLs but had renal carcinoma (RCC). 55%of patients had renal AMLs; One patient also showed polycystic kidney disease and one patient had RCC. Most showed stable growth in AMLs but at the time of the study 6 (10%) had large AML which were actively growing - three of these have had embolisation, 1 was started on an mTOR inhibitor, two are being monitored to determine if intervention is needed.5 others patients had a history of embolization. Conclusion: Renal AML's are common in the TS population and careful monitoring to allow treatment and timely intervention is crucial. Northern Ireland has a total of 4 patients currently on an mTOR inhibitor for treatment of their AML's. To our knowledge this is the first total population study of renal complications in TSC patients.

P34. Investigation of the proliferative and invasive potential of cells expressing Ywhae-Nutm2, the fusion protein resulting from t(10;17)(q22;p13) in Clear Cell Sarcoma of Kidney

Kenny[1], E O'Meara[1] and MJ O'Sullivan [1, 2,3]

[1.]School of Medicine, Trinity College Dublin, Dublin 12. [2.] Dept. of Histopathology, Our Lady's Children's Hospital, Crumlin. Dublin 12. [3.] National Children's Research Centre, Our Lady's Children's Hospital, Crumlin, Dublin 12

Clear Cell Sarcoma of Kidney [CCSK], the second commonest pediatric renal cancer, is aggressive, therapy-resistant, and has poor outcomes. The oncogenic mechanisms underpinning CCSK are poorly understood. Specific diagnostic/prognostic markers and effective therapies are lacking. Prompted by three independent published case reports of a chromosomal translocation, t(10;17)(q22;p13) in CCSK, we characterised this chromosomal translocation to show that it results in rearrangement of YWHAE on chromosome 17 and NUTM2 on chromosome 10, producing a fusion transcript comprising exons 1-5 of YWHAE fused in-frame to exons 2-7 of NUTM2. To investigate the biological effect of Ywhae-Nutm2, we have generated stably transfected HEK293 and NIH3T3 cell lines with inducible HA-tagged YWHAE-NUTM2. To ascertain whether expression of Ywhae-Nutm2 confers oncogenic potential, cell-based assays were conducted using the xCELLigence system. This system provides a platform for real-time and label-free analysis of cell proliferation, migration and invasion by utilising electrical impedance signals generated by growing cells within a user-defined time-frame. Cell migration of HEK293 cells induced to express HA-Ywhae-Nutm2 was significantly higher than of the mock-treated cells (which express no fusion protein). We are currently investigating the ability of cells expressing, and not expressing, Ywhae-Nutm2 to invade and migrate through a matrigel layer. Furthermore, molecular changes within cells expressing Ywhae-Nutm2 will be investigated by gene expression profiling at a chosen time point derived from the xCELLigence analysis. This will contribute to our understanding of the molecular events underpinning CCSK, and, in conjunction with ongoing signalling studies in the laboratory, will help to elucidate novel therapeutic targets.

P35. Functional Investigation of Celiac Susceptibility Gene LPP in T cells

B Molloy, M Freeley, E Quinn, R McGinn, A Long, R McManus.

Department of Clinical Medicine, Institute of Molecular Medicine, St. James's Hospital, Dublin 8.

CD4 T cells are known to play an important role in celiac disease etiology as they initiate an immune response to gluten displayed by antigen presenting cells. A large case control study using the Immunochip identified Lipoma-preferred partner (LPP) as the most significantly associated non-HLA risk locus.(Trynkaet al, 2011).mRNA sequence data of CD4 T cells from our lab (data not shown) shows that LPP is expressed at higher levels in celiac samples compared to controls. We aimed to investigate the role of LPP in T cells. In this study we wanted to confirm the expression of LPP in CD4 T cells and examine the effect LPP may have on cell migration through siRNA knockdown. In addition, using qPCR we tested a number of potential LPP targets that demonstrated dysregulation in our sequencing study for differences in expression when LPP is silenced. We confirmed LPP expression in peripheral blood T lymphocytes. T cells knocked down for LPP showed defects in transwell migration in response to chemotactic signals. Furthermore, preliminary data shows that when stimulated with the chemokine, CXCL12, knockdown of LPP is associated with alterations in the mRNA levels of the potential LPP interactors or transcriptional targets MMP25, TIMP1 and CXCR4 suggesting a possible mechanism by which LPP contributes to disease pathophysiology. Ongoing investigations aim to further delineate the role of LPP in T cells.

P36. Allelic expression imbalance at IL18 and CXCL16 in heterozygous clinical samples and cell lines.

JM Gahan[1,4], E Connolly[1,4], E Quinn[1,4], MM Byrne[1,4], R McManus[1,4], RJL Anney[3,4], SG Gray[1,4], RT Murphy[2,4], AW Ryan[1,4]

[1.]Department of Clinical Medicine, Trinity College Dublin, [2.]Department of Cardiology, St James's Hospital, [3.]Department of Psychiatry, Trinity College Dublin, [4.] Institute of Molecular Medicine, Trinity Centre for Health Sciences, St James's Hospital

Gene expression may exhibit allelic expression imbalance (AEI), whereby one allele produces more mRNA than the other in heterozygous individuals. This variation may be detected by performing 5'exonuclease genotyping on cDNA, thereby measuring the levels of allelic mRNAs. This provides a powerful method to detect cis-acting genetic variants, and may uncover a functional role for non-coding SNPs in GWAS analyses. The CXCL16 gene encodes a chemokine involved in the pathology of multiple diseases. It is induced by interferon gamma, which is in turn induced by interleukin 18 (IL18).We performed 5'exonuclease assays on cDNA from heterozygous Acute Coronary Syndrome (ACS) patients and heterozygous immortalized lymphoblastoid cell lines (CEPH), with or without stimulation by TNFalpha, DMSO and Sulphoraphane (SFN), a Histone Deacetylase inhibitor. A number of clinical samples showed evidence of allelic expression imbalance at both IL18 and CXCL16. Some cell lines showed AEI at IL18, but not at CXCL16 unless the cells were stimulated by TNFalpha. Among those cell lines that showed no CXCL16 imbalance, treatment with DMSO or a combination of DMSO and SFN induced imbalance. In conclusion, AEI can be observed in clinical samples and can be enhanced in cell lines by stimulation with TNFalpha, thus reproducing the pro-inflammatory environment of ACS. This effect can be further enhanced by treatment with DMSO and SFN, suggesting that at least some of the observed AEI has an epigenetic component.

P37. A genome-wide meta-analysis of aromatic anti-epileptic drug induced maculopapular exanthema

M McCormack[1], H Gui[2], D Speed[3], The International League Against Epilepsy Consortium on Complex Epilepsies, S Sisodiya[4], C Depondt[5], E Heinzen[6], D B Goldstein[6], S Petrovski[7], TJ O'Brien[7], S Cherny[2], PC Sham[2], N Delanty[8], L Baum[9], GL Cavalleri[1]

[1.]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, [2.]Department of Psychiatry, The University of Hong Kong, Hong Kong, [3.]UCL Genetics Institute, University College London, London, [4.]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, [5.]Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, [6.]Center for Human Genome Variation, Duke University School of Medicine, North Carolina, [7.]The Melbourne Brain Centre, Department of Medicine, The Royal Melbourne Hospital, University of Melbourne, Melbourne, [8.]Division of Neurology, Beaumont Hospital, Dublin, Ireland, [9.]School of Pharmacy, The Chinese University of Hong Kong, Hong Kong

Carbamazepine is one of the world's leading anti-epileptic drugs (AEDs) for treating partial epilepsy. However, it is estimated that 5-10% of patients exposed to the drug develop a cutaneous idiosyncratic adverse drug reaction (ADR) characterized by a generalized maculopapular exanthem rash (MPE). Similar hypersensitivity reactions also occur with other aromatic AEDs including lamotrigine, phenytoin and oxcarbazepine. An allele in the human leukocyte antigen (HLA) locus, HLA-A*3101, has been shown to have diagnostic value in predicting carbamazepine-hypersensitivity (OR=8.58, CI=5.55-13.28) in Europeans, Japanese and Korean populations. However there are no known genetic markers of MPE to other AEDs. In this study we have genotyped 178 AED-specific MPE cases and 806 drug-tolerant controls from epilepsy patient cohorts of European, Asian and African-American ancestry. We imputed over 6 million genetic variants from the 1000 Genomes Project across each cohort and performed logistic regression of all cases versus controls per ancestral cohort, controlling for within-population differences by principal components analysis. Within the European cohort we further stratified cases according to the specific causal drug. Finally, we performed a meta-analysis of the results to identify enrichment for global markers of hypersensitivity to AEDs. Such markers will aid in reducing overall rates of AED discontinuation due to ADRs and will serve to advance genetic testing in clinic.

P38. Comparison of whole genome and whole exome next generation sequencing techniques on the Ion Torrent Proton platform for coverage of key genetic regions in chronic kidney disease.

S Duffy, N Catherwood, AP Maxwell, AJ McKnight

Nephrology Research, Centre for Public Health, Queen's University of Belfast

Whole genome sequencing (WGS) was compared with whole exome sequencing (WES) and microarray data for the investigation of genetic regions associated with chronic kidney disease (CKD). Using a two parent-offspring trio design. WGS was compared with TargetSeq WES (hybridisation method) and AmpliSeq (multiplex PCR method) WES on the Ion Torrent Proton™. Sequences were aligned to GRCh37.p13 using Torrent Suite version 4. Partek® Genomics Suite™ version 6.6 was employed for variation detection, familial trio validation and pathway analysis. WGS yielded the most comprehensive analysis of genetic variation with an average 4x coverage on P1 chip with 1-60,000x at SNPs; however the large datasets generated creates challenges for routine bioinformatic interpretation. WES reduces the size of generated data for each sample. TargetSeq covers ~50 Mb, including >29,500 protein and RNA genes (including >1470 miRNAs), >44,000 predicted miRNA binding sites, and untranslated regions with four probes per exon. Ampliseq covers primarily protein coding regions of the genome with ~90% reads on target. Literature review revealed 355 CKD associated genes. Variation was detected in 93% of these genes by WES and 84% by low pass WGS. We have demonstrated that Ion Torrent is an efficient and cost effective technology for use in research of the genetics of complex disease states such as CKD. The transition of NGS into the renal clinic may help to "personalise" patient care.

P39. Investigating the role of the KRAS variant in breast cancer phenotype and bilaterality

TP McVeigh [1], KJ Sweeney[1], N Miller[1], MJ Kerin[1], JB Weidhaas[2]

[1.]Discipline of Surgery, NUI Galway, [2.]Yale School of Medicine, New Haven, CT, USA

The KRAS-variant rs61764370 is a functional variant in the Let7a binding site in the 3' UTR of KRAS oncogene that has been associated with increased risk of cancers of the lung, breast and ovary. The aim of this study was to investigate prevalence of KRAS-variant among Irish patients with breast cancer, and to examine the association between the KRAS-variant and bilateral breast cancer. An observational cohort study was undertaken. The study group included patients with breast cancer managed in a single tertiary referral centre. Patients with known high-risk single gene mutations were excluded from analyses. Cancer-free controls over the age of sixty were recruited from the community. DNA was extracted from whole blood, saliva and buccal swabs and genotyped for the variant using a Taqman-based platform. All data was analysed using SPSS. 531 controls, 1138 patients with unilateral and 74 patients with bilateral breast cancers were genotyped for the KRAS-variant. 79/531 (15%) controls and 162/1212 (13%) cases carried the variant. Differential expression of the variant was noted across subtypes, being identified most commonly in patients with TNBC (16%). Of patients carrying the variant, 12(7.4%) had bilateral disease compared to 62 (5.9%) patients with a wild type allele. The median age of diagnosis of patients with the wild type allele was 53years (24-96) compared to 51 years (27-86) in patients with KRAS-variant. The KRAS-variant carries an increased risk of triple negative breast cancer compared to other subtypes, and is associated with bilaterality of disease.

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Abstracts

Ulster Society of Internal Medicine
91st (Spring) Meeting Friday 23rd May 2014

Craigavon Area Hospital

PROGRAMME:

2.00 pm **An unusual case of wrist pain.** D McCormick, R Stewart, M Neill, C Donnelly, H McCormick, M Mchenry. Rheumatology department, MPH, Orthopaedic department, RVH, Infectious diseases department, RVH. Microbiology department, RVH.

2.15 pm **The use of novel oral-anticoagulants in the prophylaxis of stroke in non-valvular atrial fibrillation. A review of prescribing practise and outcomes in the Belfast HSC Trust.** M Monaghan, K Goodwin, B Proctor, C Monteith, M Jackson, G Manoharan. Cardiology Department, Belfast Health & Social Care Trust.

2.30 pm **Auditing the Launch of Formal Oxygen Prescribing Practice.** G Patterson, S Graham, E McRory, R Convery. Respiratory Medicine, Craigavon Area Hospital.

2.45 pm **Guest Lecture:** "The initial assessment of Syncope." **Dr. John Purvis, Consultant Cardiologist, Western HSC Trust.**

3.15 pm Afternoon Tea.

3.40 pm **Grand Rounds:** Cases from Craigavon Area Hospital **Facilitator: Dr Rory Convery, Consultant Respiratory Physician, Southern HSC Trust.**

4.10 pm **Swollen legs, a common presentation with an unusual cause.** E Teague, R Ali, E Campbell, A Hameed, Acute Medical Unit, Altnagelvin Area Hospital, Western HSC Trust.

4.25 pm **Learning from an uncommon cause of a common presentation – autoimmune encephalitis on the acute medical ward.** G McCluskey, G Lewis, P Gardiner and M McCarron. Department of Medicine, Altnagelvin Area Hospital, Western HSC Trust.

4.40 pm Presentation of prize for the best abstract.

4.45 pm **Guest Lecture:** "ACS and provision of 24/7 primary PCI in Northern Ireland." **Dr Michael Moore. Consultant in Invasive Cardiology, Western HSC Trust.**

AN UNUSUAL CASE OF WRIST PAIN

D McCormick[1], R Stewart[1], M Neill[2], C Donnelly [3] H McCormick[4], M Mchenry[1].

1. Rheumatology department, Musgrave park hospital. 2. Orthopaedic department, Royal Victoria hospital. 3. Infectious diseases department, Royal Victoria hospital. 4. Microbiology department, Royal Victoria hospital

66 year old gentleman with a significant past medical history including autoimmune hepatitis requiring Immunosuppression with azathioprine and low dose prednisolone, previous deep venous thrombosis and atrial fibrillation requiring warfarinisation, pulmonary fibrosis, gout and osteoarthritis.

Presented to rheumatology service with monoarthropathy of right wrist in April 2013. Joint injection provided minimal benefit. Symptoms progressed over the following six months with increased pain and diffuse swelling of distal forearm and hand. Wrist aspirate in August suggested calcium pyrophosphate crystals but also cultured candida albicans on enrichment which was felt to be a contaminant. Further wrist aspirate in October, however, again cultured candida albicans.

MRI of wrist showed gross tenosynovitis of extensor and flexor tendons as well as synovitis and effusion in wrist. A low grade inflammatory process was suspected likely secondary to candida. Aspirate from olecranon bursa swelling also cultured Candida albicans.

There was no evidence of systemic candidiasis and the source of infection is unclear but case reports suggest rose thorns as a potential route of entry.

Despite 2 weeks of intravenous anti-fungal therapy, repeat joint aspirates continued to culture candida.

Repeat MRI scan showed further progression and suggested osteomyelitis of carpal bones. MRI elbow showed a large distended olecranon bursa as well as likely osteomyelitis of the olecranon.

Failure of conservative management of this rare and complex condition prompted transfer to orthopaedics where he has subsequently undergone endoscopic olecranon bursectomy and at a later date tenosynovectomy and ultimately may require amputation.

We await the outcome of this unfortunate gentleman.

THE USE OF NOVEL ORAL-ANTICOAGULANTS (NOACS) IN THE PROPHYLAXIS OF STROKE IN NON-VALVULAR ATRIAL FIBRILLATION (NVAF). A REVIEW OF PRESCRIBING PRACTISE AND OUTCOMES IN THE BELFAST HEALTH & SOCIAL CARE TRUST.

M Monaghan, K Goodwin, B Proctor, C Monteith, M Jackson, G Manoharan.

Cardiology Department, Belfast Health & Social Care Trust, The Royal Hospitals, 274 Grosvenor Road, Belfast BT12 6BA.

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence of 1.5-2% of the population. AF is associated with increased mortality, a three-fold increase in congestive cardiac failure and a five-fold increase in incidence of stroke.[1] The ESC advise that stroke risk should be assessed using the CHA2DS2VASC scoring system and oral anticoagulation commenced in patients that score 1 or more.

Until recently, VKAs (Warfarin) were the only oral-anticoagulants available for the prophylaxis of stroke in patients with NVAF. The NOACs can be classified into: the direct thrombin inhibitors (e.g. Dabigatran) and direct factor Xa inhibitors (e.g. Rivaroxaban, Apixaban).

A retrospective study was undertaken to investigate the prescribing of NOACs across the Belfast Trust from November 2012 to November 2013. 367 patients (Male 50%) with an average age of 70 years (+/- 17 years SD) were identified: (157 (42%) Dabigatran), (119 (32%) Rivaroxaban); (89 (24%) Apixaban). The average CHA2DS2VASC was calculated as 4 (+/- 2SD) with hypertension (51%), stroke or TIA (40%) and vascular disease (35%) identified as the most commonly occurring risk factors for stroke.

21 (5.7%) patients were admitted with bleeding predominantly from a gastrointestinal source(8, 2%), intracranial (4, 1.0%) or haematuria (4, 1.3%). One patient required blood transfusion. 6 patients (1.6%) were admitted with cerebral infarction. NOACs were discontinued in 4 (1%) patients. All-cause mortality was calculated at 6.8% with no patients dying from bleeding.

NOAC prescribing represents 9% of the total percentage of patients receiving oral anticoagulants. This study has shown that NOACs are generally well tolerated, safe and not associated with life-threatening bleeds.

REFERENCES

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AUDITING THE LAUNCH OF FORMAL OXYGEN PRESCRIBING PRACTICE

G Patterson, S Graham, E McRory, R Convery

Respiratory Medicine, Craigavon Area Hospital, Portadown, County Armagh

The 2008 British Thoracic Society (BTS) guidelines on the use of oxygen were published to ensure that oxygen was prescribed according to a target saturation range, rather than device and flow rate. In response, we conducted an audit on the prescription of oxygen in Craigavon Area Hospital (CAH).

Using the BTS Emergency Oxygen Audit 2012 template, we conducted an initial and subsequent re-audit, following MDT oxygen training sessions conducted by ourselves, during May and July 2013 respectively. We collected data from 10 wards auditing kardexes of patients who were on oxygen at the time of data collection.

In the first audit 38/287 patients were on oxygen at the time of data collection. 9/38 (24%) were prescribed oxygen on their kardex; 2/9 (22%) of these patients had oxygen correctly signed for on medication rounds. On re-auditing following staff training, we saw an 11% increase in the number of patients prescribed oxygen, and a 7% improvement in the number of kardexes signed.

This audit has shown that with appropriate education, formal oxygen prescribing practice has improved in CAH. As a result we have facilitated a move towards better oxygen prescribing amongst the oxygen sensitive population, in keeping with BTS guidelines.

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1. O'Driscoll, B.R., Howard, L.S., Davison, A.G. (2008) 'British thoracic society guideline for emergency oxygen use in adult patients', Thorax, **63(6)**, pp. 1-68.

SWOLLEN LEGS, A COMMON PRESENTATION WITH AN UNUSUAL CAUSE.

E Teague, R Ali, E Campbell, A Hameed, Acute Medical Unit, Altnagelvin Area Hospital, Londonderry.

We present the case of a previously fit and well 32 year old man with a 10 day history of left flank pain and bilateral leg swelling. On examination he had pitting oedema to the groins bilaterally and dilated abdominal wall veins. Investigations revealed a d-dimer of 4.6mg/L (normal reference range <0.5) and ultrasound Doppler of lower limb veins revealed occlusive deep venous thrombosis (DVT) in the common femoral, femoral and popliteal veins bilaterally. A computerised tomography scan of abdomen was performed and this showed an abnormal mid inferior vena cava (IVC) thought to represent congenital aplasia of the IVC. The patient was treated with low molecular weight heparin and warfarin. He was fitted with compression stockings and referred to the regional vascular surgery centre who recommended continuing with conservative management and seeking haematology advice regarding the duration of anticoagulation required. His leg swelling improved considerably and he remains on anticoagulation indefinitely.

Congenital IVC malformation is a rare vascular defect that is found in almost 5% of unprovoked DVTS in patients under 30 years old[1]. It is more common in men. The associated DVT can be unilateral but is more commonly bilateral. It can be diagnosed with CT scanning and is managed as outlined above. The necessary duration of anticoagulation has yet to be established as patients with this anomaly and thrombosis can be at increased risk of recurrent DVT[2].

We believe that this case promotes the need to consider further investigation of young patients presenting with unprovoked DVT.

REFERENCES

1. Lambert et al, Inferior vena cava agenesis and deep vein thrombosis:10 patients and review of the literature *Vasc Med* 2010 Dec:**15(6)**:451-9

2. Obsernoster et al, Anomalies of the inferior vena cava in patients with ileac vein thrombosis *Ann Intern Med* 2002 Jan 1:**136(1)**:37-41

LEARNING FROM AN UNCOMMON CAUSE OF A COMMON PRESENTATION – AUTOIMMUNE ENCEPHALITIS ON THE ACUTE MEDICAL WARD.

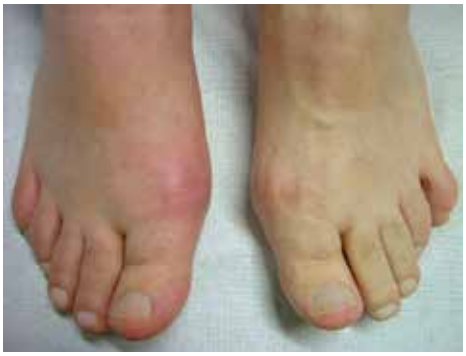
G McCluskey, G Lewis, P Gardiner and M McCarron

Department of Medicine, Altnagelvin Area Hospital, Derry, Northern Ireland

Acute confusion and hyponatraemia in the elderly commonly present to acute physicians. This case report describes a 72 year old female who presented following a fall and a 3 week history of confusion and memory impairment. She was found to be severely hyponatraemic at 108 mmol/L (normal range 133-145) and was initially treated with hypertonic saline. Once her serum sodium reached 120 she was fluid restricted as serum and urine osmolality were typical of SIADH. MRI brain revealed encephalitis, presumably from a viral cause, although CSF analysis did not show any organisms. The patient developed tonic clonic seizures and required HDU admission for 7 days. An autoimmune screen was sent and showed markedly raised titres of voltage gated potassium complex (VGKC) antibodies at 1144 pM (normal range <100). She was treated with corticosteroids and began to show improvement in her confusion and memory. Her serum sodium also returned to within the normal range. This case highlights the importance of fully investigating for uncommon causes of confusion and hyponatraemia. VGKC antibodies have been given recognition in recent years as a potentially reversible cause of encephalitis, making it essential that they are part of the differential diagnosis in patients who present encephalitis, especially if no viral organism is identified.

Curiositas

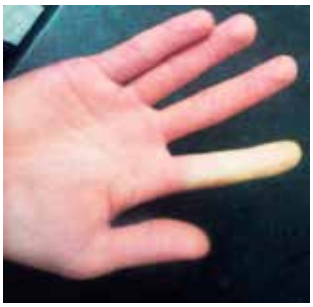
MEDICAL STUDENT QUIZ



A 64 year old man presented to his general practitioner with a painful right great toe. What is the differential diagnosis, and the most likely diagnosis? How would you investigate him, and how should the acute phase of this condition be treated?

Dr Paul Hamilton (Specialty Registrar, Chemical Pathology, Belfast Health and Social Care Trust) and Dr Gerry Gormley (Senior Academic General Practitioner, Centre for Medical Education, Queen's University Belfast, Northern Ireland.) The patient kindly gave permission for use of this image.

GENERAL PRACTICE QUIZ



A right handed 'Fettler' presented to his family doctor with intermittent episodes of tingling, numbness and coolness in some of his fingers. On occasions he noticed self-limiting episodes when some of his fingers would become pale compared to the rest of his hand. He was able to capture one of these episodes with his smart phone camera. What is the most likely diagnosis?

Dr Gerry Gormley, Senior Academic General Practitioner, Centre for Medical Education, Queen's University Belfast, Northern Ireland. (The patient kindly gave permission for use of image in this article)

HISTORICAL QUIZ

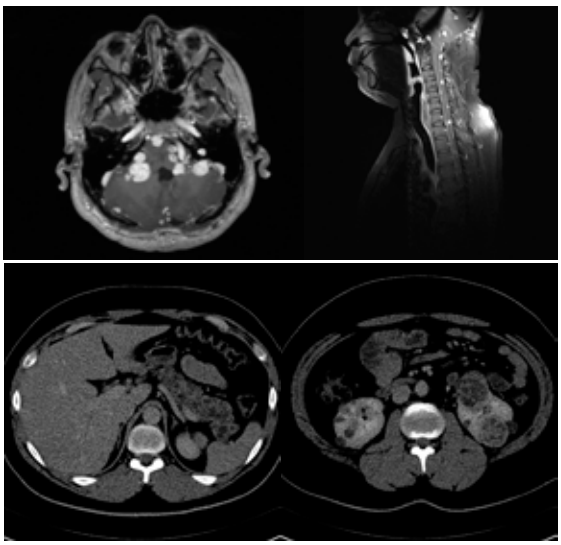
Curiositas was intrigued to discover a physician's handbook, used by a Co Tyrone doctor in 1911, entitled 'Wellcome's Medical Diary'.

What condition do you think this concoction of chemicals and potions was used to treat?

Of course it goes without saying – we would not recommend using these chemicals in current clinical practice – we have moved on considerably in the last 100 years!

POSTGRADUATE QUIZ

This 26 year old man presented to the neurosurgical department with modest posterior fossa symptomatology. He had no known family history. What abnormalities are present on these MRI and CT studies and what is the unifying diagnosis?



Dr Ian Bickle, Consultant Radiologist, Raja Isteri Penigran Anak Saleha Hospital, Bandar seri Begawan, Brunei Darussalam.

AND FINALLY…..

This solitary tree, on the perimeter of a construction site was brought to Curiositas's attention.

Do you know where this tree is? What is its local and global historical medical significance?

MEDICAL STUDENT SUBEDITOR INTERNSHIP

Curiositas is looking for a medical student to join the Curiositas Editorial team. This internship will be, in the first instance, for 1 year. The role will involve contributing to the production of the Curiositas section.

For further information on the post and the application process please email Dr Ian Bickle at firbeckkona@gmail.com. Applications for this post will be accepted up until the 14th October 2014.

ANSWERS See overleaf.

CONSIDER CONTRIBUTING TO CURIOSITAS?

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

Book Case

Dr John Purvis
6 favourites from my bookshelf.

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Holmes explores the relationship between the Arts and Science through the eyes of Joseph Banks. Banks began his scientific career as botanist on Captain Cook's expedition to Tahiti (a somewhat erotic journey) and rose to become President of the Royal Society where he nutured the blossoming careers of William and Caroline Herschel and Humphrey Davy. The Romantic poets and authors of those days were fascinated by "natural philosophy" as science was then known – Coleridge and Davy got high on nitrous oxide together whilst Mary Shelley wrote "Frankenstein – the Modern Prometheus" in response to experiments on "galvanism". A fascinating book.

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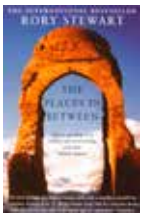
THE PLACES IN BETWEEN



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I enjoy a good adventure story. This is set in modern London but is haunted by unresolved secrets from the past. There is much about old family trades such as watchmakers and undertakers. An interesting fact – Undertakers like to hire people who have the "acquaintance" – a familiarity with death - so Doctors, Nurses and Police are apparently ideal.

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Curiositas: Answers

MEDICAL STUDENT QUIZ

The differential diagnosis would include crystal arthropathy (gout or pseudogout), septic arthritis or haemarthrosis. The site involved in this case is particularly typical of gout, and this would be the most likely diagnosis. In the presence of a typical history and examination, and in the absence of evidence to suggest another diagnosis (e.g. joint trauma or features of infection), gout at this site is often diagnosed on clinical grounds alone. Detailed investigation might include an x-ray of the joint, aspiration of fluid with subsequent fluid microscopy (including polarised light examination) and culture, and blood tests (full white blood count, C-reactive protein, uric acid level and coagulation screen). Drugs to be considered for an acute flare of gout include non-steroidal anti-inflammatory drugs, colchicine and corticosteroids.

GENERAL PRACTICE QUIZ

The patient most likely has Vibration White Finger (VWF). 'Fettling' is the skill of removing excess moulding material from a cast component – typically using grinding power tools. The risk of developing VWF increases with the duration and intensity of exposure to vibration. Such patients need to ensure that they keep their hands warm, stop smoking and make appropriate work place changes in order to reduce or cease exposure to vibrating tools.

HISTORICAL QUIZ

The condition was Pneumonia. In this 'pre-antibiotic' era Cursiositas was particualry bemused to see the use of Leeches, Alcohol, Strychnine and Liquorice in the treatment of this condition. With increasing antibiotic resistance, Curiositas wonders what might we be using in the next 100 years?

(Extract from 'Wellcome's Medical Diary, 1911' reproduced with kind permission from the Wellcome Library, London)

POSTGRADUATE QUIZ

The MRI brain and spinal cord studies demonstrate numerous small avidly enhancing lesions, which are most pronounced in the posterior fossa. These lesions are haemangioblastomas, albeit not the classical appearance of a cyst with an enhancing mural nodule. The CT study of the abdomen demonstrates; pancreatic cysts, renal cysts and an enhancing cortical based mass in the lower pole of the left kidney, in keeping with a renal cell carcinoma. The later was confirmed on image guided biopsy. This correlation of findings is in keeping with Von Hippel Lindau disease – an autosomal dominant multisystem disorder.

AND FINALLY…..

This is an Oriental Plane (Platanus Orientalis) tree, which is planted near to Erskine house, on the Belfast City Hospital site. Professor Dimitrios Oreopoulos brought seeds from the Plane tree of Kos, and saplings from these seeds were planted across the Belfast City Hospital site in 1969. The Plane Tree of Kos is best known to the medical profession as the tree on the Aegean island of Kos, under which Hippocrates, the 'father of medicine', reputedly sat to consult and teach in the 5th Century. Professor Dimitrios Oreopoulos moved to Canada from Northern Ireland, where he became Professor of Nephrology at Toronto, gaining international fame for his development of continuous ambulatory peritoneal dialysis. For futher infomration on this interesting story Dr James Douglas wrote an article in the UMJ *(Douglas J, Dimitrios Oreopoulos, the Plane Tree of Kos and the Belfast City Hospital. Ulster Med J 2014;***83(1):***31-36).* To read this article follow this link: http://www.ums.ac.uk/umj083/083(1)031.pdf

The 'Erskine House' Plane Tree of Kos (Belfast City Hospital) and ***Dr James Douglas*** *(Retired Consultant Nephrologist, Belfast City Hospital) author of the the article '****Dimitrios Oreopoulos, the Plane Tree of Kos and the Belfast City Hospital.*** *Ulster Med J 2014;83(1):31-36. (The author kindly gave permission for use of this image)*

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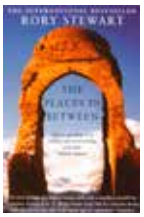

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Game Changers

GAME CHANGERS: ANOTHER REVOLUTION IN HEART ATTACK TREATMENT

Dr Michael J Moore

Major advances in the treatment of coronary artery disease (CAD) over the last three decades have resulted in dramatic improvements in mortality. Despite this, CAD remains a dominant cause of death. The thrombolytic era in Northern Ireland (NI) revolutionised outcomes for ST elevation myocardial infarction (STEMI) in the early 80's. More recently however, Primary Percutaneous Coronary Intervention (PPCI) has replaced thrombolysis in many parts of the world. Randomised controlled trials have demonstrated the significant advantages of PPCI (1).

The National Infarct Angioplasty Project (NIAP) demonstrated the feasibility of PPCI in the UK. The Department of Health (DoH) planned a national rollout of PPCI. The NHS UK have stated that all STEMI's should be treated in designated Heart Attack Centres (HAC's). These HAC's will have 24/7 Cardiac Catheterisation Lab availability with an on call PPCI team. The HSC Board has designated 2 HAC's for NI, The Royal Victoria Hospital (RVH), Belfast Trust and Altnagelvin Area Hospital (AAH), Western Trust. The RVH commenced 24/7 PPCI in 2013, covering mostly east of the River Bann, AAH is due to commence on 15th September 2014 for the West and North West. Outcomes for PPCI are dependent on procedural volume. Two HAC's allows coverage for NI's 1.6 million population while maintaining critical volume for each centre.

Thrombolysis was innovative and life saving but with its imminent departure NI is set for another revolution in Heart Attack treatment.

Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003; **361(9351)**: 13-20

EVIDENCE BASE FOR THE ROLE OF SINUS SURGERY IN CHRONIC RHINOSINUSITIS GAINS BETTER DEFINITION.

Dr Brendan Hanna

The landmark paper "Evaluation of the Medical and Surgical Treatment of Chronic Rhinosinusitis: A Prospective, Randomized Controlled trial"[1] demonstrated that 3 months of topical corticosteroids combined with saline nasal rinses and oral macrolide antibiotics produced clinical outcomes equivalent to surgical intervention, in all but those patients with nasal polyposis. The authors' concluded that this medical therapy regimen should be deployed as first line in patients with chronic rhinosinusitis. Many clinicians extrapolated these results, forming the opinion medical therapy to be as good as sinus surgery in chronic rhinosinusitis.

Due to the inherent risks of invasive therapy, surgery is usually reserved for patients who have not had a satisfactory response to medical treatment. In this study randomising patients, at presentation, to either surgery or medical therapy diluted the beneficial effects of surgery by including patients who would have had good outcomes from medical management alone. Here underscores the problem with randomising surgical treatments; patient selection is critical for good surgical outcomes but the process of selection is incompatible with randomisation.

The apparent discrepancy between patient treatment in the randomized trial and in the real clinical world has now been addressed[2]. In this non-randomised study patients with an unsatisfactory response to medical therapy were offered either continued medical therapy or surgery, with a cross-over arm from medical to surgical treatment. There were no statistical differences in disease severity between the cohorts. At one year follow-up surgical patients reported significantly more improvement than medically managed patients.

An evidence base is thus developing for the deployment of sinus surgery as an adjunct to medical therapy where initial medical therapy alone fails.

1. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective , randomised controlled trial. *Laryngoscope.* 2004: **114(5)**; 923-30

2. Smith TL, Kern R, Palmer JN, Schlosser R, Chandra RK, Chiu AG et al. Medical therapy versus surgery for chronic rhinosinusitis: a prospective multi-instituitional study with 1-year follow-up. *Int Forum Allergy Rhinol.* 2013;**3(1)**:4-9

'WHAT'S THE POINT OF A GP LOCUM?'

Dr Fiona McEvoy

A partner I had worked with for several years asked me this question recently. Having worked as a long term locum in their practice, doing fully booked surgeries, bloods, letters and housecalls, it was clear that the challenges I had (as a locum GP), and volume of work I had done, were not respected or noticed. I was a commodity with no terms and conditions, no boundaries.

At times in the past I had meekly suggested ways in which the workload could be addressed, or ways I could safely net a housecall when I was on my way to another practice, but these attempts where ignored. I was a ghost.

This is what is faced daily by GP locums all over Northern Ireland. I know that because the locums I know are friends and colleagues. Initially when the question was asked I was angry and hurt. On reflection I realised that it was important and needed addressed.

Sessional / non practice based GPs make up 40% of the workforce in the UK.[1] They provide cover for doctors when they are on holidays and when they are sick or need to care for loved ones, but they do not have the team or financial support they need when in the same situation. They are isolated and paid less than partner counterparts who received the same

training as them. They work in multiple locations, sometime miles apart, on different computer systems and with different colleagues daily.[2]

Locum GP's need to start to take professional and personal responsibility for their work, it is a service provided and as such should have set terms and conditions and Professional boundaries.

The work done needs to be respected not demanded, so patient safety can be assured and locums are not left feeling unequal to their partner counterparts.

1. National Association of Sessional GPs. How many locum GPs in the UK? [Internet]. Chichester, UK: NASGP; 2008. Available online from: http://www.nasgp.org.uk/download/locumnumbers/nasgp_how_many_gp_locums_in_UK.pdf. Last accessed August 2014.

2. National Association of Sessional GPs. Locum GPs: The skills we need and how we achieve them [Internet]. Chichester, UK: NASGP; 2010. Available online from: http://www.nasgp.org.uk/download/locum/skills/locum_gps_the_skills_we_need_and_how_to_achieve_them.pdf. Last accessed August 2014.

So you want to be an **Otorhinolaryngologist?**

Mr Philip R Bell

Royal Victoria Hospital Belfast
Correspondence to: Philip Bell
bellpr@hotmail.co.uk

Accepted 21 July 2014

INTRODUCTION

Otorhinolaryngology is a very broad speciality with six subspecialties recognized by the Royal Colleges. These include otology, rhinology, laryngology, head and neck surgery, facial plastics and paediatrics, however each of these is then further subspecialised. The scope of the speciality has changed over the last twenty years with increasing integration with other head and neck specialities and with other specialities such as oncology and radiology. The spectrum of disease and the number of treatment modalities is also increasing with otorhinolaryngology being at the forefront of technical innovations such as robotic surgery and 3D endoscopy. So if you thought all we did was remove tonsils and stop nose bleeds...things have changed.

WORKING AS AN OTORHINOLARYNGOLOGIST

Life as an Otorhinolaryngologist is particularly rewarding in many aspects ranging from the practical and procedural nature of the speciality to the wide range, diversity and complexity of the patients that we encounter. Like most surgical specialities much of the reward comes from the instant gratification of "fixing something" and ENT is unique in that this often becomes apparent in the early stages of training.

Despite being a relatively busy speciality 'in-hours', the vast majority of our work is preplanned and as a result an excellent work life balance can be achieved when compared to other surgical specialties. Most otorhinolaryngologists work between 1:6-7 weeks oncall, however in regional centres additional airway rotas exist which are currently 1:4. Currently there is a 60:40 male to female ratio in trainees with additional options to work part time or undertake research, while still being able to obtain excellent training opportunities.

Like all specialities in medicine and surgery an underlying core competency in clinical knowledge and reasoning is required. Otorhinolaryngology also requires excellent planning skills, the ability to engage with children and adults alike in often life threatening situations as well excellent hand-eye coordination, spacial awareness and dexterity.

Otorhinolaryngology is a diverse speciality managing a wide variety of elective conditions to life threatening emergencies and complex oncology work. Often combined clinics with plastic surgeons, neurosurgeons and pediatricians are required to comprehensively manage our patient population leading to excellent networking opportunities and a chance to see how other teams work. Most otorhinolaryngologist undertake between 2 and 3 outpatient sessions per week and during training this can occasionally be up to 4 sessions depending on the subspeciality. In addition most surgeons will undertake between 2 and 4 theatre sessions per week with trainees undertaking a minimum of 4 sessions. Other sessions are dedicated to SPA, administration and research and teaching opportunities.

THE TRAINING PROGRAM

During F1 and F2 years experience can be gained in ENT as either a 4 month placement during F2 or as a 1-2 week work experience post and this is essential in developing a rapport with staff as well as gaining some insight into what the job really entails! Following F2 competitive entry is via the Core Surgical Training program during which 6 month rotations are available. While undertaking one of these rotations the trainee will gain competency in managing common conditions both in outpatients and as emergency admissions. The Royal Colleges recommend a minimum of 12 months experience in otorhinolaryngology before application for higher surgical training in addition to completion of the Intercollegiate Surgical Exams and the Diploma of Otolaryngology and Head and Neck Surgery. Entry to higher surgical training is via competitive interview and at present occurs both locally and regionally (with local competition rates in 2013 of 1:21). Following selection to higher surgical training a further 6 years of training is to be carried out in four hospitals in Northern Ireland with specialized training in The Royal Victoria Hospital and The Royal Belfast Hospital for Sick Children. An ENT exit exam must be completed prior to completion of higher training. A selection of courses, publications and research should be completed during this time period. Opportunities for fellowships and out of program research degrees are also available.

THE FUTURE

As previously mentioned the speciality is expanding and diversifying and as a result will inevitably bring with it changes for the future in much the same way the HiB vaccine has almost made us redundant in managing epiglottitis. The challenges over the next decade will be the emergence of increasing numbers of young patients with HPV related oral and laryngeal cancers and the technological and pharmaceutical changes in how we manage these patients. If you enjoy dealing with a diverse patient population and like a speciality where each day is different from the last then otorhinolaryngology might be for you...but bear in mind you may need a Sherpa to get you to us as we reside in the most remote part of the Royal Victoria Hospital....Ward 29!

THE ULSTER MEDICAL JOURNAL

Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. United Kingdom.
Contact details: T/ F: (+44) 028 9097 5780 E: umj@qub.ac.uk W: www.ums.ac.uk

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1. Articles submitted for consideration should be typewritten in single spacing, with wide margins, preferably in Times Roman 12pt font. They should be fully corrected and alterations in proof may be disallowed or charged to the authors. Please submit electronic files on CD or memory stick along with **ONE** hard copy of each article (including tables and figures). Those unable to submit an electronic version should contact the editorial office. Colour images and tables are encouraged and there is currently no charge for colour reproduction. **Electronic copies of images and tables should be included as separate high resolution .jpg or .tif files and NOT embedded in the Word manuscript file.**

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