ISSN 0041-6193

THE ULSTER MEDICAL JOURNAL

Volume 78 (1) January 2009

Published by
THE ULSTER MEDICAL SOCIETY
www.ums.ac.uk

The Ulster Medical Journal

The Journal of the Ulster Medical Society. First published in 1932.
Successor to the Transactions of the Ulster Medical Society (1862-1929), and the
Transactions of the Belfast Clinical and Pathological Society (1854-1860)

The Ulster Medical Society was founded in 1862
by the amalgamation of the Belfast Medical Society (founded 1806)
and the Belfast Clinical and Pathological Society (founded 1853)

Editorial

Deliberate and accidental self-harm.

One of the great privileges of editing a journal is seeing how, through the peer review process, a journal issue often develops a subject theme without much help from the editorial staff. This issue contains three stark papers on a topical area of medicine – psychiatry – and particularly the areas of addiction, suicide and death. The incidence of suicide has been rising steadily in Northern Ireland and Largey *et al*[1] show how hanging – particularly in young males, is on the increase. This is mirrored by the increase in drug dependency and the perceived decline of values in society. Lucas[2] shows how nearly 15% of electrocutions have been suicides – again mostly males, the remainder being accidental, and there is a warning here for DIY enthusiasts (of either sex) to be careful about electrical safety. The good news, however is that opioid dependency treatment is showing increased efficacy with improvements in dependency and a reduction in physical, psychological and social problems[3].

THE ULSTER MEDICAL JOURNAL DIGITAL ARCHIVE

Searching the entire scanned archive of the *Ulster Medical Journal* for suicide and self harm, (which is now complete on Pub Med Central and includes volumes 1-74 (1932-2005) in addition to other back content and prospective issues from 2005[4]), produces 27 relevant articles. You may be interested to note that the use of Bromide of ammonium, which was cutting edge treatment in 'the depressive phase of Manic-Depressive insanity' as described by Robert Thompson[5] in an excellent review in 1941, has now been superseded by more evidence based treatments (figure 1).

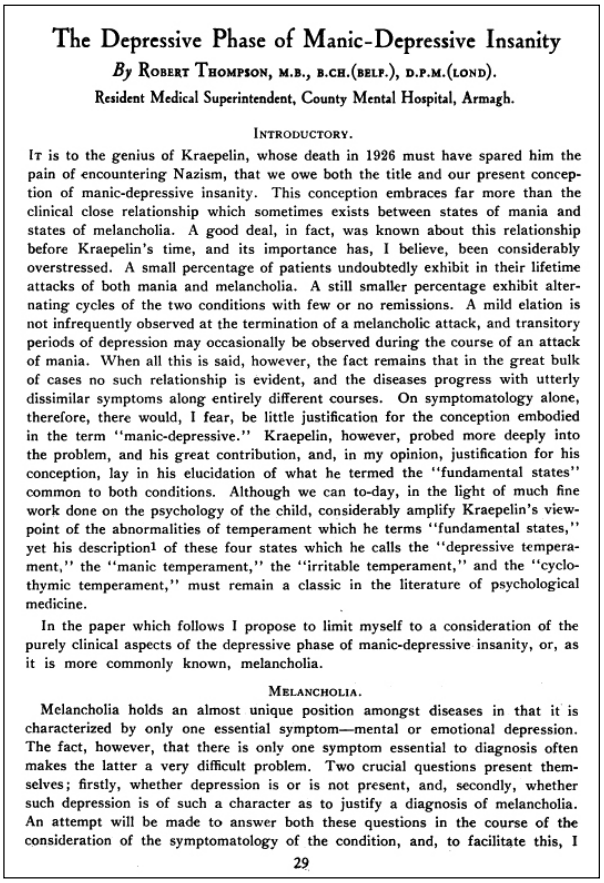
TRADITIONAL CURES

One area where the evidence base is sadly lacking is in alternative medical therapies and traditional cures. This issue attempts to redress that imbalance and in time for the festive season, provides evidence that although an eel skin bandage may not help sprains sustained during the season[6], those of you who added garlic to your turkey stuffing may now be reaping the benefit as it now appears to have some potent antibacterial and antifungal properties[7].

We thank all our reviewers for their help during 2008 and for all of you for sending in particularly high quality manuscripts this year - causing the acceptance bar to be raised to a higher standard than ever.

We wish you all a happy and successful 2009!

Patrick J Morrison, Honorary Editor.



The Depressive Phase of Manic-Depressive Insanity

By Robert Thompson, M.B., B.Ch.(Belf.), D.P.M.(Lond).

Resident Medical Superintendent, County Mental Hospital, Armagh.

Introductory.

It is to the genius of Kraepelin, whose death in 1926 must have spared him the pain of encountering Nazism, that we owe both the title and our present conception of manic-depressive insanity. This conception embraces far more than the clinical close relationship which sometimes exists between states of mania and states of melancholia. A good deal, in fact, was known about this relationship before Kraepelin's time, and its importance has, I believe, been considerably overstressed. A small percentage of patients undoubtedly exhibit in their lifetime attacks of both mania and melancholia. A still smaller percentage exhibit alternating cycles of the two conditions with few or no remissions. A mild elation is not infrequently observed at the termination of a melancholic attack, and transitory periods of depression may occasionally be observed during the course of an attack of mania. When all this is said, however, the fact remains that in the great bulk of cases no such relationship is evident, and the diseases progress with utterly dissimilar symptoms along entirely different courses. On symptomatology alone, therefore, there would, I fear, be little justification for the conception embodied in the term "manic-depressive." Kraepelin, however, probed more deeply into the problem, and his great contribution, and, in my opinion, justification for his conception, lay in his elucidation of what he termed the "fundamental states" common to both conditions. Although we can to-day, in the light of much fine work done on the psychology of the child, considerably amplify Kraepelin's viewpoint of the abnormalities of temperament which he terms "fundamental states," yet his description[1] of these four states which he calls the "depressive temperament," the "manic temperament," the "irritable temperament," and the "cyclothymic temperament," must remain a classic in the literature of psychological medicine.

In the paper which follows I propose to limit myself to a consideration of the purely clinical aspects of the depressive phase of manic-depressive insanity, or, as it is more commonly known, melancholia.

Melancholia.

Melancholia holds an almost unique position amongst diseases in that it is characterized by only one essential symptom—mental or emotional depression. The fact, however, that there is only one symptom essential to diagnosis often makes the latter a very difficult problem. Two crucial questions present themselves; firstly, whether depression is or is not present, and, secondly, whether such depression is of such a character as to justify a diagnosis of melancholia. An attempt will be made to answer both these questions in the course of the consideration of the symptomatology of the condition, and, to facilitate this, I

29

Fig 1. First page of the review by Robert Thompson from 1941.

REFERENCES

1. Largey M, Kelly CB, Stevenson M. A study of suicide rates in Northern Ireland 1984-2002. *Ulster Med J* 2009;**78(1):**16-20.
2. Lucas J. Electrical fatalities in Northern Ireland. *Ulster Med J* 2009;**78(1):**37-42.
3. Collins R, Boggs B, Taggart N, Kelly M, Drillington A, Swanton I, Patterson D. Efficacy of treatment in an opioid –dependent population group using the Maudsley Addiction Profile (MAP) tool. *Ulster Med J* 2009;**78(1):**21-25.
4. http://www.pubmedcentral.nih.gov/tocrender.fcgi?action=archive&journal=461 (Accessed 5th November 2008).
5. Thompson R. The Depressive Phase of Manic-Depressive Insanity *Ulster Med J* 1941;**10(1):**29-39.
6. Ballard LM. An approach to traditional cures in Ulster. *Ulster Med J* 2009;**78(1):**26-33.
7. Woods-Panzaru S, Nelson D, McCallum G, Ballard LM, Millar BC *et al.* An examination of antibacterial and antifungal properties of constituents described in traditional Ulster cures and remedies. *Ulster Med J* 2009;**78(1):** 13-15.

Ulster Med J 2009; **78 (1)** 2-3

Commentary

A High Quality Workforce

John Jenkins

Accepted 3 November 2008

Last summer, as part of the NHS next stage review, Lord Darzi, Ann Keen and David Nicholson (the NHS Chief Executive) published "A High Quality Workforce"[1]. In this report they emphasised that delivering the vision of a quality health service requires the provision of the best possible education and training for future generations, together with support for existing staff to continuously improve their skills. Professor John Tooke responded that the proposals in this document address many of the challenges set out in his inquiry report.

Box 1:
Darzi's six core principles:

focused on quality
patient centred
clinically driven
flexible
valuing people
promoting lifelong learning

The report sets out six core principles which should inform all the planned health service changes (Box 1), together with an explicit commitment to ensure that all models of care, service planning and consequent workforce planning link directly to eight pathways of care covering all the areas of clinical practice - from maternity and newborn care through to end of life care. The report highlights the importance of education curricula and training programmes integrally linked into current and emerging models of care, and into scientific and technological advances. All healthcare staff need to be supported with ongoing learning and continuing professional development, linked to patient, service and staff needs. As part of this best use needs to be made of modern educational techniques such as e-learning and simulation. This support is necessary if clinicians are to respond effectively to patient expectations, as well as in leadership, management, research and educational roles.

The report reflects the General Medical Council (GMC) core guidance *Good Medical Practice* which makes it clear that the first duty of the doctor is to *'make the care of your patient your first concern'*. Doctors are also to '*work with colleagues in the ways that best serve patients' interests'*[2]. Within the team approach which is essential for the delivery of modern healthcare clinicians' first and primary duty as **practitioners** will always be to deliver high quality care for patients based on their individual needs. To do this they must be **partners** in care delivery, with individual and collective accountability for the performance of health services and for the appropriate use of resources in the delivery of care. However, the report goes further - clinicians must also be prepared and trained to offer **leadership** within the clinical team, departments, organisations and the health service itself. This links closely to work undertaken by the GMC, Royal College of Physicians of London, the King's Fund and others in recent years to develop the concept of medical professionalism, including these three core roles of practitioner, partner and leader.

Patients and the public expect doctors to achieve accurate and timely diagnoses, ensure safety, help them navigate through the healthcare pathway(s), contribute appropriately in the clinical team, to healthcare research, development and innovation, and to train future generations of healthcare professionals. In order to support doctors to meet these expectations the report proposes the development of a reformed postgraduate training pathway for doctors covering the entire medical career from graduation to retirement. This will include development of plans to introduce modular credentialing for the medical workforce in order to give assurance to patients and employers that professionals have the right skills to deliver high quality care, to facilitate movement in and out of training programmes at the appropriate level, and to give greater flexibility to professionals to move between specialty training programmes or employers whilst having their capabilities and learning properly recognised. Training in leadership, management and teaching is to be integrated into postgraduate medical curricula for all junior doctors, with educational supervisors in secondary care undergoing mandatory training and review of their performance for this role (as currently exists in primary care). The current UK Consultant contract provides a framework within which this can be taken forward, but to date progress has been patchy in raising the profile of and adequately resourcing the education and training of medical students and doctors. The perceived conflict between the use of resources for these activities and the delivery of healthcare today must end – after all they are the necessary basis for the effective delivery of healthcare tomorrow.

Whilst the primary relevance and application of this report is to the English NHS, the principles are applicable to all UK healthcare systems. The months since its publication have

Senior Lecturer in Child Health & Consultant Paediatrician, Paediatric Department, Antrim Hospital, Antrim, BT41 2RL, United Kingdom.

Correspondence to Dr Jenkins j.jenkins@qub.ac.uk

provided time for reflection on its contents, and it is now vital that its implications for health and social care here result in early and effective action by the Department of Health, Social Services and Public Safety, the Northern Ireland Medical and Dental Training Agency, the Universities and all others involved in the commissioning and provision of healthcare and of medical education and training.

The author is chairman of the GMC Standards and Ethics Committee.

REFERENCES:

1. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085840 Last accessed November 2008.
2. www.gmc-uk.org/guidance/good_medical_practice/index.asp. Last accessed November 2008.

LIST OF REFEREES FOR 2008

We pass on our sincere thanks to all of our referees for 2008

Dr Derek Allen
Dr Christopher Armstrong
Dr Robin Ashe
Prof Patrick Bell
Dr Tim Beringer
Dr Richard Best
Mr Colman Byrnes
Prof Charles Campbell
Dr Neta Chada
Prof Stephen Cooper
Dr Paul Darragh
Dr Lisa Devlin
Dr Olivia Early
Dr Wesam Elbaz
Prof Stuart Elborn
Dr Peter Ellis
Prof Howard Fee
Dr Ian Fraser
Mr Ian Garstin
Dr Gerard Glynn
Dr Paul Hanley
Dr Stanley Hawkins
Dr Niall Herity
Dr Steven Hunter
Prof Denis Johnston
Dr Barry Kelly
Mr Stephen Kirk
Dr Mark Love
Dr Anne Loughrey
Dr Maurice Loughrey
Dr Claire Lundy
Dr Alex Magee
Prof Peter Maxwell
Dr John Moore
Prof Patrick Morrison
Dr Jim Morrow
Prof Rajinder Mirakhur
Dr Joe MacMahon
Mr Bill McCallion
Dr Conall McCaughey
Prof Glen McCluggage
Prof Neil McClure
Mr Kenneth McCune
Dr Rowan McClean
Dr Kieran McGlade
Dr Eugene McKenna
Mr Lloyd McKie
Prof Gary McVeigh
Dr Hans Nagar
Mr Jarsoslav Novak
Prof Victor Patterson
Prof Michael Patton
Dr Nambi Rajan
Dr Jackie Rendall
Dr Charles Shepherd
Prof Chee Soong
Professor Roy Spence
Dr Vinod Tohani
Dr Tong Lioe
Mr Michael Whiteside
Dr Colin Willoughby
Dr David Wilson

Ulster Med J 2009; **78 (1)** 4-6

Review

Magnet induced perforated appendicitis and ileo-caecal fistula formation.

Andrew J Robinson, Janne Bingham, Ronald LE Thompson

Accepted 1 September 2008

ABSTRACT

Foreign body ingestion is a common paediatric problem. In the majority of cases spontaneous passage occurs. Magnet ingestion is rare and solitary magnet ingestion usually does not cause any complications. A number of gastrointestinal complications have been reported, such as fistula formation, perforation and volvulus following multiple magnet ingestion. We review magnet ingestion and describe the first case in the literature of magnet induced perforated appendicitis with an associated ileo-caecal fistula.

Keywords: appendicitis, foreign body ingestion, magnets, small bowel fistula.

INTRODUCTION

Foreign body ingestion is frequent in children, particularly in those aged between 6 months and 3 years and is generally associated with little or no morbidity[1,2]. Fortunately, in 80% of cases, spontaneous passage will occur. However, 10% to 20% require endoscopic retrieval and in 1% of cases there may be complications requiring surgical intervention, such as intestinal obstruction, perforation or fistula formation[3].

Appendicitis is the commonest surgical emergency. The diagnosis is predominantly a clinical one. However, not all patients present in a typical manner. The cause of appendicitis is unknown but is thought to be multifactorial: luminal obstruction, dietary and familial factors have all been suggested[4].

ILLUSTRATIVE CASE REPORT:

A three year old boy was admitted to the paediatric surgical ward at a District General Hospital giving a one day history of acute crampy abdominal pain which was worse in his right side. The pain was associated with anorexia and four episodes of non-bilious vomiting. His last bowel motion was three days prior to admission (not unusual for this child). He was noted to be generally lethargic and reported a five day history of a non-productive cough and a one day history of a wheezy chest. This was associated with intermittent temperatures and coryzal symptoms. He had no past medical history.

On examination he was pyrexic with a temperature of 38.8°C. His abdomen was soft and non-tender. There was no peritonism, abdominal distension or organomegaly. Bowel sounds were present and normal.

Initial investigations showed a leucocytosis of 14.64 x 10^9/L (reference range 4.0 – 11.0) and an elevated C - reactive protein of 92 mg/L (reference range 0 – 10). His electrolyte profile was normal. Urinalysis showed ketones and a trace of blood.

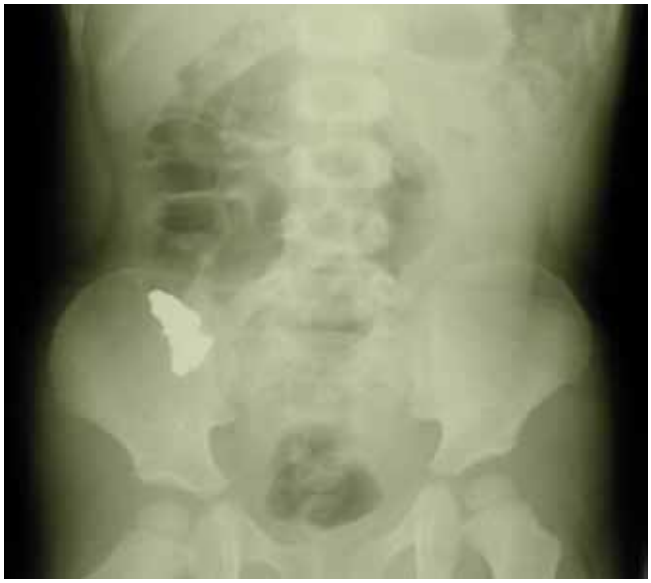


Fig 1. Abdominal X-ray: demonstrating a foreign body in the region of the ileo-caecal valve. There was no small bowel dilatation and there was air in the rectum.

Radiological investigations performed were an erect chest X-ray and plain abdominal X-ray. His chest X-ray showed no pneumoperitoneum and his abdominal film showed what appeared to be a foreign body in the region of the ileo-caecal valve (figure 1). It did not show any small bowel dilatation and there was gas evident in the rectum.

Initially, the boy was admitted for observation and conservative management. The following morning he was in severe pain, with right iliac fossa tenderness and localised peritonitis. He proceeded to laparotomy through a Lanz incision in the right iliac fossa. There was peritoneal contamination with turbid fluid, a perforation at the proximal end of the appendix was noted and there was an ileo-caecal

Department of Surgery, Altnagelvin Area Hospital, Glenshane Road, Londonderry, United Kingdom.

Correspondence to: Mr Robinson

arobinson13@hotmail.co.uk

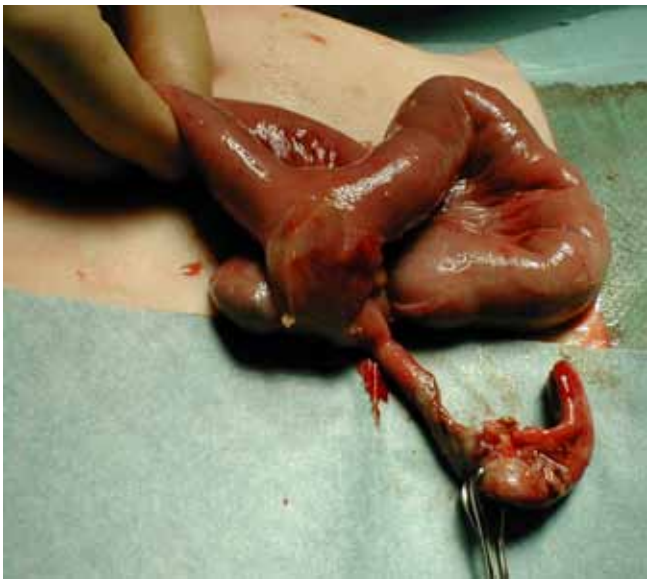


Fig 2. Intra-operative photograph demonstrating an ileo-caecal fistula and perforated appendix

Fig 3. Foreign bodies found in the caecum and ileum, which turned out to be magnets

fistula found 5cm proximal to the ileo-caecal valve (figure 2). Foreign bodies, which after removal were found to be magnets, were found in the caecum and in the terminal ileum (figure 3).

The appendix was resected and the fistula was taken down. Defects in the caecum and ileum were oversewn and peritoneal lavage was performed prior to closure of the abdomen. Post operative recovery was uneventful and the asymptomatic ileo-caecal fistula was coincidental.

On questioning the child's mother after the operation, it transpired that his elder sister had brought magnets home from a school trip some 3-4 months previously. We hypothesised that the boy had swallowed several magnets 3 - 4 months prior to his hospital admission.

DISCUSSION:

Ingestion of foreign objects is more common in children than in adults. There are about 100,000 cases annually in the United States of foreign body ingestion, with over 80% of these occurring in the paediatric population[3]. Historically, treatment algorithms for ingested foreign bodies have documented that the vast majority, approximately 80% of foreign bodies reaching the stomach, pass through the gastrointestinal tract spontaneously[5]. These patients can therefore usually be observed for the development of symptoms. Objects swallowed vary considerably and those that cause perforation can range from accidental cocktail stick ingestion[6], food such as chicken bones[7] right through to dangerous objects including razorblades and more serious items[8].

Magnet ingestion is rare. There have been thirteen reported cases. A history of solitary magnet ingestion usually does not cause any complications, but multiple magnet ingestion causes problems. Even though the majority of magnets are small enough to pass through the gastrointestinal tract, complications arise when magnets get separated as they pass through the pylorus into duodenum.

The pathogenesis of the complications is the attraction of two or more magnets across the walls of multiple loops of bowel. This causes ischaemia and necrosis of the pinched bowel wall leading to ulceration and eventually perforation or fistulation. Magnet ingestion has resulted in obstruction, fistula formation, ulceration, perforation, volvulus of the small and large intestine and strangulation of adjacent loops of small bowel between the attracted segments[1-3, 9-12].

Clinically, it is safe to observe the ingestion of a solitary magnet that has reached the stomach. The ingestion of multiple magnets should prompt immediate referral for endoscopy and attempted removal[1,11]. Magnets in the stomach can generally be removed via endoscopy and a magnetic tube. For those that have passed into the duodenum and travelled more distally, careful observation with serial abdominal X-rays is accepted initial management. Once symptoms of increasing abdominal pain or signs of intestinal obstruction or perforation develop then prompt exploratory laparotomy should be performed[9].

There are no reports of magnet ingestion being associated with or causing appendicitis. We believe the mechanism in this case was luminal obstruction by a magnet occluding the appendix orifice, leading to its perforation.

CONCLUSION.

Magnet ingestion is rare. Multiple magnets within the stomach require endoscopic retrieval in an attempt to avoid subsequent complications. Once multiple magnets have entered the small bowel, they can cause numerous gastrointestinal complications including perforation of the appendix and fistula formation.

The authors have no conflict of interest.

REFERENCES:

1. Wildhaber BE, Le Coultre C, Genin B. Ingestion of magnets: innocent in solitude, harmful in groups. *J Pediatr Surg* 2005;**40(10):**e33-35.

2. Hernández Anselmi E, Gutiérrez San Román C, Barrios Fontoba JE, Ayuso González L, Valdés Dieguez E, Lluna González J, Roca Molla A, García-Sala Viguer C, Gómez Montes J, Cortina Orts H. Intestinal perforation caused by magnetic toys. *J Pediatr Surg* 2007;**42(3):**E13-6.

3. Butterworth J, Feltis B. Toy magnet ingestion in children: revisiting the algorithm. *J Pediatr Surg* 2007**;42(12):**E3 – E5.

4. Larner AJ. The aetiology of appendicitis. *Br J Hosp Med* 1988;**39(6):**540-542.

5. Vijaysadam V, Perez M, Kuo D. Revisiting Swallowed Troubles: Intestinal complications caused by two magnets – A case report, review and proposed revision to the algorithm for the management of foreign body ingestion. *J Am Board Fam Med* 2006;**19(5):**511-516**.**

6. Lindsay R, White J, Mackle E. cocktail stick injuries – the danger of half a stick. *Ulster Med J* 2005;**74(2):**129-131.

7. Aktar S, McElvenna N, Gardiner KR, Irwin ST. Bowel perforation caused by swallowed chicken bones – a case series. *Ulster Med J* 2006;**76(1):**37-38.

8. Bisharat M, O'Donnell ME, Gibson N *et al.* Foreign body ingestion in prisoners – the Belfast experience. *Ulster Med J* 2008;**77(2):**110-4.

9. Chung JH, Kim JS, Song YT. Small bowel complication caused by magnetic foreign body ingestion of children: two case reports. *J Pediatr Surg* 2003**;38(10):**1548 – 1550.

10. Lee SK, Beck NS, Kim HH. Mischievous magnets: unexpected health hazard in children. *J Pediatr Surg* 1996;**31(12):**1694-95.

11. Pryor HI, Lange PA, Bader A Gilbert J, Newman K. Multiple magnetic foreign body ingestion: a surgical problem. *J Am Coll Surg* 2007;**205(1):**182-6.

12. Nui A, Hirama T, Katsuramaki T, Maeda T, Meguro M, Nagayama M, Matsuno T, Mizumoto T, Hirata K. An intestinal volvulus caused by multiple magnet ingestion: an unexpected risk in children. *J Pediatr Surg* 2005;**40(9):**e9-11.

Ulster Med J 2009; **78 (1)** 7-9

Review

Surfactant Metabolism Dysfunction and Childhood Interstitial Lung Disease (chILD)

Lynne McFetridge[1], Aoife McMorrow[1], Patrick J Morrison[3], Michael D Shields[1,2]

Accepted 1 September 2008

SUMMARY

Surfactant deficiency and the resultant respiratory distress syndrome (RDS) seen in preterm infants is a major cause of respiratory morbidity in this population. Until recently, the contribution of surfactant to respiratory morbidity in infancy was limited to the neonatal period. It is now recognised that inborn errors of surfactant metabolism leading to surfactant dysfunction account for around 10% of childhood interstitial lung disease (chILD). These abnormalities can be detected by blood sampling for mutation analysis, thereby avoiding the need for lung biopsy in some children with chILD.

Key Words: Surfactant, child, mutation analysis.

INTRODUCTION

The role of surfactant deficiency in the development of RDS in preterm infants has long been appreciated and surfactant replacement is now a well established treatment modality. Term infants can also present with the clinical picture of RDS as a result of surfactant inactivation, secondary to conditions such as meconium aspiration or congenital pneumonia. However, it is less well known that inborn errors of surfactant metabolism leading to surfactant dysfunction are now thought to be an important cause of childhood interstitial lung disease.

chILD

Childhood interstitial lung disease (chILD) is much rarer than interstitial lung disease (ILD) in adults and is typically associated with respiratory distress, diffuse infiltrates on chest imaging and abnormal lung histology. ChILD, like ILD in adults, comprises a spectrum of heterogeneous disorders. Until recently these have been poorly described, with the relevant literature consisting of case reports and small case series only. Previous attempts to classify chILD on the basis of the lung histology have used adult classifications, but it is now recognised that the histology and associated clinical outcome seen in children, especially those under 2 years, differs significantly from that of adults. Common histopathological findings of ILD in adults include desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP) and usual interstitial pneumonia (UIP). UIP has not been reported in any paediatric cases to date. Although some overlap in histology does occur, for example with DIP, chILD is associated with a different aetiology compared to adults. This further emphasises that the adult classification of ILD is of little benefit in defining ILD in children. A recent review of 187 open lung biopsies in young children has identified pathology largely unique to children presenting in infancy, the majority presenting as either a term baby with features of RDS or with 'chronic tachypnoea of infancy'. The underlying histology, clinical course and resultant prognosis have been described[1] and are summarized in Table I.

The overall mortality associated with chILD is 21%[2], but almost all deaths occur in those with developmental lung disorders and some of the surfactant deficiencies. In contrast, infants with pulmonary interstitial glycogenosis (PIG) or neuroendocrine cell hyperplasia of infancy (NEHI) often demonstrate significant clinical improvement over time. Although the presentation of these disorders is often similar, the age at presentation offers an important clue to the underlying diagnosis and subsequent prognosis. Children under two years with ILD present either in the neonatal period or in early infancy.

NEWBORN WITH chILD

This is commonly a term infant who presents shortly after birth with severe parenchymal lung disease causing respiratory distress and oxygen requirement. Both the clinical presentation and the radiological features of diffuse ground glass opacities are similar to those more typically seen with prematurity and surfactant deficiency. Differential diagnoses such as pneumonia or meconium aspiration syndrome, leading to transient surfactant inactivation, must be excluded. Despite intensive respiratory support with mechanical ventilation, inhaled nitric oxide or ECMO, this presentation is almost invariably fatal. The types of chILD associated with such an early and aggressive course include disorders of lung development (alveolar dysplasia and alveolar capillary dysplasia) and two of the surfactant dysfunction disorders (surfactant protein B deficiency and ABCA3 gene mutations - although the latter may also have a less severe clinical course). PIG can also present perinatally but has a much more favourable outcome relative to the other causes, with very low reported mortality.

[1]Royal Belfast Hospital for Sick Children, [2]Department of Child Health, Queens University Belfast, Grosvenor Road, Belfast BT12 6BA. United Kingdom and [3] Northern Ireland Regional Genetics Centre, Belfast Trust, Belfast BT9 7AB, United Kingdom.

Correspondence to: Michael D Shields, Professor of Child Health, Dept. Of Child Health, Clinical Institution, Queen's University Belfast, Grosvenor Road, Belfast, BT12 6BJ.

m.shields@qub.ac.uk

Table I:

Classification of interstitial lung disease in children less than 2 years

Disorders	Prevalence
Primary Disorders of Lung Development (Aberration in primary molecular mechanism of lung and/or pulmonary vascular development)	5.8%
Lung Growth Abnormality (Impaired pre or post natal alveolarisation, largely secondary)	24.6%
Pulmonary Interstitial Glycogenosis (PIG)	3.2%
Neuroendocrine cell hyperplasia of infancy (NEHI)	9.6%
Surfactant Dysfunction Disorders	9.6%
Miscellaneous (e.g. systemic disease processes, immunocompromised states)	35.5%
Unable to classify	11.7%

INFANT WITH chILD

This group of children with ILD present with 'chronic tachypnoea of infancy', usually in the first few months of life. Clinically this is characterised by persistent tachypnoea, hypoxia, crackles and intercostal recession. The ongoing oxygen requirement and increased work of breathing cause failure to thrive. Important differential diagnoses in these children are cystic fibrosis, aspiration and immunodeficiency with recurrent infection. These must be excluded before chILD is considered. A number of conditions can give rise to chILD in infancy and include PIG, NEHI, surfactant protein C deficiency and less commonly ABCA3 gene mutations. The majority of the infants with these diagnoses experience clinical resolution over time.

The ability to define chILD using both the clinical picture and lung histology, is an extremely important development as it ensures that the most appropriate treatment and counselling are offered to children and their families. However, the recent development that surfactant dysfunction disorders underlie up to 10% of chILD may avoid the need for lung biopsy with its associated potential risks, as these conditions can be identified by genetic testing.

SURFACTANT DYSFUNCTION DISORDERS

Pulmonary Surfactant

Pulmonary surfactant is a complex mixture of phospholipids and proteins, with surfactant proteins A, B and C constituting 10% of surfactant. It is secreted by type II epithelial cells into the airways of the lung from 24 weeks gestation, although only in adequate amounts from 35 weeks gestation. Its main role is to reduce surface tension in the alveoli following the onset of breathing thereby facilitating lung expansion and preventing alveolar collapse during expiration. Following birth, mechanical stretch of the lung further contributes to the secretion of lamellar bodies, the intracellular storage granules of surfactant, which unravel to form extended tubes and sheets characterised by the formation of tubular myelin. Both surfactant proteins A and B and surfactant lipids are necessary for the formation of tubular myelin. The surfactant forms a film at the alveoli-air interface, which is respread after each expiration to maintain a low surface tension and prevent lung collapse. The spreading and stability of the surfactant film requires SP-B and SP-C. Following secretion, both surfactant proteins and lipids are recycled by the respiratory epithelium. As well as reducing surface tension, surfactant also plays a role in the innate host defence of the lung. Surfactant protein

Table II:

Surfactant metabolism dysfunction 1,2 and 3 genes.

Gene	Type 1 (SFTP-B)	Type 2 (SFTP- C)	Type 3 (ABCA3)
MIM numbers	265120, 178640	610913, 178620	610921, 601615
Inheritance	Autosomal recessive	Autosomal dominant, sporadic	Autosomal recessive
Chromosome	2p12-11.2	8p21	16p13.3
Clinical features	Neonatal respiratory failure and death	Infantile and older chILD with respiratory failure	Neonatal and early infantile respiratory failure. Some cases reported of older children with similar pattern to adult DIP
Lung histology	Alveolar type II cell hyperplasia and alveolar proteinosis, interstitial inflammation and fibrosis	Variety of patterns including DIP, UIP, non-specific interstitial pneumonitis	Alveolar type II cell hyperplasia, accumulation of macrophages and proteinacious material in airspaces

A and D primarily exert their effect in this area and are not necessary for the other functions of surfactant. ABCA3 is present in the membranes of the lamellar bodies in type II alveolar cells, where its main function is the transport of lipids important for surfactant.

It is now known that surfactant proteins B, C and ABCA3 are necessary for surfactant homeostasis and mutations in the genes encoding these proteins leads to surfactant dysfunction, giving rise to both lethal and chronic respiratory disease in infants (table II).

Surfactant Protein B

Surfactant protein B deficiency is invariably fatal within the first few months of life. It is an autosomal recessive condition, most commonly due to a mutation at 121ins2. Gene frequency of this mutation is estimated to between 1 in 1000 to 1 in 3000[3]. Infants present soon after birth with both clinical and radiological features of respiratory distress syndrome, which has a rapidly progressive course. This is refractory to standard therapies such as surfactant replacement and assisted ventilation, with the only effective treatment being a lung transplant. Lung histology shows pulmonary alveolar proteinosis (PAP).

Surfactant Protein C

Surfactant protein C is encoded by the SFTPC gene on chromosome 8. Inherited surfactant protein C deficiency is a rare cause of both acute and chronic lung disease in both infants, children and into adulthood. Infants usually present with interstitial lung disease that may be exacerbated by respiratory infections. Histologically the condition is characterised by chronic pneumonitis of infancy (CPI) or non-specific interstitial pneumonitis (NSIP)[4]. As with some other surfactant deficiencies, the only effective management is lung transplantation. Definitive diagnosis is made by genetic testing to identify the SFTPC gene.

Surfactant Protein ABCA3

ABCA3 is an ATP-binding transporter of lipids found in the membrane of lamellar bodies in type II alveolar cells. Initially mutations in this gene were thought to cause fatal lung disease in term neonates, but it is now recognised as a cause of chronic interstitial lung disease in older patients. One study looking at nine children with surfactant protein ABCA3 mutations found that the range of presentation in these children varied from birth to four years[5]. Clinical features found included cough, crackles, clubbing and failure to thrive. Histopathological findings from lung biopsy were variable and included pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonitis (DIP) and non-specific interstitial pneumonitis (NSIP). In one cohort of eight patients, three had lung transplantation and a further five children who did not require transplant had survived up to 18 years at the time of publication. Although some children clearly have a milder course, this mutation can cause severe respiratory insufficiency leading to death[6].

CONCLUSIONS

chILD represents a varied group of disorders which are difficult to distinguish on clinical presentation and examination alone. The importance of obtaining an accurate diagnosis cannot be overstated as there is considerable disparity between the morbidity and mortality of these disorders. In the past, lung biopsy has been the only useful investigation and the diagnostic gold standard despite the potential complications associated with it. However, the identification of the genes responsible for surfactant dysfunction disorders avoids the need for a biopsy in approximately 10% of children. We therefore suggest that blood sampling for gene analysis be offered to all infants presenting with ‘chronic tachypnoea of infancy’ as the initial investigation and that lung biopsy is considered only if gene analysis is normal.

Conflict of interest: the authors have no conflict of interest to declare.

REFERENCES

1. Deutch GH, Young LR, Deterding RR, Fan LL, Dell SD, Bean JA *et al.* Diffuse Lung Disease in Young Children: Application of a Novel Classification Scheme. *Am J Respir Crit Care Med* 2007;**176(11)**:1120-1128.
2. Fan LL. Evaluation and therapy of chronic interstitial pneumonitis in children. *Curr Opin Pediatr* 1994;**6(3)**:248-254.
3. Cole FS, Hamvas A, Rubinstein P, King E, Trusgnich M, Nogee LM, deMello DE, Colten HR. Population-based estimates of surfactant protein B deficiency. *Pediatrics* 2000;**105(3):**538-41.
4. Whitsett JA, Weaver TE. Hereditary Disorders of alveolar homeostasis in the newborn. In: The Newborn Lung. Neonatology Questions and Controversies. Editors: Eduardo Bancalari, Richard A Polin. Saunders Elsevier, 2008 Chapter 2, Pages 42-49.
5. Doan ML, Guillerman RP, Dishop MK, Nogee LM, Langston C, Mallory GB, Sockrider MM, Fan LL. Clinical, radiological and pathological features of ABCA3 mutations in children. *Thorax* 2008;**63(4)**:366-373.
6. Anandarajan M, Paulraj S, Tubman R. ABCA3 Deficiency: an unusual cause of respiratory distress in the newborn. *Ulster Med J* 2009;**78(1):**51-52.

Ulster Med J 2009; **78 (1)** 10-12

Mini - Review

Total Jejunoileal Intussusception: A Case Report and Literature review

Ros Smyth, William A McCallion§ Anne Paterson

Accepted 1 September 2008

ABSTRACT

Small bowel intussusceptions are much less common than the ileocolic type, with jejunoileal intussusceptions being amongst the most rare[1]. We review the literature on small bowel intussuception, using a case of an 11-year-old girl with a jejunoileal intussusception involving the whole of the small bowel, from the level of the duodenojejunal flexure to the ileocaecal valve, as an illustrative history. The typical CT features of an intussusception and value of CT with regard to identification of complications are highlighted.

Key Words: Small bowel intussusception, Polyp, CT scan.

INTRODUCTION

Small bowel intussusceptions (SBI) are much less common than the ileocolic variety, with jejunoileal and duodenojejunal intussusceptions being the rarest types of all[1]. SBI may be difficult to diagnose preoperatively, with a consequent increase in ischaemic complications, secondary to delayed surgery.

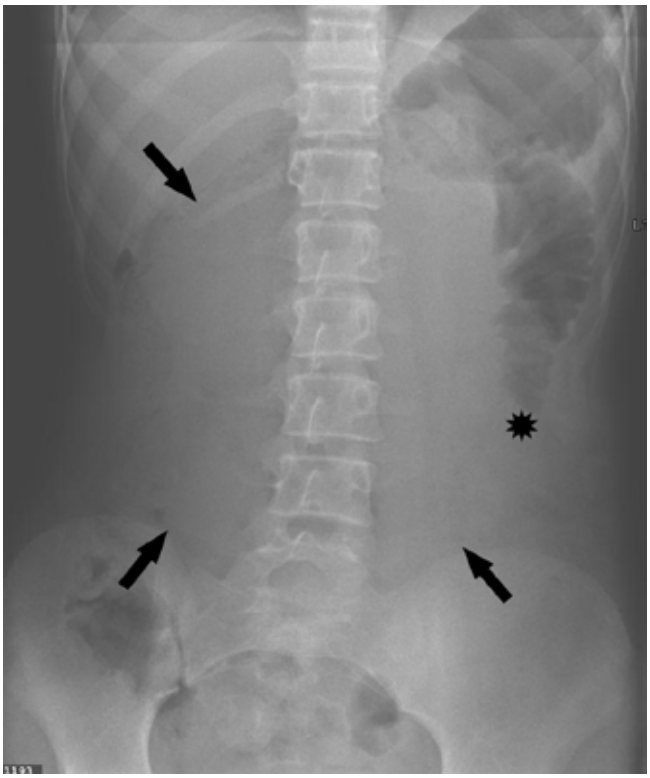


Fig 1. Abdominal radiograph demonstrating a large, central abdominal mass (arrows) and an associated high small bowel obstruction (asterisk).

ILLUSTRATIVE CASE REPORT

An 11-year-old girl was admitted with an 8-hour history of acute abdominal pain. On physical examination, she was clinically anaemic, shocked and had a palpable central abdominal mass. A past history of iron deficiency anaemia had been attributed to a poor dietary intake.

A plain abdominal radiograph (Fig.1) confirmed the presence of the mass, and showed gaseous distension of the stomach and (displaced) duodenum. Following fluid resuscitation, the duty surgeon requested an emergency CT scan of the abdomen and pelvis, both to determine the cause of the mass, and to aid in his decision as to the timing of an exploratory laparotomy. The CT images (Fig.2) demonstrated an enormous small bowel intussusception, which extended from the duodenojejunal flexure (DJF) to the ileocaecal valve. The colon was clearly seen to be separate from the mass. Fluid was trapped between the layers of bowel, and lying freely in the pelvis. The bowel loops caught up in the mass enhanced poorly, indicative of ischaemia. Axial source images at the level of the superior mesenteric vessels showed them to be dragged over to the left side and entangled in the intussuscepted loops, reminiscent of a small bowel volvulus.

Surgery performed later on that same evening, confirmed the CT findings. The intussusception was successfully reduced, and a proximal jejunal polyp was found to have acted as a pathological lead point. Mesenteric venous thrombosis and consequent bowel wall ischaemia necessitated a total of four further laparotomies, for resection of non-viable bowel and an ischaemic stricture. Four months following her emergency admission, the patient was finally discharged from hospital. She has been left with 200cm of small bowel, and an intact ileocaecal valve and colon. The surgical team remain optimistic about her future, and she was progressing well when seen at her first outpatient visit. It remains speculative, but it is possible that the jejunal polyp removed at surgery may have been responsible for her chronic iron deficiency anaemia.

Department of Radiology and §Paediatric Surgery, Royal Belfast Hospital for Sick Children, 180 Falls Road, Belfast BT12 6BE

Correspondence to Dr Anne Paterson,

annie.paterson@belfasttrust.hscni.net

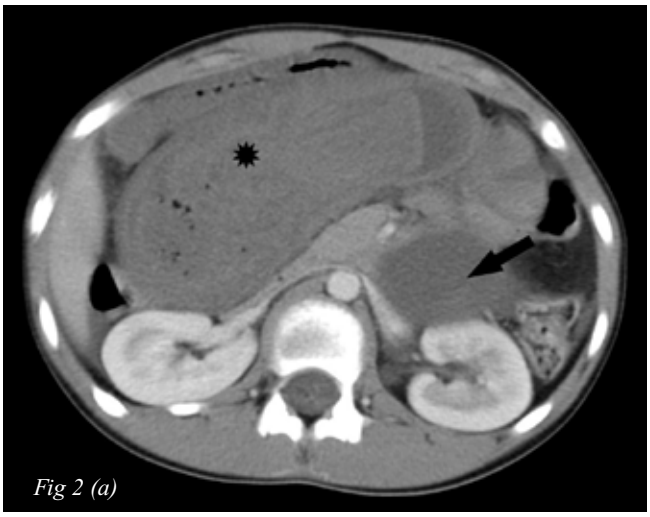


Fig 2 (a)

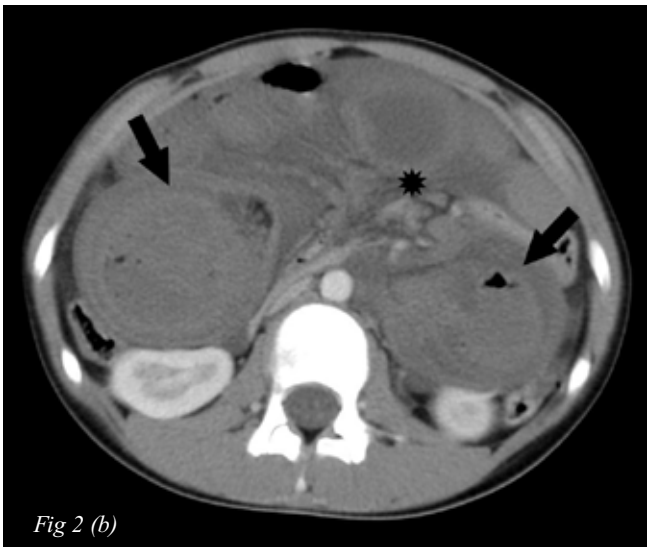


Fig 2 (b)

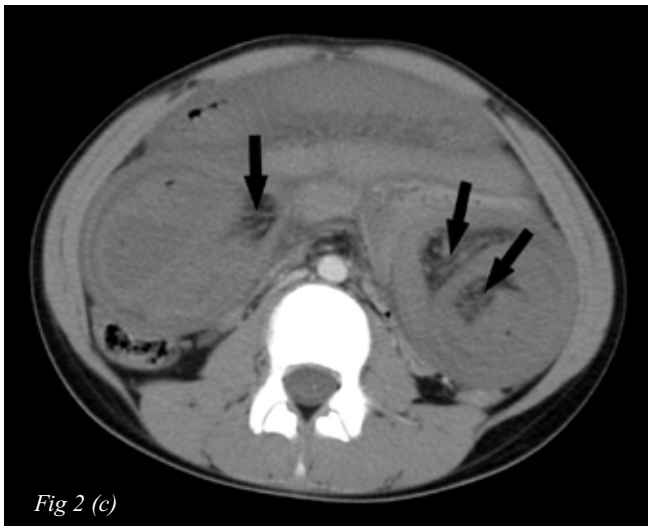


Fig 2 (c)

Fig 2 (a). Axial CT image at the level of the superior mesenteric artery origin, where the 3rd part of the duodenum crosses anterior to the spine. The start of the intussusception is seen as a fluid filled structure, to the left of the midline at the DJF (arrow). More anteriorly lie further components of the intussusception (asterisk) (shown to be one contiguous mass on consecutive images). (b) Axial CT image at the level of the lower poles of the kidneys. The layers of the intussusception are clearly visualised, with fluid trapped between them (arrows). The superior mesenteric vessels are displaced to the left side and appear twisted, reminiscent of a small bowel volvulus (asterisk). The bowel wall is thickened and enhances poorly, in keeping with ischaemia. The ascending and descending limbs of the colon are seen lying posteriorly adjacent to the kidneys, and separate from the intussusception (c) Axial CT image at a more caudal level. Layers of fat are seen trapped within the intussusceptum (arrows).

DISCUSSION

Ileocolic intussusception is one of the most common causes of an acute abdomen in children and has a characteristic clinical picture of vomiting, red 'currant jelly' stools, severe colicky abdominal pain and mass. The incidence of acute intussusception in Europe is reported to range from 0.66 to 2.24 cases per 1000 children[2]. 70% of cases occur in the first year of life with the incidence declining rapidly thereafter to less than 2% of cases in 10-15 year olds. SBI is unusual, representing 1-10% of all intussusceptions but up to 50% of cases in older children. Ileoileal, jejunojejunal, jejunoileal and duodenojejunal intussusceptions are described in descending order of frequency. Subacute presentation of SBI is typical and therefore difficult to diagnose preoperatively, leading to an increased risk of ischaemic complications[3,4].

A 2-3cm doughnut-like lesion found in the left abdomen or paraumbilical region with ultrasound is suspicious for SBI. An intussusception length >3.5cm has been reported as a sensitive and specific predictor of those SBIs that require surgical intervention, as compared to those that will resolve spontaneously[5,6]. The diagnosis of SBI can confidently be made with CT, due to their virtual pathognomic appearance: they are seen as a complex soft tissue mass, with a target, layered, sausage-shape or reniform configuration. An eccentric area of fat density within the mass represents intussuscepted mesenteric fat, and the mesenteric vessels themselves may be visible within this fat layer[7]. The superior anatomic detail of CT over ultrasound, mean that ensuing complications such as mesenteric thrombosis or small bowel volvulus may also be easily recognised. Whilst ultrasound remains the primary imaging modality used both to diagnose intussusception and for the evaluation of an abdominal mass lesion, the clinical condition of the patient (as in this case), may dictate that CT be sometimes used as a first-line investigation. It was additionally of value as the size of the intussusception may have led to an errant diagnosis of a large bowel intussusception, unnecessary therapeutic enema and delay of appropriate surgery.

CONCLUSION

Intussusception is an unusual but important differential in older children presenting with an acute abdomen. In this scenario CT may have a significant diagnostic advantage over ultrasound.

The authors have no conflict of interest

LEARNING POINTS.

- Intussusception should be considered in the differential diagnosis of all children who present with an acute abdomen, regardless of age.
- Small bowel intussusceptions cannot be reduced with air (or fluid) enema techniques.
- Ultrasound remains the first line imaging investigation both in children who present with an abdominal mass and in those in whom intussusception is clinically suspected.
- CT is of value in those children in whom complex intra-abdominal mass lesions are detected or when the presenting clinical picture is complicated.

REFERENCES

1. Koh EP, Chua JH, Chui CH, Jacobsen AS. A report of 6 children with small bowel intussusception that required surgical intervention. *J Pediatr Surg* 2006;**41(4)**:817-20.
2. Huppertz HI, Soriano-Gabarró M, Grimprel E, Franco E, Mezner Z, Desselberger U *et al.* Intussusception among young children in Europe. *Pediatr Infect Dis J* 2006;**25(1 Suppl)**:S22-9.
3. Reijnen JA, Joosten HJ, Festen C. Intussusception in children 5-15 years of age. *Br J Surg* 1987;**74(8)**:692-3
4. Schuh S, Wesson DE. Intussusception in children 2 years of age and older. *CMAJ* 1987;**136(3)**:269–272.
5. Munden MM, Bruzzi JF, Coley BD, Munden RF. Sonography of pediatric small-bowel intussusception: differentiating surgical from nonsurgical cases. *AJR Am J Roentgenol* 2007;**188(1):**275-79.
6. Lvoff N, Breiman RS, Coakley FV Lu Y Warren RS. Distinguishing features of self-limiting adult small-bowel intussusception identified at CT. *Radiology* 2003;**227(1)**:68-72.
7. Gayer G, Zissin R, Apter S, Papa M, Hertz M. Pictorial review: adult intussusception – a CT diagnosis. *Br J Radiol* 2002;**75(890):**185-90.

Ulster Med J 2009; **78 (1)** 13-15

Paper

An examination of antibacterial and antifungal properties of constituents described in traditional Ulster cures and remedies

Simon Woods-Panzaru[1,2], David Nelson[3], Graham McCollum[3], Linda M Ballard[4], B Cherie Millar[1], Yasunori Maeda[1,5], Colin E Goldsmith[1], Paul J Rooney[1], Anne Loughrey[1], Juluri R Rao[3], John E Moore[1,5]

Accepted 1 October 2008.

ABSTRACT

Traditional herbal cures and remedies have played an important historical role in the treatment of a variety of illnesses and diseases in Northern Ireland for the last three hundred years. Recently, these have been reviewed in the publication by Linda Ballard from the Ulster Folk and Transport Museum at Cultra, Co. Down, which details the variety of local plants used and for what purpose. From this publication and another related publication, we note the description of several plant species that consistently appear in traditional cures and remedies, particularly used to treat infections and infectious diseases. Unfortunately, although these plants have strong associations with the local historical evidence base, there are very limited and mainly no formal publications in the medical/scientific evidence base, examining their scientific background and clinical efficacy.

INTRODUCTION

Since the discovery and exploitation of antibiotic agents in the 20th century, the targeted selective toxicity of such agents has ensured their widespread and largely effective use to combat infection, however it has paradoxically resulted in the emergence and dissemination of multi drug resistant pathogens. Antimicrobial resistance in both medicine and agriculture is now recognized by the World Health Organisation (WHO), along with other various national authorities, as a major emerging problem of public health importance. It represents a significant challenge of global dimensions to human and veterinary medicine with the prospect of therapeutic failure for life-saving treatments now a reality. In order to minimise the potential development of further antimicrobial resistance "*The Copenhagen Recommendations: Report from the Invitational EU Conference on The Microbial Threat*" were published (http://www.im.dk/publikationer/micro98/index.htm), which outlined the need for the development of "*Novel principles for treating or preventing infections in humans and animals.*" Such an approach may thus be to examine the antimicrobial properties of native plants used in herbal medicine, as a novel source of such agents, as well as the employment of such novel compounds, and thus limit the use of conventional antibiotics to cases of severe and life-threatening infections, thus minimising the development of resistance to such agents. Although several traditional plant extracts have historically been known to have antimicrobial activity, to date, there has been relatively little or in some cases, no reports examining the activity against several medically important bacterial and fungal pathogens.

The aim of this small study was to scientifically examine the antimicrobial properties of seven plant species, all native to N. Ireland and which have been associated as the principal consitituents in several local traditional cures and remedies.

METHODS

Seven plant species were selected from previous literature[1,2] and included (i) cloves of garlic *(Allium sativum)*, (ii) onion *(Allium cepa),* (iii) Yarrow leaf (*Achillea millefolium)*, (iv) Meadow sweet leaf (*Filipendula ulmaria*), (v) Confrey leaf (*Symphytum officinale)*, (vi) Ragwort (*Senecio jacobaea*) and (vii) Dandelion leaf and roots (*Taraxacum officinale).* These plants were identified botanically and approximately 100g fresh weight of each were collected from the grounds of the Ulster Folk & Transport Museum, Cultra, Co. Down [54°39'05.23"N; 5°47'50.73"W] in June 2008. The harvested plants were divided into subsamples comprising leaf, stem and root tissues only. For the extraction of aqueous components from each plant, a recorded fresh weight of each subsample type was added to three times that weight (volume) of sterile distilled water in a Braun Food Processor and homogenised. This pureed sample was transferred to a suitably sized Schott bottle, capped and incubated overnight at ambient temperature on an orbital shaker at 150 rpm. Extracts were then centrifuged at 9000xg for 10 minutes using an Heraeus Biofuge Primo R centrifuge. Following this, the supernatants were carefully decanted to fresh containers and placed in an Edwards Supermodulyo Freeze drier, at -40°C for a minimum of 48 hours or until complete dryness. For assay purposes, a recorded weight of freeze dried powder was reconstituted

[1] Northern Ireland Public Health Laboratory, Department of Bacteriology, Belfast City Hospital, Lisburn Road, Belfast, Northern Ireland, BT9 7AD, [2]Clongowes Wood College SJ, Clane, Co. Kildare, Ireland, [3]Applied Plant Science Division, Agri-Food & Biosciences Institute, Newforge Lane, Belfast, Northern Ireland, BT9 5PX, [4]Ulster Folk and Transport Museum, Cultra, Holywood, Co. Down, Northern Ireland, BT18 0EU, [5]School of Biomedical Sciences, Centre for Molecular Biosciences, University of Ulster, Cromore Road, Coleraine, Co. Londonderry, Northern Ireland, BT52 1SA.

Correspondence to Professor Moore

jemoore@niphl.dnet.co.uk

with an equal weight/volume of sterile 0.1% (w/v) peptone saline (CM0733, Oxoid Ltd., Basingstoke, UK) to give a known concentration for each extract solution, as detailed in Table I. For the onion and garlic extracts, fresh produce was peeled, finely chopped and stomached at ambient temperature employing a Stomacher 400 (Fisher Scientific Ltd., UK) for 15mins, prior to recovery of supernatant, which was subsequently filter-sterilised through a 0.22 syringe filter (Millipore Inc., USA), before microbiological challenge.

Thirty four microorganisms, including 24 bacteria and 10 fungi were challenged in this study to ascertain the antimicrobial properties of the eight plant extracts as detailed above. Of the bacterial isolates selected, 15 were Gram-negative organisms, which included seven genera, as well as nine Gram-positive organisms from four genera. Of the fungi examined, five were yeasts, with the remaining five being filamentous fungi, from five genera overall. These organisms and their origins are detailed in Table I. In order to prepare the inocula for challenge, all organisms were cultured

TABLE 1:

Results of antibacterial and antifungal activity of eight different aqueous plant extracts challenged with 34 pathogenic bacterial and fungal isolates.

Blank = no inhibition; *, fresh undiluted extracts; NCTC = National Collection of Type Cultures; NCIMB = National Collection of Industrial Food and Marine Bacteria; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-sensitive *Staphylococcus aureus*; QC=quality control isolate; ATCC=American Type Culture Collection.

	Diameter of zone of inhibition (mm)								
Organism/concentration (mg/ml)	**Garlic (*Allium sativum*) ***	**Onion (*Allium cepa*) ***	**Yarrow leaf (*Achillea millefolium*)** [100mg/ml]	**Meadow sweet leaf (*Filipendula ulmaria*)** [150mg/ml]	**Confrey leaf (*Symphytum officinale*)** [50mg/ml]	**Ragwort (*Senecio jacobaea*)** [150mg/ml]	**Dandelion leaf (*Taraxacum officinale*)** [130mg/ml]	**Dandelion root (*Taraxacum officinale*)** [200mg/ml]	**Ciprofloxacin** [5μg disk]
Bacteria									
***Bacillus cereus* NCTC 7464**									**24**
***Bacillus subtilis* NCTC 10400 (NCIMB 8054)**	**19**								**33**
***Bacillus pumilus* (wildtype hand isolate)**	**15**								**26**
***Cupriavidus* sp.**									**27**
***E. coli* NCTC 25922**	**16**								**29**
***E. coli* NCTC 9001**									**27**
***E.coli* 0157 NCTC 12900**	**15**								**27**
***E.coli* DH5**									**11**
***Enterobacter/Klebsiella* sp.**									**34**
***Enterococcus faecalis* NCTC 775**									**15**
***Klebsiella aerogenes* NCTC 9528**									**24**
***Klebsiella pneumoniae* 700603**									**23**
***Listeria monocytogenes* NCTC 11994**									**28**
***Pseudomonas aeruginosa* NCTC 1662**									**25**
***Pseudomonas aeruginosa* NCTC 27853**	**6**								**28**
***Pseudomonas* sp**									**20**
***Pseudomonas* sp 20**									**18**
***Salmonella poona* NCTC 4840**									**26**
Serratia marcescens									**26**
***Serratia/Rahnella* sp.**									**40**
***Staphylococcus aureus* (MRSA) 43300**	**25**								**19**
***Staphylococcus aureus.* NCTC 6571**	**30**								**27**
***Staphylococcus aureus* (MSSA) 25923**	**25**								**25**
***Staphylococcus epidermidis* NCTC 14990**	**25**								**28**
Fungi									
***Aspergillus flavus* QC 6658**									
***Aspergillus fumigatus* 27.5**									
***Aspergillus niger* 27.5**									
Candida albicans									
***Candida glabrata* ATCC 2001**									
***Candida krusei* ATCC 6258 27.5**									
***Candida parapsilosis* ATCC 22019**	**30**								
***Exophiala* (*Wangiella*) *dermatitidis* QC 7895**									
***Penicillium* sp. QC 743275**									
***Scedosporium apiospermum* QC 7870**									

on Columbia Blood Agar (Oxoid CM0331) supplemented with 5% (v/v) defibrinated horse blood and incubated for 24h at 37°C (for bacterial and yeast organisms) and for 1 week (for filamentous fungi). Under aseptic conditions, serial dilutions of each isolate were prepared individually in 0.1% [w/v] peptone saline (PS) (Oxoid CM0733), equating to a 0.5 McFarland Standard (approximately 10^6 colony forming units (cfu) per ml) which was inoculated on to fresh Mueller-Hinton Agar (Oxoid CM0337), by means of a sterile cotton swab. To this, fresh extracts (10 l) were added and the inoculum allowed to dry prior to incubation, as detailed above. Following this, plates were examined visually and any inhibition noted and its diameter measured and recorded. Sterile PS and antibiotic susceptibility disks containing 5 g ciprofloxacin (Mast Diagnostics Ltd., Bootle, Merseyside, UK) were employed as a negative and positive control, respectively.

RESULTS

The antimicrobial activity of the eight plant extracts against the 34 microorganisms tested is shown in Table I. No antimicrobial activity was observed with any bacterial or fungal pathogen, for onion *(Allium cepa),* Yarrow leaf (*Achillea millefolium)*, Meadow sweet leaf (*Filipendula ulmaria*), Confrey leaf (*Symphytum officinale)*, Ragwort (*Senecio jacobaea*) or for Dandelion leaf and roots (*Taraxacum officinale)*. Only the aqueous extract from cloves of garlic showed inhibition against nine bacterial isolates (range: 6-30mm zone of inhibition; mean = 19.5mm) and only the *Candida parapsilosis* isolate was inhibited by the garlic extract (30mm). There was complete microbial confluence at the site of inoculation of the negative control,(0.1% PS) and all organisms gave a clear zone of inhibition, ranging from 11-40mm diameter zone of inhibition, with a mean zone of inhibition of 23mm,when tested against the positive control (ciprofloxacin).

DISCUSSION

Historically, Yarrow leaf (*Achillea millefolium),* named after Achilles, who used extracts of this plant to treat wounds, has been used with anti-inflammatory, spasmolytic, haemostatic and digestive effects[3]. Although the essential oil[3] and total acid[4] of two other species of this genus, namely A. *clavennae* and *A. alpina*, respectively, have been reported in the literature, as displaying antibacterial properties, we did not observe any antimicrobial activity during this study, with the species *A. millefolium*, which we tested. Likewise, we were not able to demonstrate any activity with Meadowsweet leaves (*Filipendula ulmaria*) or ragwort (*Senecio jacobaea*), although other species within these genera, other than those tested, have been shown to exhibit some antimicrobial activity. Although these plants may not be able to exert a direct physiological antimicrobial effect, it may be that their clinical efficacy lies in their associated activity in the stimulation of other systems, such as macrophages or nitric oxide. For example, Kim *et al.*[5] suggested that there was an activation of inducible nitric oxide synthase by *Taraxacum officinale* in mouse peritoneal macrophages. These results suggest that the capacity of *Taraxacum officinale* to increase NO production from rIFN-gamma-primed mouse peritoneal macrophages is the result of TO-induced TNF-alpha secretion. Likewise, Dolganiuc *et al.*[6] examined the effect of *in vivo* stimulation with an aqueous extract obtained from roots of *Symphytum officinale* on mouse peritoneal macrophages and showed that *Symphytum officinale* initially activated the respiratory burst of the cells and later inhibited it, activating the synthesis of catalase, SOD etc. Hence, such plants materials may exert a physiological effect through an alternative modality to antimicrobial inhibition.

Previously, Ballard demonstrated that garlic has been used in traditional Ulster cures to treat asthma, epilepsy, measles and whooping cough[1]. More recently, a further reference to garlic as an ingredient in a cure for measles has been found, which like the previous one came from north Co Londonderry. However, the sources of this information do not specify whether *Allium sativum or Allium ursinum* is indicated. Our data demonstrated that the aqueous extracts of garlic were the most potent plant material examined against bacterial and fungal pathogens, which is in general agreement with the published literature, where garlic is known as a potent antimicrobial. Garlic contains organosulphur groups, that can act as metal chelators, powerful nucleophiles or electrophiles and hence confer antimicrobial properties on this compound.

CONCLUSION

Our data has qualitatively shown that cloves of garlic had a limited antibacterial activity against 9/24 isolates tested and exhibited some antifungal properties against 1/10 fungal isolates examined. These data would suggest that traditional cures and remedies solely reliant on the antimicrobial properties of aqueous extracts of these plants would have little or no microbiocidal activity.

Acknowledgements: SWP was supported by a Nuffield Science Bursary administered by Sentinus.

The authors have no conflict of interest

REFERENCES

1. Ballard LM. An approach to traditional cures in Ulster. *Ulster Med J* 2009;**78(1):**26-33.
2. Allen DE, Hatfield G. *Medicinal plants in folk tradition: an ethnobotany of Britain and Ireland.* 2004. Timber Press Inc. Portland, Oregon, USA.
3. Skocibusić M, Bezić N, Dunkić V, Radonić A. Antibacterial activity of *Achillea clavennae* essential oil against respiratory tract pathogens. *Fitoterapia* 2004;**75(7-8)**:733-736.
4. Peng Y, Yan H, Wang SQ, Liu XT. 65 cases of urinary tract infection treated by total acid of *Achillea alpina*. *J Tradit Chin Med* 1983;**3(3)**:217-218.
5. Kim HM, Oh CH, Chung CK. Activation of inducible nitric oxide synthase by *Taraxacum officinale* in mouse peritoneal macrophages. *Gen Pharmacol* 1999;**32(6)**:683-688.
6. Dolganiuc A, Radu LD, Olinescu A. The effect of products of plant and microbial origin on phagocytic function and on the release of oxygen free radicals by mouse peritoneal macrophages. *Bacteriol Virusol Parazitol Epidemiol* 1997;**42(1-2)**:65-69.

Ulster Med J 2009; **78 (1)** 16-20

Paper

A Study of Suicide Rates in Northern Ireland 1984-2002

Maeve Largey, Christopher B Kelly*, Michael Stevenson+

Accepted 17 September 2008

SUMMARY:

Annual figures collected by the Samaritans from the Registrar Generals' figures for suicides for the years 1984-2002 inclusive were analysed. Trends by gender, age group, marital status and method were examined. Suicide rates were standardised where appropriate. The mean annual rate was calculated for the 10 year period 1984-1993 and compared with the nine year period 1994-2002. The mean annual rate of suicide increased by 4.7%. Female suicide rates decreased by 17%, male suicides increased by 13.2%. The highest percentage increase was seen in males aged 25-34, (34%) followed by the 15-24 age group, (26.5%). There was a significant upward trend in suicide rates at $p<0.01$ in young males aged 10-34 and a significant fall in total suicide rates in those aged 35+. The greatest increase in the mean annual rate was seen in those of single status in sexes, males 24.2% and females 28.6%. There was a decrease in the mean annual rate for all methods of suicide except hanging with an increase of 99.37% in males and 87.80% in females.

The overall rate of suicide in Northern Ireland appears to be rising. This trend is largely a result of the increase in suicides amongst young males aged 10-34. Violent methods of suicide, namely hanging have increased, suggesting that this more lethal method is contributing to the higher suicide rate.

INTRODUCTION

The issue of suicide in Northern Ireland (NI) has been addressed by a number of initiatives. Suicide prevention was one of the four key areas in the Promoting Mental Health Strategy and Action Plan 2003-2008 which envisaged a 10% reduction in overall suicide rate by 2008[1]. The Bamford Review of Mental Health and Learning Disability has recommended that a suicide strategy be developed as a matter of urgency[2]. The Suicide Prevention Strategy for NI was launched in October 2006 as a result of concern about an increase in suicides in the province of particularly among young people[3]. The aim of this strategy is "to reduce the Northern Ireland suicide rate, particularly among young people and those most at risk" and a target of reduction in suicides by 15% by 2011[3].

As part of the suicide prevention strategy an analysis of suicide and self harming in NI was commissioned using data held by the General Register Office[4]. The use of five year moving averages highlighted that the rate of male suicides in NI had increased steadily from 1991-2004[4].

The World Health Organisation has estimated that in 2004 the total suicide rate was 7.0/100,000 in the UK[5]. Within the UK, Scotland has the highest suicide rate followed by NI with rates in England and Wales falling in recent years[6]. This rate was less than that in the Republic of Ireland, which was estimated at 9.7/100,000 with Lithuania having the highest suicide rate at 40.2/100,000[5].

The Samaritans in NI have been at the forefront of highlighting the issue of suicide. They provide a 24-hour confidential help line to those in distress and have been involved in public awareness campaigns and, since 1984, have been collecting suicide figures on a yearly basis. Accurate yearly figures are notoriously difficult to ascertain - official mortality figures underestimate the true mortality, therefore official data should be treated with caution.

All deaths by suicide in NI require an inquest. When a death is suspected to be a suicide it is referred to the coroner and goes through a formal inquest. Upon completion, coroners provide a summary of their finding to the Registrar. Death is then recorded as a suicide by the General Register Office. The Office of National Statistics has drawn attention to the problem they have in obtaining timely information from coroners until an inquest is complete. Based on General Register Office figures 1999-2003, 24.3% of suicides are registered within six months, 93.7% within one year and 96.9% within two years. A time delay occurs between actual death occurring and date of registration of up to several years in some cases, making it difficult to monitor trends. The difficulty in the formal recording of suicide in Northern Ireland was also highlighted in the Promoting Mental Health Strategy and Action Plan[1] as well as the Luce Report investigating the death certification in Britain and NI in 2003[7].

The suicide statistics collected by the Samaritans in NI were used as the basis of this study. Figures for suicides occurring in a particular year at inquest and adapted for year of death, differ from official figures collected from the Office of National Statistics, and are based on registered deaths. By using the data from the Samaritans we hypothesize that this data may more accurately reflect time trends than official figures as they record suicides in the actual year in which they took place. We undertook to identify if there was a time increase in suicide rates and which particular groups were affected.

Windsor House, Belfast HSC Trust, City Hospital Campus, Lisburn Road, Belfast BT9 7AB, United Kingdom and Departments of Psychiatry*, and Epidemiology and Public Health+, Queens University Belfast, Belfast BT7.

*Correspondence to Dr Kelly

chris.kelly@belfasttrust.hscni.net

METHODS

Figures collected on a yearly basis by the Samaritans from for suicides in NI from 1984 to 2002 were analysed. These were collected from Registrar General for suicides occurring that particular year at inquest and adapted for year of death. These do not take account of "undetermined deaths". In discussion with the General Register Office and other researchers it has been established that there are ~20 such deaths in Northern Ireland per year; if all of these deaths were suicide it would increase the Northern Ireland suicide statistics by about 15%.

Suicides for those aged 10 years and above were considered. Trends by gender, age group, method and marital status were examined. Calculation of suicide rates per 100,00 of the population was done using the 1981 census figures for the years 1984-1990, the 1991 census figures for the years 1991-2000 and the 2001 census figures for the years 2001-2002. Suicide rates were standardised when appropriate by gender, age or marital status using the population figures for these groups from the appropriate census. The mean annual rate was calculated for the 10-year period 1984-1993 and compared with the 9-year period 1994-2002. The percentage change between these two groups was then calculated.

When comparing time periods for marital status the period used was 1985-1993 and 1994-2002 as available data from 1984 was incomplete.

Standardised suicide rates by age and sex were further analysed. A correlation matrix was applied enabling touching age bands that showed similar patterns to be combined. In females this resulted in two groups to be analysed, age 10- 34 and 35^{+}. In males, four groups, age up to 34, 35-54, 55-74 and 75^{+}. Combining the two sexes resulted in four groups, age 10-24, 25-34, 35-64 and 65^{+}. A linear regression model with year as the key explanatory variable was then fitted to each of these groups. Allowances were made for non-random components, for example in a year with a high suicide rate strategies maybe put in place the following year to address this, by in all cases applying an autoregression of lag size 1 year term only progressing to autoregression of lag size 2 when auto regression 1 was significant. $P<0.05$ was taken as the significant cut-off value.

Table I:

Changes in Recorded Suicide Rates by Sex

	1984 -1993		*1994-2002*			
	Mean Annual Number	**Mean Annual Rate**	**Mean Annual Number**	**Mean Annual Rate**	**Change in Mean Annual Rate**	**% Change**
Male	93.6	15.35	112.3	17.47	2.12	13.20%
Female	32.3	4.94	28.8	4.10	-0.84	-17.0%
Total	125.9	10.00	141.1	10.47	0.47	4.70%

Table II:

Changes in Recorded Suicide Rates by Age

		1984-1993		*1994-2002*			
Age	**Sex**	**Mean Annual Number**	**Mean Annual Rate**	**Mean Annual Number**	**Mean Annual Rate**	**Change in Mean Annual Rate**	**% Change**
10-14	M	0.7	1.03	0.6	0.82	-0.21	-20.3%
	F	0.3	0.44	0.3	0.52	0.08	18.2%
15-24	M	21.4	16.2	26.2	20.5	4.3	26.5%
	F	3.5	2.76	4.6	3.7	0.94	34.1%
25-34	M	22	20.97	32.9	28.1	7.13	34%
	F	4.4	4.29	6.1	5.01	0.72	16.8%
35-44	M	15.3	17.39	21.3	20.97	3.58	20.6%
	F	6.3	6.96	6.8	6.52	-0.44	-6.3%
45-54	M	12.4	16.64	15.2	17.6	0.96	5.8%
	F	7.0	8.56	5.7	6.48	-2.08	-24.3%
55-64	M	11.7	17.58	7	10.2	-7.38	-42%
	F	5.1	6.75	2.3	3.1	-3.65	-54.1%
65-74	M	6.2	12.55	5.7	10.79	-1.76	-14%
	F	4.2	6.52	2	3.18	-3.34	-51.2%
75+	M	3.9	16.44	3.4	11.82	-4.62	-28.1%
	F	1.5	3.3	0.9	1.57	-1.73	-52.4%

RESULTS:

Changes in Recorded Suicide Rates by Gender:

Table I compares the mean annual suicide rate standardised by gender for the periods 1984-1993 with 1994-2002. There was a 4.7% increase in

the mean annual rate from 10 to 10.47. There was an increase in the mean annual rate of male suicides from 15.35 to 17.47 (13.2%). Female suicides decreased from a rate of 4.94 to 4.1 (–17%). The male: female suicide ratio increased from 2.9:1 to 3.9:1.

Changes in Recorded Suicide Rates by Age Only:

In the 10-24 group a regression coefficient of b = 0.05 suggested a flat series (b = 0.05 +/- 0.18, P = 0.609). In the 25-34 age group a positive regression coefficient of b = 0.15 indicated a non-significant upward trend toward an increase in suicide rates in this group (b = 0.15 +/- 0.21, P = 0.192). In the 35-64 group a regression coefficient of b = -0.68, indicated a significant downward trend in suicide rates in this group (b = -0.68 +/- 0.49, P = 0.015). In the 65^{+} group there was a highly significant downward trend in suicide rates, with a regression coefficient of b = -0.60 (b = -0.60 +/- 0.25, P<0.01). In all cases autoregression of lag size 1 was not significant and therefore not considered.

Changes in Recorded Suicide Rates by Age and Gender:

Table II compares the mean annual suicide rate standardised according to age group for the periods 1984-1993 with 1994-2002. There were few suicides for either gender recorded for the 10-14 age group. Comparing the two groups in table II. The mean annual rate increased for males for those aged 15-55. The highest percentage increase was in the 25-34 group with an increase in the mean annual rate of 34%. This was followed by the 15-24 age group with an increase of 26.5%. There was a decrease in male suicide rates between the two groups for all those aged 55+. The mean annual rate increased for females in the 15-24 and 25-34 age groups. The highest percentage increase was in the 15-24 age group with an increase of 34.1%. The 25-34 age group had a percentage increase of 16.8%. There was a decrease between the mean annual rates of the two groups for all females aged 35+.

Male Suicide Rates:

In the 10-34 age group a positive regression coefficient of b = 1.26 indicated a statistically significant upward trend in suicide rates in this group (b = 1.26 +/-0.35, P<0.01). In the 35-54 group a regression coefficient of b = 0.34 indicated a non-significant upward trend (b = 0.34 +/- 0.58, P = 0.266). In the 55-74 a negative regression coefficient of b = -0.52 indicated a non- significant downward trend in suicide rates (b = -0.52 +/- 0.55, P = 0.082). In the 75+ group there was a negative regression coefficient of b = -1.25 indicating a significant downward trend in suicide rates in this group (b = -1.25 +/-0.89, P = 0.014). In all but one case autoregression of lag size 1 was not significant and therefore not considered. In the 10-34 age group autoregression of lag size 1 was significant at -0.49 +/- 0.45, P = 0.05, auto regression of lag size 2 was not significant.

Female Suicide Rates:

In the female 10-34 group there was a positive regression coefficient of b = 0.20 indicating a non-significant upward trend in suicide rates (b = 0.20 +/- 0.28, P = 0.185). In the 35+ group a negative regression coefficient of b = -1.29 indicated a highly significant downward trend in suicide rates amongst this group (b = -1.29+/-0.54, P<0.01).

Changes in Recorded Suicide Rate by Marital Status:

Table III compares the mean annual suicide rate standardised by marital status for the periods 1985-1993 and 1994-2002. The mean annual rate increased for both males and females of single status. The mean annual rate decreased for both males and females of married status with a decrease of 8.3% for females and 36.7% for males. There was a small increase in the mean annual rate for widowers of 3.37% but the rate for widows decreased by 29.4%. There was little change in the rate for male divorcees and a marked decrease for the females of 54.8%. Male divorcees had by far the highest mean annual suicide rate, six times greater than married males.

TABLE III:

Changes in Recorded Suicide Rates by Marital Status

		1985-1993		*1994-2002*			
Status	Sex	Mean Annual Number	Mean Annual Rate	Mean Annual Number	Mean Annual Rate	Change in Mean Annual Rate	% Change
Single	M	43.5	16.5	57.3	20.5	4.0	24.2%
	F	8.3	3.5	11.3	4.5	1.0	28.6%
Married	M	42.7	13.2	40.8	12.1	-1.1	-8.3%
	F	16.1	4.9	10.9	3.1	-1.8	-36.7%
Widowed	M	4.7	26.7	5.1	27.6	0.9	3.37%
	F	5.0	6.8	3.3	4.8	-2.0	-29.4%
Divorced	M	4.1	75.2	9.1	75.3	0.1	0.1%
	F	3.1	38.9	3.2	17.6	-21.3	-54.8%

Changes in Recorded Suicide Rates by Method:

Table IV compares the mean suicide rate by method available classified according to ICD9 for the periods 1984-1993 and 1994-2002. The most common method of suicide in males in both time periods was hanging. In females overdose was the most common method of suicide for both time periods. There was a decrease in the mean annual rate from 1984-1993 to 1994-2002 for all methods of suicide used except for hanging with a percentage increase in males of 99.37% and in females 87.80% an almost doubling of the mean annual rate.

DISCUSSION

The results of this study indicate that the total suicide rate in Northern Ireland appears to be rising. This appears to be largely as a result of the increase in young male suicides aged 10-34, with a statistically significant upward trend at $p< 0.01$. Suicide rates appear to be falling in the older population with a significant decrease in the 35^{+} age group in total suicide rates. The small number of female suicides make trends difficult to establish, however again they showed a non-significant upward trend in those less than 35 and a highly significant fall in suicide rates for those age 35^{+}, ($p<0.01$). As the suicide rate in the younger male population rises, that in the older population is falling, cancelling out significant rises if only total trends are examined and not the age break-down.

This is the first study specific to Northern Ireland which has examined the age and breakdown of suicide rates adjusting for non-random components. It was only in the young male population aged 10-34 that autoregression of lag size 1 was significant, indicating that in this population there is a tendency for a higher than average suicide rate followed by a year where the suicide rate drops.

It is difficult to compare this data with that commissioned by the NI Suicide Prevention strategy which examined 5 year moving averages and the comparison of age standardised yearly rates[4]. They showed an increasing suicide rate in Northern Ireland from 1991-2003 with males aged 25-34 having the highest percentage of suicides, a similar trend to this data. This study would appear to mimic a trend seen in England and Wales in the 1980s and early 1990s which showed an increase in suicides in the young male population and a decrease in the elderly[8] and reflects current trends in Scotland[9].

Several limitations of this study need to be addressed. The exclusion of undetermined deaths in the data it could be argued may affect results. It has been reported in NI there was a steady reduction in recorded numbers of undetermined and accidental deaths during the period 1975-1986[10]. The generally held view that improvements in recording arrangements and greater acceptance of recording of death as a suicide may lead to an increase in the likelihood of the coroner returning a suicide verdict could we acknowledge have led to the increase in suicide rates. In the Republic of Ireland this theory has been examined. Here it was felt that the increase in suicide figures recorded over the last 20 years due to better recording accounts for only 40% of the rise and that it should affect data relating to both men and women of all ages[11]. We however feel that improvements in recording a death as a suicide is an unlikely explanation for our results as we feel this would have led to a general increase in rates across all age bands and both genders and does not explain the significant fall in suicide rates in the older populations.

The increase in the mean annual rate of suicides amongst the single population with a decrease in the married holds

TABLE IV:

Changes in Recorded Suicide Rates by Method

		1984-1993		*1994-2002*			
Method	**Sex**	**Mean Annual Number**	**Mean Annual Rate**	**Mean Annual Number**	**Mean Annual Rate**	**Change in Mean Annual Rate**	**% Change**
E950 Poison	M	14.5	2.37	14.8	2.30	-0.07	-2.95
	F	14.9	2.28	11.7	1.68	-0.60	-26.30
E952 Other Gas	M	12.3	2.03	10.1	1.57	-0.46	-23.00
	F	1.6	0.25	1.0	0.12	-0.13	-52.00
E953 Hanging	M	29.2	4.78	62.5	9.53	4.75	99.37
	F	5.3	0.82	10.8	1.54	0.72	87.80
E954 Submerge	M	11.3	1.87	5.8	0.90	-0.97	-51.87
	F	6.9	1.07	3.0	0.41	-0.66	-61.68
E959	M	19.7	3.23	13.1	2.02	-1.21	-37.46
Guns/Explosive	F	1.1	0.17	1.1	0.16	-0.01	-5.88
Others =E951	M	6.6	1.09	6.0	0.91	-0.18	-16.51
Domestic Gas	F	2.5	0.44	1.2	0.16	-0.28	-63.63
E956 Cut/Pierce							
E957 Fall from Height							
E958 Others							

with the general held belief that marriage acts as a protective factor. However as there was no age group breakdown any differential impact could potentially be explained by the age distribution of the group. The small numbers in the widowed and divorced population mean it is not possible to reach firm conclusions. Little attention is given to the method of suicide in the literature on NI[12]. This study found that suicide by most methods is falling except for hanging with an almost doubling of the mean annual rate between the two time groups for both sexes. Amongst the female population overdose remained the preferred method for both groups indicating their preference for less violent means.

The increase in hanging as a suicide method is a trend which was also seen in Scotland between 1981-1999 where hanging as a method increased as car exhaust fumes as a method decreased with the advent of catalytic converters[13]. In Australia which had a rising young male suicide rate, restriction of firearms led to a doubling in the rate of hanging, however in both cases this trend commenced even before the advent of these restrictions[14]. It has been suggested that as prevention strategies restrict access to other means, males have a tendency to seek out alternatives[13,14] and that the reduced stigma of hanging with the abolition of judicial hangings has contributed to its increasing use as a method[15].

Gunnell and colleges have argued in relation to England and Wales that changes in method preference and therefore in case fatality should be considered before concluding that changes must relate to social trends[16]. Given the rise in young male suicides found in this study, we hypothesise that hanging as a suicide method could be contributing to this higher suicide rate. This has important implications for any suicide prevention strategy, giving the difficulties in restricting access to this means and hangings case fatality of approximately 70%[17].

The causes of suicide are complex and multifactorial. We have made no examination in this study of the social and health factors behind our results. In addition NI differs from our counterparts in Scotland[9] and the Republic of Ireland[18] who are also experiencing rising young male suicides in that we have experienced 30 years of civil conflict. One of the key areas in the NI Suicide Prevention strategy is research into the existing gaps in our information both localised and shared with our counterparts above.

CONCLUSION

The overall rate of suicide in Northern Ireland appears to be rising. This trend is largely a result of the increase in suicides in the young male population, with suicides in the older population falling. The greatest rise is observed amongst the single population. Suicide by most methods is falling except for hanging which has increased dramatically in both the male and female population. We hypothesize that this more violent method could be contributing to the higher suicide rate.

Conflict of interest – the authors have no conflict of interest to declare.

REFERENCES:

1. Promoting Mental Health Strategy and Action plan. Department of Health Social Services and Public safety: 2003. Available from: http://www.healthpromotionagency.org.uk/Resources/strategies/mindingourhealth.htm (Accessed 1st October 2008).
2. Bamford Report. Mental Health Improvement and well-being- a personal public and political issue, The Bamford Review of Mental Health and Learning Disability (Northern Ireland). Available from: www.rmhldni.gov.uk/ (Accessed 1st October 2008).
3. Protect Life, A Shared Vision. Northern Ireland suicide prevention strategy and action plan 2006-2011: 2006. Available from: http://www.dhsspsni.gov.uk/phnisuicidepreventionstrategy_action_plan-3.pdf (Accessed 1st October 2008).
4. Investing for Health (Northern Ireland). Section 75 analysis of suicide and self harm in Northern Ireland (2000-2005). Available from: http://www.investing for healthni.gov.uk/documents/Suicide-Self-Harm-Assess.pdf (Accessed 1st October 2008).
5. World Health Organisation. Suicide Prevention (SUPRE): 2003-2004. Available from http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ (Accessed 1st October 2008).
6. Brock A, Baker A, Griffiths C, Jackson G, Marshall M. Suicide trends and geographical variations in the United Kingdom 1991-2004. *Health Stat Quart* 2006;**31(3)**:6-21.
7. Luce Report. Death certification and Investigation in England, Wales and Northern Ireland. The report of an independent review of coroner services, commissioned by the home office and chaired by Tom Luce. Royal College of General Practitioners. Summary Paper 2003/05. Available from: http://www.rcgp.org.uk/pdf/ISS_SUMM03_05.pdf (Accessed 1st October 2008).
8. Gunnell D, Middleton N, Whitley E, Dorling D, Frankel S. Why are suicide rates rising in young men but falling in the elderly?-a time series analysis of trends in England and Wales 1950-1998. *Soc Sci Med* 2003;**57(4)**:595-611.
9. Boyle P, Exeter D, Feng Z, Flowerdew R. Suicide gap among young adults in Scotland: population study. *BMJ* 2005;**330(7484):**175-6.
10. Darragh PM. Epidemiology of suicides in Northern Ireland 1984-1989. *Ir J Med Sci* 1991;**160(11):**354-7.
11. Kelleher MJ. Youth suicide trends in the Republic of Ireland. *Br J Psychiatry* 1998;**173**:196-197.
12. Tomlinson, M. *The Trouble with Suicide. Mental Health, Suicide and the Northern Ireland Conflict: A Review of the Evidence,* Belfast: Department of Health, Social Services and Public Safety (NI). 2007.
13. Stark S, Hopkins P, Gibbs D, Rapson T, Belbin A, Hay A. Trends in suicide in Scotland 1981-1999: age, method and geography. *BMC Public Health* 2004;**4**:49.
14. De Leo D, Dwyer J, Firman D, Neulinger K. Trends in hanging and firearm suicide rates in Australia: substitution of method? *Suicide Life Threat Behav* 2003;**33(2)**:151-164.
15. Pounder DJ. Why are the British hanging themselves? *Am J Forensic Med Pathol* 1993;**14(2**:135-140.
16. Gunnell D, Middleton N, Frankel S. Method availability and the prevention of suicide, a re-analysis of secular trends in England and Wales 1950-1975. *Soc Psychiatry Psychiatr Epidemiol* 2000;**35(10)**: 437-443.
17. Gunnell D, Bennewith O, Hawton K, Simkin S, Kapur N. The epidemiology and prevention of suicide by hanging: a systematic review. *Int J Epidemiol* 2005;**34(2):**433-42.
18. Levi F, La Vecchia C, Lucchini F Negri E, Saxena S, Maulik PK, Saraceno B. Trends in mortality from suicide 1965-1999. *Acta Psychiatr Scand* 2003;**108(5)**:341-349.

Ulster Med J 2009; **78 (1)** 21-25

Paper

Efficacy of treatment in an opioid –dependent population group using the Maudsley Addiction Profile (MAP) tool.

Ruth Collins*, Bob Boggs, Noel Taggart, Martin Kelly, Aileen Drillington, Ivy Swanton, Diane Patterson.

Accepted 21 August 2008

SUMMARY

A pilot study was performed to assess the effectiveness of treatment in an opioid dependent population using the Maudsley Addiction Profile (MAP) tool[1].

The primary outcome of the study was to assess if treatment had an effect on 1. Substance use (quantity and frequency of use), 2. Health risk behaviour (injecting and sharing injecting equipment), 3. Health symptoms (physical and psychological) and 4. Personal /Social functioning (relationships, employment and crime). A secondary outcome was also sought.

The study took place in 2007 in an inner city Belfast hospital specialising in the treatment of addiction, over a two month period. Fifteen patients, all opioid dependent and receiving outpatient community treatment, were interviewed at baseline (prior to the commencement of treatment) and at eight weeks follow up.

Three patients were lost to follow up. Two patients stopped using altogether. Of the remaining patients, improvements were seen in most areas. There was a decrease in the use of heroin (71.28%), cocaine (99.72%), crack cocaine (100%), cannabis (99.94%) and alcohol (33.17%). There was a reduction in injecting behaviour (60.93%). Improvements were observed in health with a reduction in physical (41.35%) and psychological (35%) symptoms. Overall personal and social functioning improved regarding interactions with family and friends. A reduction in crime was also observed (75%).

Opinions and views of staff involved in the study were generally positive.

This patient population presents with multiple and complex needs. Effective treatment needs to address these needs and not just drug addiction alone. The Maudsley Addiction Profile tool highlights this.

INTRODUCTION

The effect of drug misuse is felt by everyone[2]. It can affect the lives of individuals and communities. Drug misusers often have a set of complex problems. This needs to be taken into consideration if recovery is going to be successful. Problems may range from unemployment, homelessness, involvement in criminal activities to poor physical (particularly the risk of HIV, Hepatitis B, C and other blood borne infections from sharing injecting equipment) and mental health issues. In Northern Ireland drug misuse has become a significant public health issue and costs hundreds of millions of pounds a year. In 2006 the government launched "A New Strategic Direction for Drugs 2006-2011"[3]. This document contained a number of concerns around the treatment of those who misuse drugs including prevention, treatment, harm reduction and monitoring.

METHODOLOGY

Substitute prescribing became policy in Northern Ireland in April 2004. Shaftesbury Square Hospital is located in the centre of Belfast and is involved in the treatment of all forms of drug and alcohol addictions - it covers a catchment area of 370,000. The service provides substance misuse maintenance and detoxification programmes and offers a choice of methadone or buprenorphine medication. It works in liaison with social services, housing and local psychiatric services. The patients can be referred by primary care, Drug Outreach Community Team (these are teams that work exclusively in the community), secondary care mental health services and the criminal justice system. A self referral system service is also in place. The substitution prescribing team consists of a part time administrative team member, four senior full-time nurses, a full time staff grade doctor, a half -time specialist registrar doctor with a consultant psychiatrist input.

In this study all patients fulfilled the ICD10 criteria of Substance Dependence: opioid in nature[4]. The ICD10 categorises the mental and behavioural disorders due to psychoactive substance use by drug types. Informed consent was obtained. All patients were fully informed about the study. Confidentiality was assured and patients were given the option of withdrawing from the study if they decided to at any stage. Patients were interviewed at baseline i.e. prior to commencement of treatment and at an eight week follow up. Patients were assessed on both occasions using the Maudsley Addiction Profile (MAP). The MAP is a brief questionnaire developed in the UK for assessing individuals with drug and alcohol problems. It is both reliable and valid[5,6] and can be

Shaftesbury Square Hospital, 116 – 120 Great Victoria Street, Belfast BT2 7BG, and * Psychiatric Department, Mercy University Hospital, Cork, Republic of Ireland.

Correspondence to Dr Collins.

RuthE.Collins@hse.ie

administered to patients in 15 minutes or less. The 30 day period before intake of treatment is used as the recall period for the MAP interview. It looks at four main areas: substance use, health risk behaviour, physical and psychological health and personal /social functioning.

All patients received outpatient community treatment. This consisted of initial review by the medical team and weekly (or more frequent if needed) review by their team key worker (nursing and medical staff). Once stabilised this review could be decreased to fortnightly. It is the practice of this service that the majority of patients commence opiate substitution treatment as an out patient (prescribed by primary care) whether it is for a detoxification or for a stabilization programme (unless it is decided by the team that for medical or social reasons inpatient treatment is required). Urine screens were taken at regular intervals by individual key workers (i.e. nominated staff members) which would identify recent use of illicit substances. Boxes 1-4 show areas assessed.

A secondary outcome using a qualitative study approach involving staff was also looked at. All staff involved in administering MAP was asked about their views of adding MAP to their initial assessment and at definite follow up periods.

Opinions were sought to explore subjective experience regarding the advantages and disadvantages to the introduction of MAP.

RESULTS AT BASELINE

All of the patients who had been accepted onto the opiate substitution programme at the start of January 2007 were included. All received outpatient community treatment. 15 people (13 male and 2 female) were interviewed. They ranged in ages between 30 and 55 years. Ten patients had self referred, two came from their GP (primary care), one came from the community addiction team (a team that works in a structured outpatient setting), one had been referred from a secondary mental service (i.e. from a psychiatrist) and one had come from the Drug Outreach Team, (a mobile outreach team that work exclusively in the community). None had been referred through the criminal justice system.

All the patients were polydrug users i.e. using more then one type of drug at the time (Box 1). Ten patients reported using heroin. One patient had bought methadone. This was on top of his daily heroin use. Methadone is a controlled drug with a high dependency potential and a low lethal potential. Two patients admitted to buying Morphine sulphate tablets (MST). MST is an opioid analgesic and is used in severe pain. It does not have a licence to be used in opiate dependency.

Four patients admitted to buying Dihydrocodeine (DHC) tablets. This was on top of one patient's daily heroin use. Dihydrocodeine is an opioid analgesic and is used medically for moderate to severe pain. Repeated administration of DHC may cause dependency and tolerance. DHC does not have a licence for use in opiate substitution. One patient admitted to buying buprenorphine. This was not used on top of any other opioids. Buprenorphine is an opioid analgesic and its' indications for use includes moderate to severe pain. It also has a licence for opiate substitution.

Ten patients reported using alcohol for the thirty days prior to the study. This ranged from a pint of beer for one day (two units) to three pints of beer daily for seventeen days (102 units). Seven of the patients had used cocaine in the thirty days previously. Cocaine is a stimulant drug. All admitted to snorting cocaine as opposed to injecting.

Crack cocaine was used by four patients. One patient admitted to injecting crack cocaine whilst the other three took it orally. Six patients reported using Cannabis.

Regarding health risk behaviour, five (four male and one female) admitted to injecting heroin (Box 2). None reported sharing injecting equipment. Of these five, three reported injecting on a daily basis up to twice a day. One reported injecting twenty five days of the thirty previous days again up to twice a day. The one female who admitted to injecting reported that she injecting twice a day for thirteen days.

Five patients admitted to unprotected sexual contact. All five reported to be in a relationship with a partner at the time of the study (Box 2). All admitted to some form of physical symptoms (Box 3). The maximum score was 40. The highest score was 33 and the lowest score was 8. The most common symptoms were muscle pains/joint pains and tremors/shakes.

All patients admitted to some form of psychological symptoms. The maximum score was 40. The highest score was 40. The lowest score was 8. The most common symptoms were "feeling tense" and "feeling no interest in things".

In personal/ social functioning eight patients were in a relationship with their partners at the time of this study (Box 4). Six patients admitted to conflict. All patients had had some form of contact with their relatives. Four admitted to conflict with their relatives. Thirteen out of fourteen patients had had contact with friends in the previous thirty days prior to engagement in treatment. Three patients admitted to conflict with friends. Only three patients admitted to working in the previous 30 days. One had worked six day, one was in full employment and one worked four days per week. Four patients admitted to being involved in some form of crime in the previous 30 days. Two had been involved in selling drugs on eight occasions. One admitted to one episode of shoplifting whilst another admitted to two episodes of shoplifting and nine episodes of being caught for possession of heroin.

RESULTS AT EIGHT WEEKS FOLLOW UP

There were three patient lost to follow up. All three did not return to the programme after the initial assessment. Of these three drop outs two were male and one was female. All three were multiple drug users and were heavy users of illicit substances. Only one of the three had injected. Two patients had stopped using illicit drugs altogether.

For substance use (Box 1) five patients admitted to the continued use of heroin. Of these two admitted to continue injecting but denied sharing. The average total use per patient in the previous thirty days was 2.8g. This was a decrease of 71.28%. There was no reported use of DHC (dihydrocodeine). One patient had taken an MST (morphine sulphate) tablet on one occasion. Three patients continued to drink. The average total units consumed per patient were 41.3 units which was a decrease of 33.17%. Two patients continued to

use cocaine and the average total use per patient was 0.1g. This was a decrease of 99.72%. No patient reported the use of crack cocaine. Four patients continued to use cannabis. The average total use per patient was 1.01g which was a decrease of 99.94%.

BOX 1

Substance Use	Baseline Average total scores per patient	Eight week follow up Average total score per patient
Heroin (grams)	9.75	2.8
Alcohol (units)	61.8	41.3
Cocaine (grams)	35.9	0.1
Crack cocaine (grams)	21.8	0
Cannabis (grams)	18	1.01

For health risk behaviour (Box 2) two patients continued to inject. One patient injected twice one day. The other individual injected twice a day for 19 days. The average total episodes per patient were 20 episodes. This was a decrease of 60.93%. Four patients continued to have unprotected sexual activity with their partners. The average total episodes per patient were 7.75 which was a decrease of 0.6%.

BOX 2

Health Risk Behaviour	Baseline Average total scores per patient	Eight week follow up Average total score per patient
Injecting behaviour (episodes)	51.2	20
Unprotected sex (episodes)	7.8	7.75

With physical health (Box 3), all patients had reduced their scores. The average total score per patient was 11.6 which was reduction of 41.35%. All patients had reduced their scores in the psychological health domain. The average total score per patient was 13 which was a reduction of 35%

BOX 3

Health	Baseline Average total score per patient	Eight week follow up Average total score per patient
Physical symptoms	19.78	11.6
Psychological symptoms	20.1	13

In the personal/ social functioning domain (Box 4), seven patients had contact with their partners and the average total days of contact per patient was 30 days which was an increase of 9%. Three patients continued to have conflict with their partners and the average total conflict days was 16.6 days which was an increase of 10.66%.

11 patients continued to have contact with their relatives and the average total days of contact were 26.09 days which was an increase of 48.23%. Five patients continued to have conflict with their relatives and the average total days of conflict per patient were five days which was a decrease of 62.9%.

12 patients continued to have contact with friends and the average total days of contact per patient were 20.5 days which was an increase of 14.28%. Two patients continued to have conflict with their friends and the average total days of conflict per patient in the previous thirty days were two days. This was a decrease of 81%.

Two patients continued to work .One worked in full employment and one worked for nine days. The average total days of employment per patient was 14.5 days which was an increase of 3%.

Only one patient had one episode of shop lifting which was a decrease of 75%.

BOX 4

Personal / Social Functioning	Baseline Av. total score per patient	Eight week follow up Av. total score per patient
Relationship Partner contact (days) Partner conflict (days) Family contact (days) Family conflict (days) Friends contact (days) Friends conflict (days)	 27.5 15 17.6 13.5 17.5 12.33	 30 16.6 26.09 5 20.05 2
Employment (days)	14	14.5
Crime (episodes)	7	1

QUALITATIVE RESULTS ON VIEWS OF MAP

Staff views regarding the administration of the Maudsley Addiction Profile:

"The MAP was focused and direct and explored areas which may not necessarily be addressed. It provided material for work in further sessions"

"The MAP was easy to use and it did not impinge on other duties, it was completed during scheduled appointments"

"I could see the MAP been implemented into daily practice. However there were concerns raised by some patients regarding confidentiality especially those with a criminal background"

"I found the questions very direct and patients found it easy to answer"

"The MAP provided information which often gets lost when focusing on screening results"

"It helps both the patient and staff member involved to see clearly if improvements have been made with treatment"

DISCUSSION

Interpretation of results

Two patients had stopped using drugs altogether. Both of these were male. Both had injected and had been heavy users of drugs. Data was incomplete as three patients were lost

to follow up at eight weeks due to the fact that they did not remain engaged with the addiction services. All three failed to return without reason. It was impossible to obtain any information regarding the status of these patients at the end of the study. The concern here is that these dropouts may not be representative of those who completed the trial.

The majority of patients in this study were male which would reflect the majority of addiction studies. Of those that completed the study, most scores showed improvement during treatment although it is not clear whether the improvements were significant as no statistical tests were applied. All substance use i.e. in both frequency and quantity showed improvement. No patient was using crack cocaine at follow up. Multiple drug misuse is common in this patient population. Treatment outcomes can be extremely variable and varying degrees of improvement can exist. Evidence has shown that drug treatment is effective in reducing illegal drug misuse[7-9]. Better treatment outcomes have been found to be associated with time in treatment and whether treatment was completed[10]. Retaining patients in treatment considerably enhances the benefits to both patients and society in general[11]. Early treatment drop-out is associated with a high risk of relapse to problem drug risk[12].

In this study a reduction in the misuse of alcohol was seen. The World Health Organisation advises that the maximum recommended levels of weekly alcohol consumption are 21 units for men and 14 units for females. Heavy drinking especially alcohol dependence is an important problem in drug misuse treatment and can sometimes be forgotten about. Dually (drug and alcohol) dependent individuals often have higher rates of criminal involvement and more health problems than drug misusers without drinking problems[13]. Heavy drinking causes a serious threat to the health of this group, especially as many have liver disease and impaired liver function[14]. The reduction regarding alcohol intake in this study could be due to a number of factors. Regular education around the use of alcohol and opiate substitution medication can improve awareness of the dangers of alcohol misuse. Another possible factor here could be that if any staff member has concerns of a patient's use of alcohol whilst on the programme, suspension of opiate substitution medication can be sought.

Physical and psychological scores showed improvement. In this study health risk behaviour showed improvement at follow up with decreased episodes of injecting behaviour. In 2005 The "Shooting Up" Report[15] showed that there was an increase in the sharing of injecting equipment amongst injecting drug users. This recent research into drug injecting trends amongst those using heroin and crack/cocaine suggested a growing risk of blood borne virus transmission i.e. HIV, Hepatitis B and C infection. Shaftesbury Square Hospital as with other addiction services provides education around injecting risk and unprotected sexual risk behaviours. Studies show that reductions regarding instances of injecting and sharing injecting behaviour have been found 4-5 years after patients were admitted to treatment programmes[16].

Psychological symptoms are common with this patient population especially those related to anxiety and depressive mood[17]. Many receive treatment for a psychiatric health problem other than substance abuse. Studies have shown that the severity of psychiatric disorder had been found to be related to poorer treatment outcomes[18]. In this study there was no information whether any of these patients were already engaged with mental health treatment i.e. primary care or secondary mental health services.

Regarding personal/social functioning, all contact (partner, family and friends) improved. Interestingly though the average score of partner contact had improved, the average score of partner conflict showed an increase. Possible reasons for this could be that during the initial withdrawal period from drugs, patients will become more aware of their surroundings and their responsibilities. Giving up the drug life style can lead to thoughts of guilt and self- blame leading to interpersonal and intrapersonal conflict.

There was a small increase in employment, however at follow up two patients continued to work compared to three at baseline. There was a reduction observed in crime episodes with treatment and this reflects other studies findings[19].

This study showed certain strengths. The subject researched was relevant to day-to-day practice in the Addiction Unit. All patients fulfilled the ICD10 criteria of Substance Dependence Syndrome. Sampled subjects were selected from the waiting list regardless of how they had been referred. There was no stringent inclusion or exclusion criteria. Data collection was systematic.

The use of a qualitative approach was appropriate. The Opiate Prescribing team were asked about their personal opinions of incorporating the Maudsley Addiction Profile tool into their assessments. Staff were encouraged to be open and honest. Any relevant statements were written verbatim by the authors.

There were several limitations which need to be mentioned here. The study only consisted of 15 patients and had a short follow up period of eight weeks after the initial assessment. However there were a lot of similarities in the results compared to previous studies[20-22]. Mean scores were taken and there was a lack of statistical analysis in this study. There was one patient who due to his high use of illicit use tended to skew the results.

It is important to be aware that not all aspects related to a full research project can be thought of at this very early stage and may only become obvious when the larger research project is carried out e.g. problems about resources may arise later in a main study (although this pilot study did not require a significant investment of resources).

In this study all of the patients received outpatient treatment. Due to the fact that only one form of treatment was used, no comparison can be performed between inpatient and outpatient treatment. There was also no record if a patient was commencing an opiate detoxification or an opiate stabilisation programme.

The MAP tool is depending on self report of drug use and behaviour. There is the risk of the "Hawthorne effect", in that the presence of the researcher may affect the behaviour of those researched. This is difficult to control for. Doubts are frequently expressed about the extent to which self-report screening instruments can provide an accurate picture of substance use. Patients may not want to admit to their drug

taking behaviour due to the fear of possibly not been accepted or retained in the treatment programme. In this study regular urine specimens were taken by the individual key worker to validate self report drug use. However it is important to remember that many of these illicit drugs have a very short wash-out period (i.e. they can leave the body quite quickly e.g. heroin 2-4 days, cocaine 12-72 hours). These illicit substances may therefore go undetected if patients are seen on a weekly basis.

It was difficult to quantify drug amounts. Many patients buy large quantities of drugs and make up their own drugs daily e.g. a joint of cannabis or a line of cocaine. The authors attempted to control for this by using drug standardised weights.

There were certain variables/factors omitted from the MAP assessment tool that should be considered and could influence outcome. Regarding the treatment of these patients in this study all were on some form of pharmacological treatment i.e. opiate substitution medication (methadone or buprenorphine), however doses were not recorded. Although all were seen weekly by their key worker the individual sessions were not standardised. Questions regarding accommodation arrangements (i.e. whether all patients at the time of the study were in stable accommodation or homeless) were not included.

Despite the limitations of this study, the overall results were positive regarding when patients with a diagnosis of substance dependency engage with an opiate substitution prescribing service. The study addressed the effectiveness of treatment. The treatment of this population is difficult and complex. Recognition of these factors and their importance helps treatment services more effectively.

From this pilot study a research question and plan can be developed. Involved service providers appeared positive regarding their opinions and attitudes of the study. This may help to convince others that the main study is worth pursuing.

The authors have no conflict of interest.

REFERENCES

1. Marsden J, Gossop, M, Stewart, D, Best D, Farrell M, Lehmann P, *et al.* The Maudsley Addiction Profile (MAP): a brief instrument for assessing treatment outcome. *Addiction* 1998;**93(12):**1857-67.
2. Mawhinney S, Ashe R, Lowry J. Substance abuse in pregnancy: opoid substitution in a Northern Ireland maternity unit. *Ulster Med J* 2006;**75(3):** 187-191.
3. Drugs and Alcohol Strategy Team. Department of Health, Social Services and Public Safety. New Strategic Direction for Alcohol and Drugs (NSDAD) 2006-2011. Belfast: Department of Health, Social Services and Public Safety, 2006. Available online from: http://www.dhsspsni.gov.uk/nsdad-finalversion-may06.pdf. Last accessed October 2008.
4. Janca A, Ustun TB, van Drimmelen J, Dittmann V, Isaac M. ICD-10 Symptom Checklist for Mental Disorders, Version 1.1. Geneva: World Health Organisation, Division of Mental Health, 1994.
5. Marsden J, Nizzoli U, Corbelli C, Margaron H, Torres MA, Prada De Castro L, *et al.* Reliability of the Maudsley Addiction Profile (MAP- ERIT Version) In Italy, Spain and Portugal for the evaluation of treatments. *Addicciones* 2001;**13(2):**217-27. [Spanish]
6. Marsden J, Nizolli U, Corbelli C, Margaret H, Torres MA, Prada De Castro L, *et al.* New European instruments for treatment outcome research: reliability of the Maudsley Addiction Profile and treatment perceptions questionnaire in Italy, Spain and Portugal. *Eur Addict Res* 2000;**6(3):**115-22.
7. The Audit Commission. Drug Misuse 2004: reducing the local impact. London: Audit Commission, 2004. Available in full text from the website: http://www.audit-commission.gov.uk Last accessed October 2008.
8. Gossop, M, Marsden J. Factors associated with abstinence, lapse or relapse to heroin use after residential treatment. *Addiction* 2002;**97(10):**1259-67.
9. Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. *Addiction* 2003;**98(3):**291-303.
10. Simpson DD, Joe GW, Brown BS. Treatment retention and follow up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychol Addict Behav* 1997;**11(4):** 294-307.
11. Joe GW, Simpson DD, Broome KM. Retention and patient engagement models for different treatment modalities in DATOS. *Drug Alcohol Depend* 1999;**57(2):**113-25.
12. Festinger DS, Lamb RJ, Kountz M, Kirby KC, Marlowe D. Pre-treatment drop-out as a function of treatment delay and client variables. *Addict Behav* 1996;**20:**111-5.
13. Gossop M, Marsden J, Stewart D, Rolfe A. Patterns of drinking and drinking outcomes among drug misusers: 1 year follow-up results. *J Subst Abuse Treat* 2000;**19(1):**45-50.
14. Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a four year period after seeking treatment. *Addiction* 2002;**97(1):**39-47.
15. Shooting up. Infections among injecting drug users in the United Kingdom 2004. An update: October 2005. London: Health Protection Agency, Centre for Infections; 2005. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1204186219334. Last accessed October 2008.
16. Gossop M, Marsden J, Stewart D, Kidd T. Changes in use of crack cocaine after drug misuse treatment: 4-5 year follow up results from the National Treatment Outcome Research Study (NTORS). *Drug Alcohol Depend* 2002;**66(1):**21-8.
17. Marsden J, Gossop M, Stewart D, Rolfe A, Farrell M. Psychiatric symptoms among clients seeking treatment for drug dependence. Intake data from the National Treatment Outcome Research Study. *Br J Psych* 2000;**176**:285-9.
18. Crawford V. Comorbidity of substance misuse and psychiatric disorders. *Curr Opin Psych* 1996; **9:** 231-4.
19. Hammersley R, Forsyth A. Davies J. The relationship between crime and opioid use. *Br J Addict* 1989;**84(9):**1029-43.
20. Franey C, Ashton M. The Grand design lessons from DATOS. *Drug Alcohol Findings* 2002;**7:**4-19. Available online from: http://www.datos.org/DATOS-FINDINGS.pdf. Last accessed October 2008.
21. Hubbard RL, Craddock SG, Flynn PM, Anderson J, Etheridge RM. Overview of 1-year follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychol Addictive Behaviors* 1997;**11(4):** 261-78.
22. Simpson D, Sells S. Effectiveness for treatment of drug abuse: An overview of the DARP research programme. *Adv Alcohol Subst Abuse* 1982;**2(1):** 7-29.

Ulster Med J 2009; **78 (1)** 26-33

Paper

An Approach to Traditional Cures in Ulster

Linda-May Ballard

Accepted 20 August 2008.

INTRODUCTION

The collections of the Ulster Folk and Transport Museum include Archives in which are preserved large quantities of information about all aspects of the history of the local way of life. During the 1960's and 70's, Questionnaires were circulated on a regular basis from the museum to respondents throughout Ulster, and these now constitute a vital part of this Archival Collection. In 1965, a Questionnaire (UFM/65/Q2) on the subject of 'Cures and Charms' was distributed, and this paper presents an analysis of the replies received, which provide considerable insight into the subject of curing among social groups who, in the absence of freely available health care and in a period when medical knowledge was considerably less well developed than is now the case, largely needed to be self reliant when facing illness. The personal experience of the respondents reflects in most cases the early decades of the twentieth century and in a few cases the late nineteenth, but the knowledge base on which this experience is founded is likely to be much older, as can occasionally be unequivocally demonstrated. It should perhaps be stated at the outset that the paper comes with a health warning, as some of the cures mentioned in the source are at the least mildly alarming, and some likely to be downright dangerous. The approach is historical and ethnological, rather than medical. Don't try this at home!

TABLE I:

Geographical Distribution of Responses

Region	Representation
Co Antrim	32
Co Armagh	12
Co Cavan	1
Co Donegal	11
Co Down	25
Co Fermanagh	9 (+1 unidentified, probably Fermanagh)
Co Londonderry	12
Co Monaghan	2
Co Tyrone	17

GEOGRAPHICAL DISTRIBUTION

Responses to the Questionnaire came from all nine of the Ulster counties, with Co. Antrim being the best represented, Co. Cavan the least well. (Information relating to cures in Cavan is however available in Beatrice Maloney, 'Traditional Herbal Cures in County Cavan,' *Ulster Folklife* vol 18.) Table I shows that almost 50% (57 out of 112) of the data came from the eastern counties of Antrim and Down.

Fig 1. Lough Neagh Eel Fisherman, Thomas John Quinn, demonstrates the use of an eel skin bandage as a cure for sprain. (Photograph by TK Anderson).

In terms of individual cures, some responses make reference to places other than that designated by the respondent as the primary area to which he or she refers. Occasionally, this may be to a cure to be found in another region and known to the respondent for an unspecified reason, frequently to a cure available in a particular place. For instance, one respondent from Ballycastle in Co. Antrim refers to water from a certain well on Rathlin Island as a cure for warts, while occasionally Belfast is specified in relation to a visit to the gasworks to cure whooping cough.

THE DATA

In total, the 112 completed questionnaires provide 1153 individual cures. Occasionally, a respondent knew more than one remedy for a specific ailment. Table II illustrates the number of cures for individual ailments. This Table is divided into two groups, the first of which comprises the fourteen ailments on which information was solicited by the questionnaire. In terms of quantity, this accounts for the overwhelming majority of individually cited remedies.

Ulster Folk and Transport Museum, Cultra, Holywood, Co. Down BT18 0EU, United Kingdom.

Correspondence to Linda Ballard

LindaBallard@nmni.com

TABLE II:

Numbers of Cures, (Group A, Solicited, Group B, unsolicited)

Ailment	No of References Recorded
Group A	
Asthma	35
Burn(s)	101
Cramp (differently interpreted by respondents)	64 (+1 animal)
Epilepsy	28
Erysipelas	31
Headache	70
Jaundice	37
Mumps	62
Rickets	11
Sprain	120
Stye	113 (+ 1, also for 'sore eyes')
Toothache	104
Warts	162
Whooping Cough	134
Group B	
Abscesses	2
Bed Wetting	1
Bloodlessness	1
Boils	3
Cancer	4 (+1, malignant skin disease)
Chilblains	3
Cold (possibly in horse)	1
Cooling Blood	1
Corns	1
Cough (human or horse)	1
Cut	2
Earache	1
Eczema	1
Foreign Body in Eye	2
Hiccough	5
Hydrophobia	1
Infectious Diseases	1
Influenza	1
Kidney Trouble	1
Measles	3
Purgative	1
Quinsy	1
Rheumatism	3
Ringworm	7
Scald	2
Shingles	1
Sore	1
Sore Eyes	4
Sore Throat	3
Stings	3
Stomach Ache/Ailment	4
Thrush (Oral)	1
Tuberculosis	4 (+1, 'early TB')
Ulcer	1
Varicose Veins	1
Wind/Colic	1
Wounds	1

However, some respondents also provided unsolicited responses, and these are noted as Group B.

CONSISTENCY OF THE DATA

Some of the cures cited by respondents refer to commercially available products. For instance, three of the cures for asthma (one from Co. Londonderry, one from Co. Donegal and one from Co. Down) cite Friar's Balsam as an inhalant. I know from personal childhood experience that this was also used as a cure for a wheezing chest condition referred to in my family as 'croup'. Glauber Salts are cited as a cure for toothache in one response from Moneymore in Co. Londonderry, while in another from Warrenpoint in Co. Down, Glauber Salts followed by oatmeal gruel provides a cure for headache. Mrs Cullen's Powders are referred to as a cure for headache in a response from Co. Monaghan. Of the references to cures for styes, 81 refer to thorns, almost always specifying gooseberry thorns, but these vary from merely a 'touch with a gooseberry thorn' to 'seventh son of seventh son pierces stye seven times with gooseberry thorn' or 'bless three times with nine gooseberry thorns pointing' or 'pierce with twelve gooseberry thorns, throw these alternatively over left and right shoulder.' Nine of the cures for stye refer to a wedding ring, one of these combining ring and thorn ('prick with gooseberry thorn passed through gold ring.') Another specifies that the ring used must belong to a 'widow with a posthumous child.' Twenty four of the cures for burns refer to baking soda, 20 to buttermilk, most usually in combination although each is also cited independently. 18 of the cures for erysipelas refer to butter, usually unsalted butter. Goose grease and eel skins

Fig 2. Coltsfoot. (Photograph by Paul Hackney)

Fig 3. Bogbean or bogbane. (Photograph by Paul Hackney).

are each mentioned eighteen times as cures for sprain (figure 1). Twenty five of the wart remedies refer to the effectiveness of either a snail or a slug, which usually must be rubbed on the wart and then impaled on a thorn. Another frequently mentioned remedy for whooping cough is to pass the sufferer under the belly of a donkey, although some specify the animal must be male, some female; some specify a particular number of times that the action should be repeated. For mumps, a roughly similar cure is cited. The victim should wear the blinkers of an animal and be led around the farmyard, visiting the various animal houses on the way. Occasionally, these are reversed so that the first is cited as a cure for mumps, the second as the cure for whooping cough. While it is possible that a degree of confusion has crept in for certain cases, there is also a reasonable degree of consistency in the reversal. Similarly, the belief that to lick the underside of a newt or 'mankeeper' provides a cure for burns is mentioned twice, but on one occasion this is given as the cure for asthma. ('Keep newt or frog 2 or 3 days, lick back of hungry newt or frog, lick chest of sufferer.') These and other examples provide evidence that belief in the efficacy of certain cures (if with certain specific refinements) was widespread across Ulster, but it is also clear that for many ailments there were several potential cures. For some of these, there is a strong degree of consistency, but some appear quite idiosyncratic. Geographical patterning does not generally account for the consistency, although both cures for 'foreign body in the eye' come from Co. Antrim, one from near Carrickfergus, one from near Ballymena. In each case, the cure is the same, 'Charm, mote appeared in bowl of clean water'. However, it cannot be assumed that this cure was not known in other regions. The data from the questionnaire helps to provide a picture of traditional remedies in Ulster, but additional information as yet uncollated from other sources will help to contextualise and further interpret the evidence presented here.

PLANT BASED REMEDIES

Plant based remedies may appear more 'rational' than some of the cures preserved in the questionnaire, but even some of these are quite idiosyncratic. For instance, garlic is mentioned as a cure for asthma (the leaves should be chewed in one case, in another garlic should be taken in a salad, in a third the usage is not specified) for epilepsy (again the use is not given), garlic seeds steeped in whiskey are cited as a cure for measles, and garlic in the socks as a cure for whooping cough. One respondent commented that his 'own remedy' for jaundice 'would be 3 or 4 oranges a day.' The same person remarked 'I have proved that eating about half a pound of grapes will bring very quick relief from influenza , but was also aware of cures known to others, and of plants whose curative powers are widely known. For instance, he remarked, 'A friend of mine cured a leg ulcer with applications of raw plantain leaves'. Plantain is widely known as a remedial plant.[1] Table III extrapolates from the Questionnaire all references to traditional plant based cures, although some of the names given are highly localised and occasionally incomprehensible.

I have used the precise spellings for plant names given in the source. Sherlock is likely to be charlock, both bustry and bourtry are most likely to be bore tree, or elder (*Sambucus nigra*.) Botanist Paul Hackney, who has kindly provided the Latin names (Table IV) and associated information included above, remarks of vernacular plant names 'they may be very local, or inconsistently applied to quite different species, or corrupted forms of standard names.' (Personal communication, 30 May 2008.) Bearing this caution in mind, it is the case that with the exception of blackcurrant, laurel, potato, swede and the mysterious cityfast and clancummer, all of these plants are in some way included in *Medicinal Plants in Folk Tradition,* although this book does not refer to the museum's questionnaire. The respondents therefore are referring to plants with reputations as medicinal, even if the applications listed above do not always match those mentioned in the book. The information they provide sits in a framework of medical efficacy also established elsewhere, and has the potential to make an additional contribution to this body of knowledge. It should be noted that while most of the references included in the table appear purely herbal, some

Fig 4. Ribwort plantain (Photograph by Paul Hackney).

are quasi magical, also involving the use of charms.

POULTICES, OINTMENTS AND INFUSIONS

Table III illustrates that occasionally plants provided the basis for poultices and infusions, but these were also prepared from other substances. A poultice of carbolic soap, milk and sugar is recommended in one case for boils. A flour

TABLE III:

Plant Based Remedies (figures 2-7).

Plant name	**Ailment**	**Usage (if known)**
Agrimony	Headache	Tea
Apple	Stye	1 Poultice (of rotten fruit) 2 Apply roasted
Ash	Jaundice	Boiled bark
Barbary	Jaundice	Green part boiled in milk placed next to skin
Blackheads	Asthma	Boil in sweet milk, drink liquor
Bogbane	To cool blood Headache Jaundice Stomach ailment	Dried and eaten Stewed roots 'of bogbind'
Bogbane ('bog beans') and dandelion leaves	Boils (also rheumatism and 'pains')	Boil, drink liquor
Bogbane, burdock and rose noble	Bloodlessness	Simmer together, 3 tablespoons taken per day
Broom	Kidney trouble	Leaves stewed
Burdock	Eczema Jaundice	Cupful of water in which roots boiled 'A dose'
Burdock, common dock and water dock	Jaundice	Boil equal parts of roots, drink 2/3 glasses of liquor daily
Bustry	Warts	Rub with leaf, bury leaf.
Buttercup	Warts	Leaves brought to woman who rubbed these on warts; 'three good words' said nine times
Buttercup or 'cityfast' (unclear if these are alternative names for same plant or alternative cures)	Cancer	Cured by brother and sister, plaster.
Celery	Rheumatism	Tea made from seeds
Chick(en) Weed	Erysipelas Mumps Sore ears Sprain	Applied warmed and dry Roasted on red coals and applied hot Warm chick weed Hold limb in spring of water and poultice with chick weed
Clancummer	Erysipelas	Boil
Coltsfoot	Asthma	1 Dried then burned and inhaled 2 Extract from coltsfoot 'really effective'
Dandelion	Mumps Warts	Juice Juice
Dock/docken	Nettle sting (3 references) Varicose veins Small burn Cough (in human or horse) Sprain	 Boiled Cover with skin (thin and transparent) of leaf taken from at/below ground level Seed Leaves
Elderberry and Blackcurrant	Tuberculosis (early stage)	Syrup from leaves of both, stewed together and taken in quantity
Eyebright	Jaundice	Boil in milk, drink liquor
Flax	Burn Cold (in horse?) Mumps Sprain Whooping cough	1 Carron oil of linseed and lime water (5 references) 2 Raw linseed oil Seed boiled, left overnight, few spoonsful taken. Linseed poultice Flax 'straining string' (linen thread) tied round affected part (4 references, also 2 to hemp cord, 1 to red cord, 1 to black thread and 1 to string knotted 3 times) 1 Seed boiled 2 Linseed oil mixed with liquorice

Garlic	Asthma Epilepsy Measles Whooping cough	1 Leaves chewed 2 Eaten in salad 3 Unspecified Seeds steeped in whiskey Placed in socks
Ground Ivy	Stomach ache	Stewed
Heather	Warts	Hot ash
Hemlock	Jaundice Mumps	Must be applied by certain person Stewed and applied as poultice
House Leek	Erysipelas Headache Sore eyes Stye	Boil leaves and apply Poultice Juice 1 Apply leaf 2 Apply nine leaves 3 Juice (2 references)
Jaundice bush	Jaundice	1 Boiled in milk, drunk 2 Bark boiled, liquor drunk 3 Piece of 'jaundice tree' boiled, liquor strained and drunk
Laurel	Burn	Jelly of leaves stewed in unsalted lard
Liverwort	Jaundice	Boiled in milk
Moss	Sprain	Rub
Nettle	Asthma Cramp	1 Boil roots with honey 2 Roots stewed Sting limb
Onion	Chilblains	Rub
Plantain	Burn Leg ulcer Wounds	Raw leaves Raw leaves Leaves of ribwort plantain beaten to pulp, applied and covered with gauze
Poppy	Sore eyes	Steam from seeds (presumably boiled)
Potato	Mumps Rickets Quinsy Warts	'Roast potato bandage' tied round throat Patient washed in hot potato water Hot poultice Rubbed with raw potato (potato also features in quasi magical cures for warts)
Primrose and 'bourtry' bush	Burn	Primrose leaves and 'boutry' bark boiled with butter, made into salve (unclear if all boiled together or butter used to make salve of boiled plants)
Primrose, speedwell and fairy flax (square stemmed variety)	Jaundice	Roots of primrose and speedwell boiled with stems of fairy flax in milk
Rhubarb	Jaundice	Juice
Rose Noble ('figurant')	Erysipelas Tuberculosis	1 Poultice, which is made either with 'fairy thimbles' or using either plant. 2 unspecified Berries boiled, liquor drunk
Rose, wild (dwarf white)	Headache	Shoots stewed
Sage	Erysipelas	Leaves stewed in milk, liquor drunk, leaves applied as poultice
Sherlock	Sprain	Heat leaves on oven, handful of salt
Solomon's Seal	Toothache	Root
Sunspurge ('devil's churnstaff')	Malignant skin disease	Milk like juice
Swede	Boils	Boil, mash and apply as poultice.
Tansy	Purgative Jaundice	Liquor of boiled plant
Tormentil	Stomach ache	Roots stewed
Violet	Cancer	Stew leaves, drain liquor and drink each morning
Whins	Headache Influenza	Eaten green Stew blossoms, drink liquor
Yarrow	Hydrophobia	

TABLE IV:

Latin Taxonomy

Popular Name	**Latin Taxonomy (where identifiable)**
Agrimony	Probably *Agrimonia eupatoria* or *Agrimonia procera*, but may refer to 'hemp agrimony' (bastard agrimony, Dutch agrimony, water agrimony etc.) which is *Eupatorium cannabinum*
Apple	*Malus sylvestris*
Ash	*Fraxinus excelsior*
Barbary	*Berberis* (several species)
Blackcurrant	*Ribes nigra*
Bogbane	*Menyanthes trifoliate*
Boutry bush, also bustry	Probably *Sambucus nigra*
Broom	*Cytisus scoparius*
Burdock	*Arctium minus*
Buttercup	*Ranunculus* spp.
Chick(en) Weed	*Stellaria media*
Coltsfoot	*Tussilago farfara*
Dandelion	*Taraxacum* spp.
Dock/docken	Species of the genus *Rumex*
Elderberry	*Sambucus nigra*
Eyebright	*Euphrasia officinalis*
Fairy thimbles	Probably *Digitalis*
Flax	*Linum usitatissimum*
Garlic	*Allium ursinum*
Ground Ivy	*Glechoma hederacea*
Heather	*Erica cinerea, Erica tetralix, Calluna vulgaris*
Hemlock	Strictly speaking, *Conium maculatum*, but respondents might be referring to hemlock water dropwort which is a much commoner plant in the same family, also poisonous, *Oenanthe crocata*
House Leek	*Sempervivum tectorum*
Jaundice bush	Probably *Berberis*
Liverwort	Many species. The commonest ones are *Pellia* species and *Conocephalum conicum*.
Nettle	*Urtica dioica*
Plantain	Any species of *Plantago*. The two commonest ones and the most likely intended are *Plantago lanceolata* (ribwort plantain) and *Plantago major*
Poppy	*Papaver* spp.
Potato	*Solanum tuberosum*
Primrose	*Primula vulgaris*
Rose Noble	*Scrophularia nodosa*
Sherock	*Sinapis arvensis*
Solomon's Seal	*Polygonatum*
Sunspurge	*Euphorbia helioscopia*
Swede	*Brassica napus* subsp. *Rapifera*
Tansy	*Tanacetum vulgare*
Tormentil	*Potentilla erecta*
Violet	*Viola riviniana*
Whins	*Ulex europaeus*
Yarrow	*Achillea millefolium*

and honey poultice is mentioned as a cure for an abscess, one of fat bacon for corns. For erysipelas, one source cites a poultice of black peat from bog hole, which should have no contact with air and be boiled in churned buttermilk. Another recommends bog water with unsalted butter for the same ailment. Hot bran applied as a poultice is once mentioned in the context of mumps. For a sprain, the recommendation is either a poultice of salt curd of sweet milk and buttermilk, or of oatmeal porridge. A cold tea leaf poultice is cited once as a cure for stye. A sock full of hot salt, sometimes called a 'salt poultice' is frequently recommended as a treatment for mumps and for toothache. However, the most frequently cited poultice is of cow manure, occasionally with refinements such as this should come from one animal and sometimes with the specification that it must be fresh. Sometimes it is used in combination with another element, usually clay. Cow manure is recommended for abscess, burns, erysipelas (mixed with flour), and scald. A poultice of goose manure is recommended for mumps, while for jaundice goose manure should be boiled in a cloth in milk, and the milk drunk. Ginger boiled in milk as a cure for cramp is frequently mentioned and sounds much more palatable. We have seen that eel skins and goose grease are both recommended as remedies for sprain, and in one case the application of a split salted fish is also suggested, with the note that it is very effective, although it smelled 'rather badly.' The juice of a 'gunnadoir', described as a 'stingfish found under rack' is mentioned as a cure for asthma. Soup of mouse flesh provides a cure for bedwetting in one reference from Co. Down, while a Co. Fermanagh source mentions otter soup for epilepsy. Saffron tea is recommended for measles. Cold water, usually from a spring, may be used as a rub or recommended to be drunk, in one case from a cow's

Fig 5. Rose Noble (Photograph by Paul Hackney).

horn. Blacksmith's cooling water (in which hot iron has been cooled) is recommended as a remedy for both rickets and warts (on one occasion, it is stipulated that the water must be taken without the knowledge of the smith, but it is impossible to know if this was to ensure efficiency or because the smith in question disapproved). Simple massage is also recommended in several cases. Occasionally, human urine features in cures. For jaundice, one cure suggests that the patient drinks his or her own urine, another that the patient urinates on an egg, then while praying places the egg in a south flowing stream. In one case, drops of liquor amnii are recommended as a cure for both styes and sore eyes. Pig's blood is frequently recommended as a cure for warts, and sometimes it is necessary for the sufferer to thrust wart infested hands into the throat of a newly slaughtered animal. Other substances mentioned as having curative properties are saltpetre, brown paper, mustard, whiskey, flannel, cloves, tobacco and one of the more alarming, for toothache, is a 'pea of "carobine" and light when wet in mouth.'

Fig 6. Violet (Photograph by Paul Hackney).

CHARMS

Occasionally, all of the above categories of cure may involve a particular person, the repetition of a prayer or formula, or a combination of these. Sometimes, for example in the case of using gooseberry thorns to cure styes, substance, individual and ritual all contribute to the remedy. The distinction between differing categories of cure is not always completely clear cut. In the case of blacksmith's cooling water, it is not clear whether the cure relates to the powers traditionally associated with this craft or to a chemical property of the water. The blacksmith is cited or implied in certain other cures too. In one case, the eldest blacksmith in the area is said to have a cure for rickets. Passing 'three times over the anvil' is mentioned as a cure for asthma. One cure for epilepsy in a child is described, 'child's head placed on anvil, other side of which struck by smith'. Reference to a terrifying experience of this sort is also found in other sources. For example Dr Francis McPolin, the principal of Ballymaghery Boys' School in Hilltown who made an important collection of folklore in his home area during the 1940's, mentions in his notebooks that a certain 'Blacksmith, (at) the Alt, tells me he is of the third or fourth generation of Blacksmiths and so he can cure, and did cure, rickets in children. He strips the kid, lays him out on the anvil, makes nine winds at him with the sledge hammer, washes him in the cooling water and then blesses him with a crucifix'. (These Notebooks are preserved in the Archive of the Ulster Folk and Transport Museum.) Other people referred to as acquiring cures by virtue of their status are children born in a particular point of the family sequence, occasionally third, but most usually seventh or seventh of seventh, sometimes but not always in a chain of the same gender. Married women, or occasionally a couple in which the wife's surname is unchanged, posthumous children, widows and widows with posthumous children are also mentioned. There is a reference to an occasion on which a person who has the power to cure loses this when the charm is used for an animal instead of a human. Cures may also be obtained at certain places, especially holy wells. In one cure for toothache, from Donegal, the recommendation is to say prayers to St Columbcille at certain stone in the graveyard of the abbey in Templedouglas, after which the afflicted jaw should be rubbed on the stone.

Fig 7. Whins (photograph by Paul Hackney).

The practices both of leading a person around animal houses (or to a well) while wearing blinkers and passing him over and under a donkey are sometimes described as 'charms', and may involve a degree of ritual, especially in the number of times or the time at which the action is repeated. However, some of the respondents refer to the possibility of there being a curative aspect in animal proximity. One remedy for mumps is that the sufferer should rub a cheek against 'the pigcroo door.' Another, for asthma, recommends the patient to 'remain in or above stable, "ammonia of urine"'. Similarly, the numerous wart cures that recommend rubbing the affliction with a snail also insist that the snail must then be impaled on a thorn, while those that prefer rubbing with raw potato sometimes state that this must be cut into certain number of pieces and/or be disposed of in a certain way. Warts may also be sold, or disposed of in various ways in the proximity of funerals. Whooping cough is frequently said to be cured by a woman whose name is unchanged at marriage, although occasionally she must give something, most usually food, the type and/or quantity of which may be specified, to the patient. A pinch of a material 'that cannot be counted' should be thrown at someone suffering from epilepsy. Another cure for epilepsy, one that is perhaps surprising in a local context, is 'Bury a live hen at patient's head' (if necessary carry the person to

suitable place in order to carry this out.) Cures for sprain are often attributed to a certain person who must be visited and who recites prayers or incantations while rubbing the wounded part. This cure is still extant, and I can vouch for its effectiveness (at least for a short time) as I have experienced it myself. Finally, the Questionnaire responses include a version of the ancient charm *Super petram*, a cure for toothache which Jonathan Roper has traced to the tenth century[2].

The Archive of the Ulster Folk and Transport Museum includes in addition to this Questionnaire various other sources relating to traditional cures. These are in the form of notebooks and audio recordings, which offer additional potential resources for the study of traditional medical practice in Ulster. However, this Questionnaire itself provides a substantial amount of data, which demonstrates that curers in past society had the capacity to draw on a range of skills, including no doubt psychological insight. It also shows that belief must frequently have been a powerful element in curative practice, as on occasion must a considerable degree of risk. Recently an examination of the in vitro antibacterial and antifungal efficacy of several of the plant remedies in table III has been reported[3].

Acknowledgements. Thanks to Paul Hackney for scientific identification of plant species. I am also grateful to Prof JE Moore for his encouragement to prepare this paper. All photographs are reproduced courtesy of the Trustees of the National Museums and Galleries of Northern Ireland.

The author has no conflict of interest to declare.

REFERENCES:

1 David E Allen, Gabrielle Hatfield. *Medicinal plants in Folk Tradition: an Ethnobotany of Britain and Ireland,* Timber Press, Cambridge UK, January 2004.

2 Jonathan Roper, English Verbal Charms, Academia Scientiarum Fennica, 2005) Folklore Fellows Communication No 288, Helsinki, 2005. pp 122-125.

3 Woods-Panzaru S, Nelson D, McCallum G, Ballard LM, Millar BC *et al*. An examination of antibacterial and antifungal properties of constituents described in traditional Ulster cures and remedies. *Ulster Med J* 2009;**78(1)**:13-15

Ulster Med J 2009; **78 (1)** 34-36

Paper

How useful is dual energy lateral vertebral assessment in a clinic setting?

Bernadette McGuinness[1], Sandra Stewart[2], Hugh Taggart[2]

Accepted 24 July 2008

ABSTRACT

Screening for osteoporotic vertebral fractures traditionally involves X-ray of the thoracic and lumbar spine. We evaluated use of dual energy X-ray technology in patients with osteoporosis. We found this technology useful in the clinic setting and it has advantages in that less radiation is delivered to the patient.

INTRODUCTION

Osteoporotic vertebral fractures are a major cause of morbidity. Those who have had a vertebral fracture are at an increased risk for future fracture but this risk is significantly reduced by appropriate treatment[1]. Many of these fractures cause little or no pain and it is has been suggested that less than one third are diagnosed clinically[2].

The use of routine x-rays for screening is inappropriate but dual energy X-ray technology can be used to assess vertebral morphometry with much less radiation exposure. We have assessed the practicality of using this technique in a clinic setting.

METHODS

Subjects

An osteoporosis specialist nurse assessed each patient attending an outpatient osteoporosis clinic. Those with suspected vertebral fracture were eligible. If a patient had suffered new onset of back pain, loss of height or a recent fall they were asked if they would like to participate, and 95 patients were enrolled. Written informed consent was obtained. The study was approved by the Queen's University of Belfast Ethics Committee.

Vertebral Morphometry

Dual-energy X-ray absorptiometry was performed by lateral vertebral morphometry (LVM) using a Hologic 4500A densitometer. Time taken to carry out this study was recorded for the first fifteen patients. The LVM image was evaluated independently by two non-radiologist clinicians (BMcG, HT) and agreement was reached after discussion.

Radiography

Patients had lateral thoracic and lumbar spine X-rays at the clinic or equivalent X-rays taken within the preceding three months were accepted. These images were independently and blindly assessed by the non-radiologist clinicians (BMcG, HT) using a digital calliper to calculate anterior, mid and posterior heights to the nearest one-hundredth of a millimetre.

All adequately visualised vertebrae (using both methods) were evaluated using an established semi quantitative visual scoring system[3,4]. A grade 1 fracture (mild) was defined as a 20-25% reduction in either anterior or middle or posterior height relative to the adjacent vertebral bodies; a grade 2 fracture (moderate) was 25-40% reduction in any height and a grade 3 fracture (severe) was a reduction of greater than 40% in any height.

Statistical Analysis

The grade of fracture seen on X-ray compared to that on LVM was evaluated using the weighted kappa score. Only those vertebral bodies that could be adequately visualised on LVM were included in the kappa score calculation.

RESULTS

95 subjects were recruited for this study over a three-year period, 70 females and 25 males. Age ranged from 29-89 years, mean age 59.5 (s.d.14.2) in males and 65.9 (s.d.11.3) in females. All patients had T scores <- 2.5 at lumbar spine.

LVM Analysis

There was difficulty analysing some of the upper thoracic vertebrae. L4 to T12 only was seen on one patient's images, L4 to T10 in 5 patients' images, L4 to T8 in 8 patients' images, L4 to T7 in one, up to T6 in 22 patients' images and L4 to T5 in 10 patients' images. In the remaining 48 patients images L4 to T4 was adequately visualised. An example of an image obtained is shown in Figure 1 with a crush fracture of L1 clearly visible. Of 1235 potentially evaluable vertebrae from T4 to L4, 1108 (89%) were adequately visualised. Mean time taken to complete the study on the first 15 patients was 19 minutes.

[1] Department of Geriatric Medicine, Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, United Kingdom, and [2]Belfast Health and Social Care Trust, Belfast, BT9 7AB, United Kingdom.

Correspondence to Dr McGuinness

b.mcguinness@qub.ac.uk

Vertebral Fracture Analysis

The number of vertebral fractures per patient ranged from 0 to 9 on X-ray. 12 patients had no fractures, 41 patients had 1 fracture, 21 patients had 2 fractures, 7 patients had 3 fractures and 14 patients had 4 or more fractures. In total 173 fractures were detected on X-ray.

Agreement between LVM and radiography

20 fractures visible on X-ray could not be visualised on LVM and so were not included in kappa score calculation (20/173=11%). A weighted kappa was used and overall agreement was very good (0.82; 95% CI 0.72, 0.92). There were no false positives with LVM analysis when compared to x-ray examination. There was one grade 1 fracture not seen on LVM, 3 grade 2 fractures not seen on LVM and one grade 3 fracture not seen on LVM. There was one grade 1 fracture graded as 2 on LVM, four grade 2 fractures graded as 1 on LVM, two grade 2 fractures graded as 3 on LVM and six grade 3 fractures graded as 2 on LVM. Apart from this there was agreement between both methods [Table I].

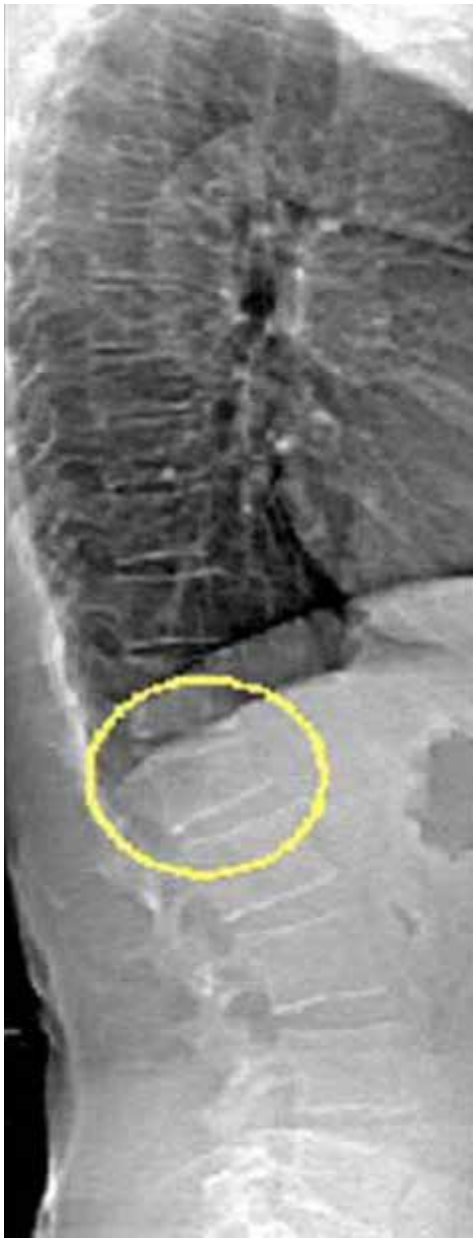


Fig 1. Example of an image with a crush fracture of L1 clearly visible.

DISCUSSION

LVM assessment of vertebral fractures is comparable in efficacy to radiography if adequate images are obtained. Most difficulty was found analysing upper thoracic images especially T4-T6 as there was interference from the lungs. The weighted kappa statistic of 0.82 implies very good agreement between both methods. LVM was able to detect 88.4% of fractures visible on X-ray; there were 20 fractures visible on X-ray that were not detected on LVM. This is comparable to a previous paper in which clinicians correctly identified 94% of radiographically defined grade 2 and 3 vertebral compression fractures[5].

The advantages of LVM include less radiation to the patient. The radiation dose of one X-ray is 800µSv whereas the dose received from LVM is 19µSv per exposure. Images are collected at the same time as bone densitometry so there is ease of use for both patient and operator. The average time spend from consent to exit from scanner was 19 minutes so most patients found the method acceptable. The use of clinical triggers e.g. recent onset of back pain, led to the osteoporosis specialist nurse correctly identifying those patients who required additional imaging in most instances.

TABLE I:

Comparison of fracture grade between X-ray and vertebral morphometry

	LVM Grade				
X-Ray Grade	**0**	**1**	**2**	**3**	**Total**
0	12				12
1	1	13	1		15
2	3	4	51	2	60
3	1		6	59	66
Total	**17**	**17**	**58**	**61**	**153**

The disadvantages of LVM include the difficulty in assessing the upper thoracic vertebrae. Twenty of the fractures detected on X-ray but not on LVM were in the upper thoracic vertebrae. This methodology is more useful for assessing the lower thoracic vertebrae and the lumbar vertebrae. If there is any doubt, lateral thoracic X-rays should be obtained. There was difficulty at times in choosing the correct point placement for height measurement. Very small changes in point placement led to differences in fracture rate and training and experience were required to read the images correctly. There was also difficulty analysing the images if the patient had osteoarthritic changes in the vertebrae.

Limitations of the study

We aimed to recruit as many patients as possible over a two-

year period. Due to time constraints at the clinic we were able to recruit only 95 patients. A larger group of patients would have improved statistical power. Another limitation was that the X-rays were not reviewed by a radiologist. A consultant with many years experience running osteoporosis clinics and a senior specialist registrar reviewed each film. Consensus was reached for each X-ray after discussion. The use of the digital calliper to measure vertebral height accurately also enhanced ability to detect each fracture.

Overall, LVM is a useful tool to assist in the diagnosis and management of osteoporotic vertebral fractures. It does not replace radiography, which remains the gold standard but is useful in a clinic setting reducing the frequency of patients' exposure to X-ray. This is particularly true for nurse/ radiographer led scan only clinics and it has been implemented in the local osteoporosis clinic.

Acknowledgements: We wish to thank Karen McCoy and Kerry Rafferty for their technical help, and Dr Chris Patterson for help with the statistical analysis.

The authors have no conflict of interest.

REFERENCES

1. Binkley N, Krueger D, Gangnon R, Genant HK, Drezner MK. Lateral vertebral assessment: a valuable technique to detect clinically significant vertebral fractures. *Osteoporos Int* 2005;**16(12)**:1513-1518.

2. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ,3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res* 1992;**7(2):**221-227.

3. Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1996;**11(7):**984-996.

4. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;**8(9):**1137-1148.

5. Melton LJ,3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. *Osteoporos Int* 1999;**10(3):**214-221.

Ulster Med J 2009; **78 (1)** 37-42

Paper

Electrical Fatalities in Northern Ireland

James Lucas

Accepted 22 July 2008

SUMMARY

A review of autopsy reports in cases of electrocution in Northern Ireland revealed that there were 50 accidental electrocutions and 9 suicidal electrocutions over a 22 year period (1982 – 2003). No cases of homicidal electrocution were detected in this jurisdiction. Analysis of the cohort of accidental electrocutions showed that there was a clear skew towards young and middle-aged male adults with deaths occurring more frequently in the summer months. Almost 60% of individuals were engaged in occupational tasks when they were accidentally electrocuted. High and low voltage-related deaths occurred with similar frequency and electrical appliances were found to be responsible for approximately one third of accidental electrocutions. The potential hazards of electricity must continue to be stressed in public safety campaigns if these relatively uncommon but tragic deaths are to be prevented.

INTRODUCTION

Given the widespread use of electricity, it is perhaps surprising that fatalities related to its use are not more common. Extensive legislation to ensure electrical safety, both in the home and at work, has almost certainly limited the potential for harm in developed countries. Nevertheless, it is estimated that about 1500 electrical-related deaths occur annually in the United States[1] with an average of one death occurring every day in the workplace[2]. Provisional data from The Royal Society for the Prevention of Accidents indicates that there were 27 deaths involving electric current in the United Kingdom in 2002[3], however this figure probably represents an underestimate of the actual number killed. Electrocution ranks in the top five occupational killers in the United States[2]. Statistics from the National Institute of Occupational Safety and Health show that although the number of electrical incidents is relatively small, there is a disproportionate fatality rate[4].

MATERIALS & METHODS

This study examines electrical fatalities which occurred in Northern Ireland over a 22 year period (1982 – 2003) using retrospective review of autopsy reports at the Northern Ireland State Pathologist's Department. Pathologists at the department undertake post-mortem examinations in almost all cases of sudden unnatural death instructed by Coroners in the province.

The search term 'electrocution' was entered into the electronic register of the State Pathologist's Department. Following case ascertainment, the author reviewed the autopsy report for each fatality and the relevant details were entered into a printed pro-forma.

The average annual incidence of accidental and suicidal deaths was calculated on the basis of historical population data for the study period, available from the Northern Ireland Statistics and Research Agency (www.nisra.gov.uk). The average population for the region during 1982 – 2003 inclusive was 1,625,682.

RESULTS

Fifty-nine cases of electrocution were identified in Northern Ireland in a 22 year period from January 1, 1982 to December 31, 2003. It is common practise for the examining pathologist to enter his opinion as to the manner of death into the register. This had occurred in most instances; in any case the nature of the death was generally obvious from the circumstances described. Of the 59 deaths, 50 were accidental and 9 were suicides. No cases of homicide were encountered. The suicidal electrocutions were subject to separate analysis.

ACCIDENTAL DEATHS

In most years there were two or three fatalities. In two years there were four deaths per annum and in four years there was only one death per annum. No cases were recorded in 1992 (figure 1). The average annual incidence of accidental electrocutions was 0.14 cases per 100,000 population per year. The victims of electrocution were overwhelmingly male (94%) with only three female fatalities encountered. There was a peak of cases in the summer months of the study period with nine deaths occurring in the month of July. Only one case occurred in the month of January (figure 2). The age range of the victims was 17 months to 80 years however there was a clear skew towards young and middle-aged adults (figure 3). The 17 month-old victim was the only young child identified in the cohort. This child was electrocuted by the live metal structure of a caravan, which had not been earthed. The oldest victim, an 80 year-old man, was in the process of recharging a car battery when he died. It would appear that he might have touched the live crocodile clips of the charging apparatus.

Fifty-eight percent of cases occurred outdoors, in various

Honorary Clinical Lecturer in Forensic Medicine, Institute of Forensic Medicine, The Queen's University of Belfast, Grosvenor Road, Belfast, BT12 6BS. United Kingdom.

Correspondence to Dr Lucas.

jwlucas_med@hotmail.com

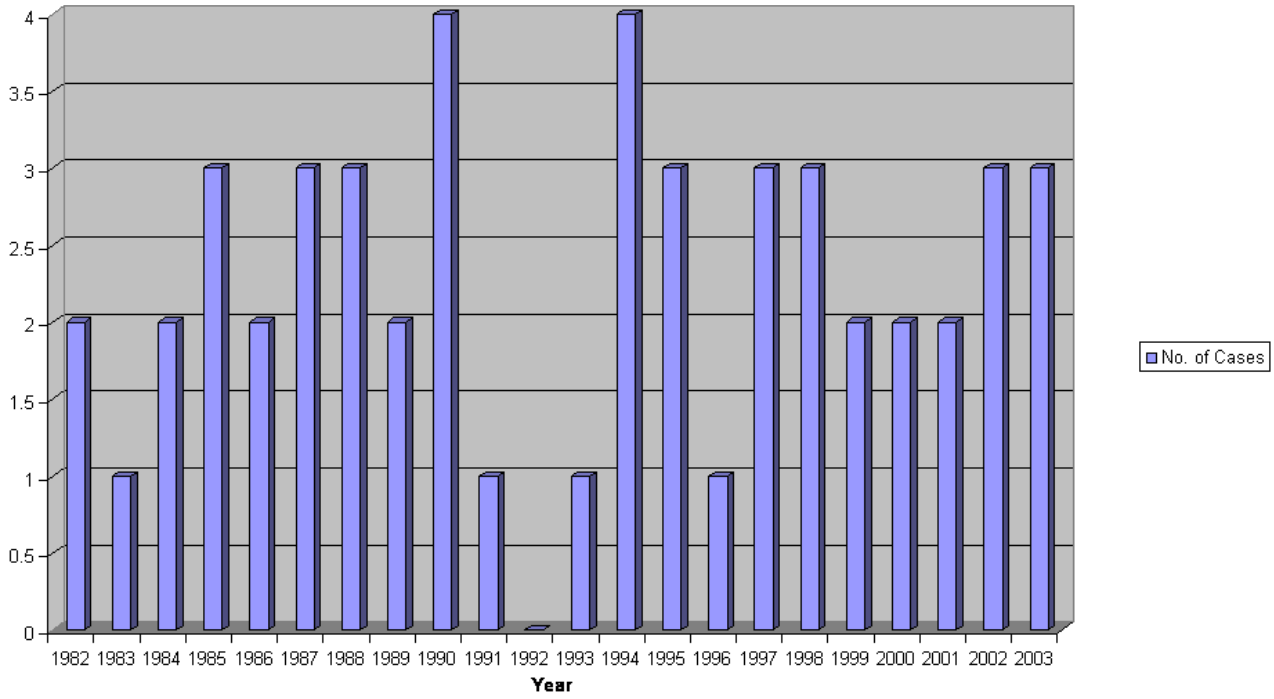


Fig 1. Fatal accidents per year

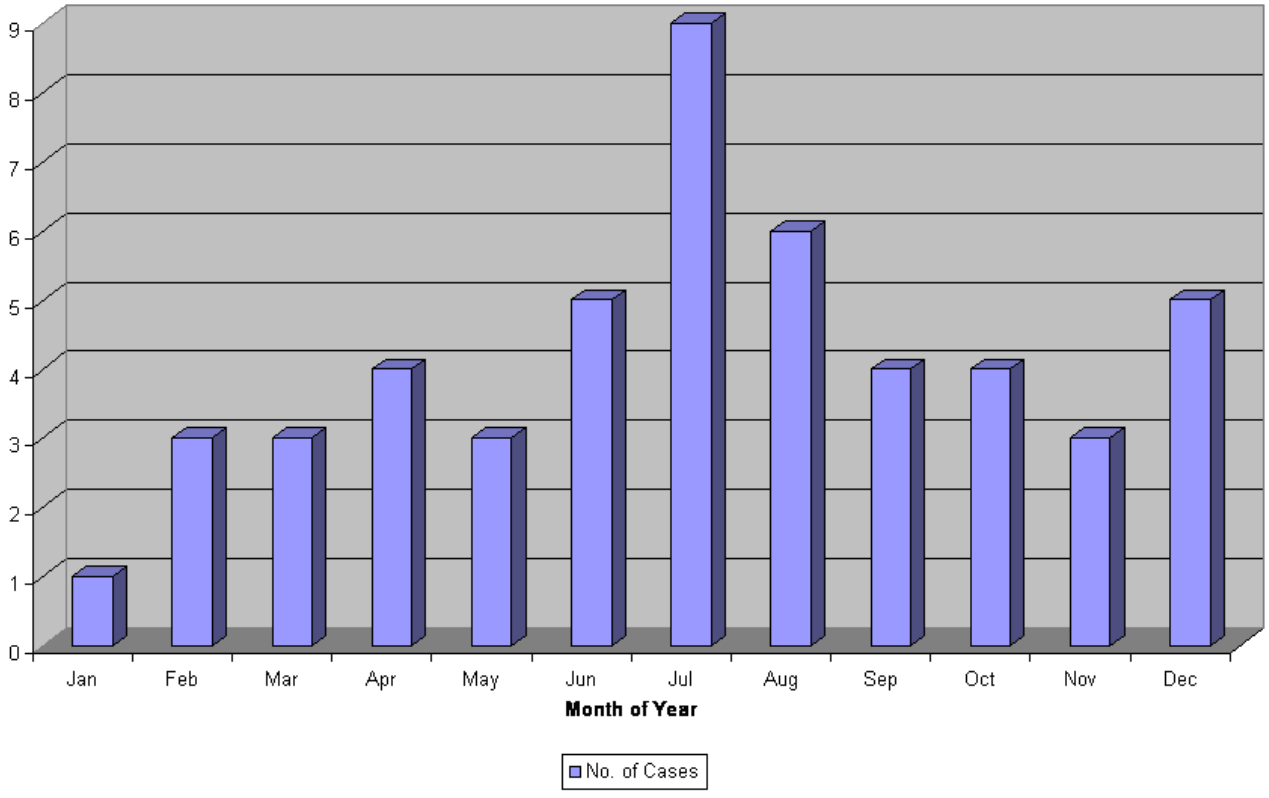


Fig 2. Case distribution by month

locations at home and in the workplace. Occupation-associated fatalities were identified in 58% of cases whilst 38% occurred in the domestic setting. In one case it was not clear whether the victim was engaged in DIY or occupational tasks. Another case was classified as para-occupational as the victim was a customer who was electrocuted at a business premises (figure 4). There were six farming-related deaths: four of these involved an electrical appliance (two cases involving electric sheep-shears, one case involving a chain-saw and in another an electric heating lamp). In two of the farming deaths, electrified cattle wire was being manipulated when it appeared to make contact with overhead cables. Six

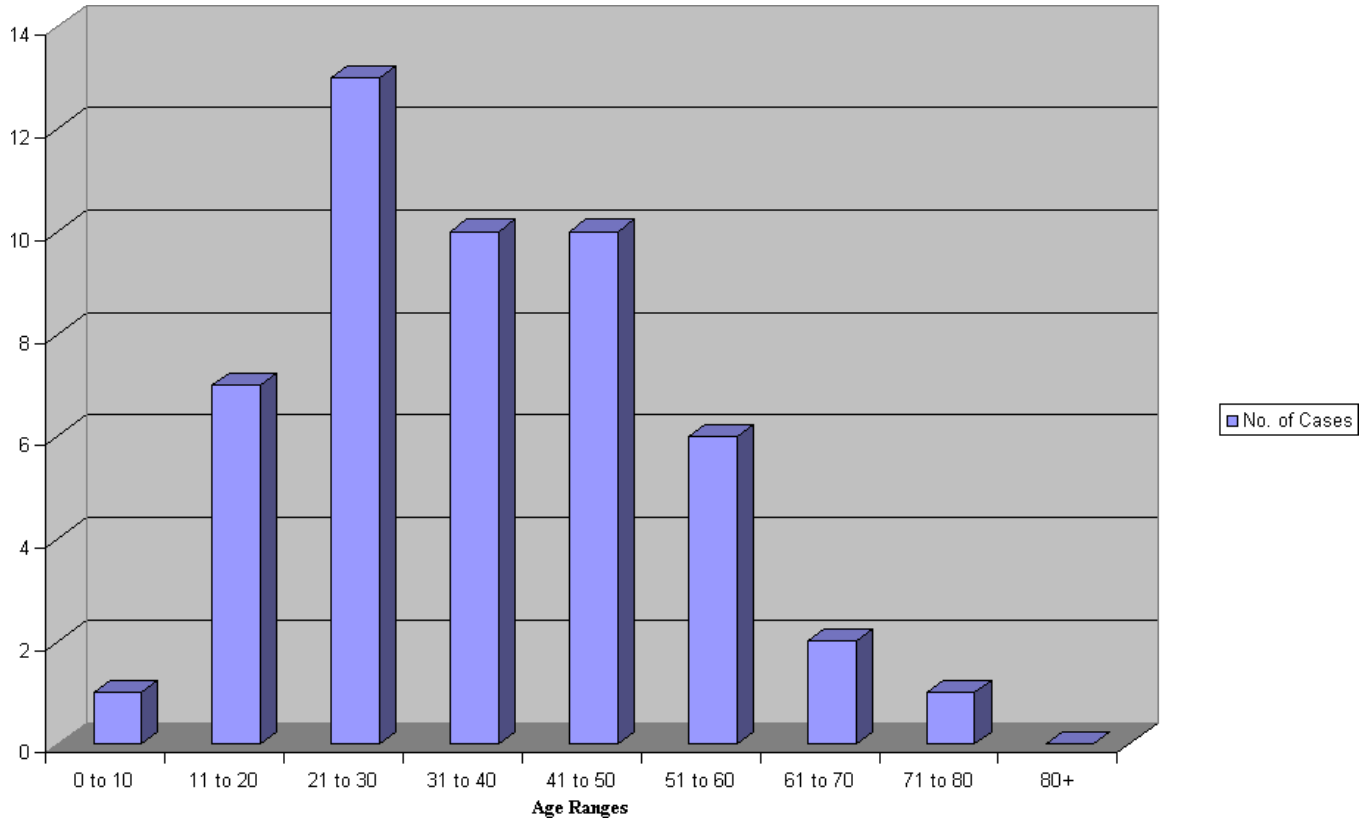


Fig 3. Age categories of accidental deaths

of the victims were electricians or electrical engineers; five of these deaths were clearly occupation-related. It would seem that in most instances, the electrician was not aware that the circuit was live, either through his own carelessness or due to that of others. One of the engineers failed to follow standard safety procedures and was electrocuted whilst working on high voltage wires.

The magnitude of the voltage involved was classified as high voltage (>1000 V) in 44% and low voltage (<1000 V) in 52% of cases. The voltage magnitude was not known or specified in 4% of cases (figure 5). Most of the high voltage cases (20 of 21) occurred in association with overhead cables whilst the individual was at work. These fatalities were sub-classified according to the object making contact with high-tension wires (table I). In several cases, there was no clear evidence that contact had been made with the overhead line and the possibility of arcing (dielectric breakdown) was considered.

Faulty electrical appliances were deemed responsible for electrocution in 32% of cases. The defective appliance varied with no one specific type of equipment emerging as a particular problem. Examples included white goods (cooker, washing machine and spin dryer), extension cables, power hoses and DIY equipment (drill, chain-saw, arc-welders), a television and video recorder, and a combined hand washing/ drying machine. A recurring finding was the presence of perished cable where exposed live wires had often been repaired with insulation tape. Some appliances were incorrectly wired at the plug with the earth wire loose or not connected and touching the live terminal.

Blood alcohol determinations were carried out in almost every case. Two cases were positive and in these instances the deceased was at least moderately intoxicated at the time of death (247 and 206 mg of alcohol per 100 ml respectively). A drug screen was performed in only three of the fifty cases, revealing a cannabis metabolite in the blood of one individual.

Apart from electrical marks, no other serious injuries were encountered although resuscitation injuries and trivial 'collapse' marks were very common. None of the victims appeared to have suffered significant bony injury as a result of the electric shock.

TABLE I:

Contact with overhead electricity cables (cases):	
Directly with the body	1
Crane or Hoist	7
Tipper truck/ other vehicle	6
CB aerial	1
Wire fencing	2
Steel lamppost	1
Football post	1
Other (tree branch)	1
Total	**20**

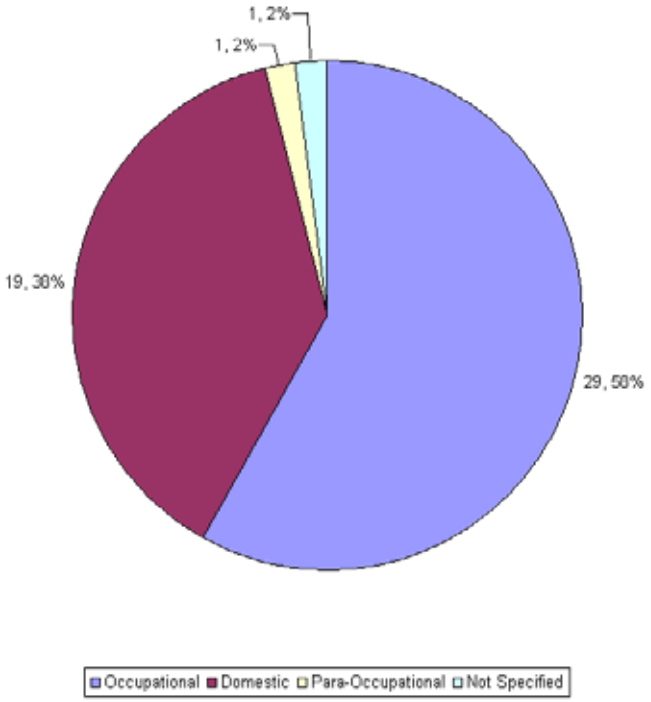


Fig 4. Nature of fatal accidental electrocutions

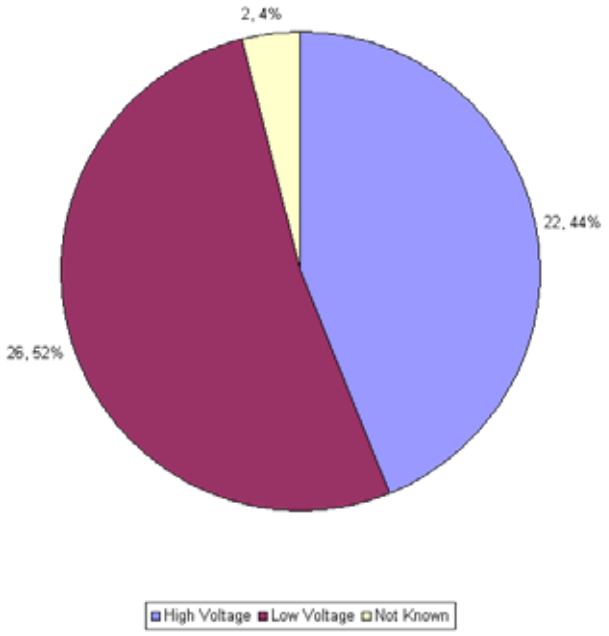


Fig 5. Type of voltage in fatal accidental electrocutions

Recognisable electric marks were detected in 94% of cases and these commonly affected more than one site (figures 6 - 8).

SUICIDAL ELECTROCUTIONS

The average annual incidence of suicidal electrocutions was 0.025 cases per 100,000 population per year. The victims ranged in age from 22 to 81 years old. Eight of the nine were male. All had used the domestic electricity supply, usually by removing the insulating sleeving of electrical flex so as to expose the wires. In six cases the exposed wires had been wound around both wrists; in two cases the wires had been attached to the chest in some way and one victim was found dead in the bath with an electric heater in the water. Eight of the deaths occurred at home in various rooms. One electrocution occurred in a hospital side room. This was the only case of delayed death following electrocution in either the accident or suicide group. He died from bronchopneumonia secondary to cerebral anoxia about three weeks after the electric shock. Electric marks were present in all cases except for the victim who died in the bath. Blood alcohol concentrations (BAC) were determined in eight cases and were positive in five of these. In three instances the victim was moderately intoxicated at the time of death but in two cases the BAC was less than 80 mg per 100 ml and had possibly accumulated in the post-mortem interval due to the effects of decomposition. In eight of the nine cases there was a documented history of depression and two victims had attempted suicide in the past (although neither had utilised electricity before). No psychotic illnesses were described in any of the victims. The only individual without a history of depression was the eldest of the group, a semi-retired electrician.

DISCUSSION

The results of this study were broadly similar to those previously published, showing that accidental deaths form the greatest proportion of cases[5-8]. In common with the published reports, suicides are relatively uncommon and homicides extremely rare. Overall case numbers were comparable with the Adelaide study[5] but significantly lower than the rate of fatal accidental electrocutions in Florida[6]. Electrocution is overwhelmingly seen in young and middle-aged males, probably a reflection of the fact that men are more commonly employed in industries at risk from electricity and are more likely to undertake home or garden improvement, or 'DIY'. Most studies have shown a preponderance of low-voltage related deaths, apart from one study from the Armed Forces Institute of Pathology in the United States[7]. This study was restricted to serving members of the armed forces. Published data reflects a higher incidence of fatal cases in the summer months, possibly as a result of increased humidity and the lower resistance of moist skin but other behavioural factors may be involved[8].

Suicidal electrocutions are relatively rare[9-11]. Only two of two hundred and twenty victims in Florida had used electricity to commit suicide[6]. Twenty-eight deaths were attributed to suicide in Australia, representing 29% of the total number of electrocutions over a thirty-year period[5]. In the latter study, eight victims had committed suicide immersed in the bath and eleven had wrapped electrical wires around various parts of the body. In Northern Ireland, just one suicide had used the bath.

Like other forms of 'violent' suicide, this method showed a strong male bias. There was a history of depression in all but one case - surprisingly there was no definite indication of psychotic illness in any of the victims. Electrical timers were not used by any of the victims during the study period although they have been reported in the literature[5]. Interestingly, the risk to individuals discovering the dead body was highlighted in a number of instances when family members or medical personnel received a shock after touching

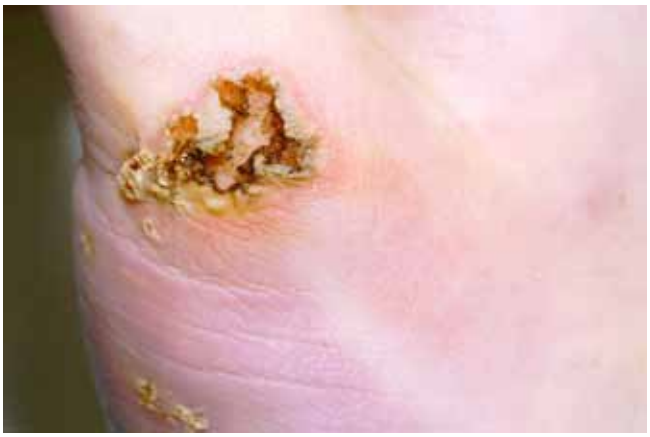


Fig 6. An electric mark at the base of the right thumb. The lesion consists of a ruptured blister with a scorched base and a bordering zone of hyperaemia.

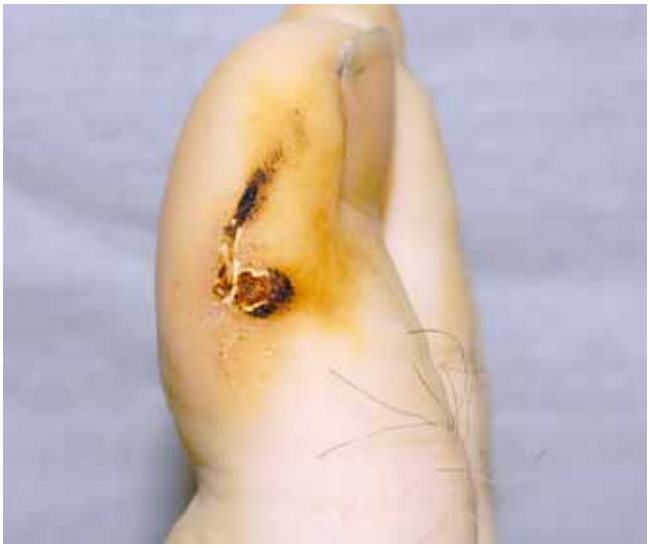


Fig 7. An 'earthing' or 'grounding' lesion on the great toe of the right foot, indicating the point of exit of the electric current. This is the same case as illustrated in Figure 6 - an occupational fatality caused by contact with overhead power lines.

the body, although none of these secondary shocks were fatal. Diagnosis of electrocution was straightforward in most cases, the majority of victims sustaining typical electric marks subjacent to the live wires. The death in the bath showed no such signs however, due to the dispersion of electricity across the body surface.

It is perhaps surprising that electricity is not utilised more frequently as a means to commit suicide. It is almost universally available to most homes in the developed world and must be considered, like hanging, to have a high success rate. One possible explanation might be that many people have had an unpleasant experience with electricity, such as a painful shock, in the past. Another explanation may be that electrocution is inextricably linked to judicial execution, to 'death row' and to the notorious electric chair. The marked differences in suicidal electrocution cases in published literature from the United States, where judicial electrocution is still used and from other parts of the world where it is not, provides some supportive evidence for this

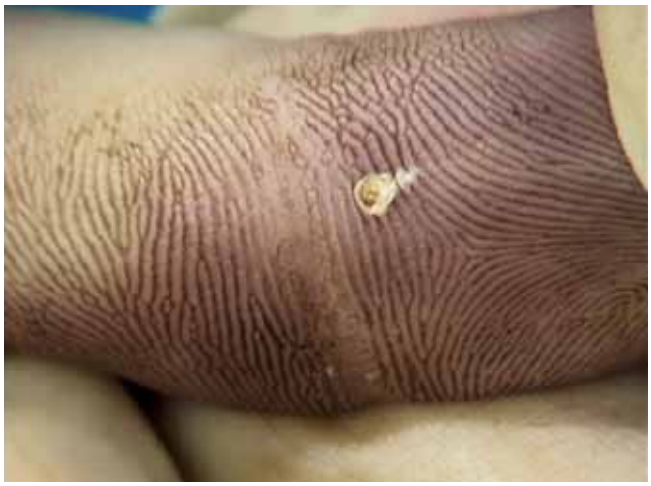


Fig 8. An extremely subtle electric mark on the index finger, highlighting the need for careful examination of individuals who have sustained an electric shock.

theory. The situation is somewhat analogous to the increase in suicidal hangings in Britain since the abolition of capital punishment[12]. One can only speculate as to the reasons why the nine individuals in this study had used electricity to commit suicide, as opposed to the thousands who had chosen hanging, poisoning, drowning or some other technique during this period. Only one victim, an electrician, could have been expected to have above-average knowledge of electric circuitry.

Homicidal electrocutions are vanishingly rare; none were detected in this jurisdiction during the study period. Sporadic case reports have appeared in the literature[13] and three cases were recounted by Saukko and Knight[14]. It has been suggested that the cited rates of homicidal electrocutions are possibly an underestimate of the true numbers as it may be difficult to distinguish the manner of death in certain circumstances, such as when the victim is found dead in the bath with an electrical appliance in the water[5]. This reinforces the importance of a thorough scene investigation in all cases.

DIELECTRIC BREAKDOWN

The phenomenon of arcing or dielectric breakdown is well recognised as occurring. The higher the voltage, the greater distance over which arcing can take place. Chandrasiri described a fatal case where electrocution had occurred without the victim touching the live conductor[15]. In this instance it was found that there was about a one-metre gap between an aluminium staff, which the victim was holding, and overhead power lines. According to this author, when voltages are of the order of 33 000 V, the sparking gap could be as large as 50cm. The Northern Ireland study indicated that dielectric breakdown fatalities were considered in several cases.

The most extreme form of dielectric breakdown occurs with lightning strikes. Fatalities are extremely uncommon in temperate regions however a number of deaths occur each year in warmer climates such as in the Southern United States[16]. No lightning deaths were described in Northern Ireland during the study period however one case occurred in 2006. This involved a young man who was walking in

the Mountains of Mourne, County Down. His body was discovered at the top of Slieve Donard, the highest mountain in this region. A thunderstorm was reported that morning. At autopsy there were fairly extensive cutaneous burns as well as defects in his all-weather clothing, typical of those due to high-voltage electrocution. Classical Lichtenberg figures (arborescent marks) were not observed.

CONCLUSIONS

Many of the accidental electrocutions occurring during the study period were readily preventable. Public safety organisations, government and industry must continue to promote electrical safety in the home and at work. Despite the readily available supply of electricity, suicidal electrocutions remain relatively rare.

The author has no conflict of interest.

REFERENCES

1. Perper JA, Electrical Injuries In Wecht CH (ed.), Legal Medicine Annual: 1976, New York, Appleton-Century-Crofts, 1977, 135-43.
2. Cawley JC, Homce GT, Occupational electrical injuries in the United States, 1992-1998, and recommendations for safety research, *J Safety Res* 2003;**34(3)**:241-8.
3. Accidents involving Electricity, The Royal Society for the Prevention of Accidents, Information Services, October 2004. http://www.rospa.com/homesafety/info/electricity.pdf (accessed 1st September 2008).
4. http://www.cdc.gov/niosh (accessed 1st September 2008).
5. Wick R, Gilbert JD, Simpson E, Byard RW, Fatal Electrocution in Adults – a 30 year study, *Med Sci Law* 2006;**46(2)**:166-72.
6. Wright RK, Davis JH, The investigation of electrical deaths: a report of 220 fatalities, *J Forensic Sci* 1980;**25(3):**514-21.
7. Mellen PF, Weedn VW, Kao G, Electrocution: A review of 155 cases with emphasis on human factors, *J Forensic Sci* 1992;**37(4)**:1016-22.
8. Rautji R, Rudra A, Behera C, Togra TD, Electrocution in South Delhi: a retrospective study, *Med Sci Law* 2003;**43(4)**:350-352.
9. Fernando R, Liyanage S, Suicide by electrocution, *Med Sci Law* 1990;**30(3)**:219-220.
10. Marc B, Baudry F, Douceron H, Ghaith A, Wepierre JL, Garnier M, Suicide by electrocution with low-voltage current, *J Forensic Sci* 2000;**45(1)**:216-22.
11. Bligh-Glover WZ, Miller FP, Balraj EK, Two cases of suicidal electrocution. *Am J Forensic Med Pathol* 2004;**25(3)**:255-8.
12. Pounder D, Why are the British hanging themselves? *Am J Forensic Med Pathol* 1993;**14(2)**:135-140.
13. al-Alousi LM, Homicide by electrocution, *Med Sci Law* 1990;**30(3)**:239-46.
14. Saukko P, Knight B, Knight's Forensic Pathology (3rd edition), London, Arnold, 2004.
15. Chandrasiri N, Electrocution by dielectric breakdown (arcing) from overhead high tension cables, *Med Sci Law* 1988;**28(3)**:237-40.
16. Wetli CV, Keraunopathology: an analysis of 45 fatalities. *Am J Forensic Med Pathol* 1996;**17(2)**:89-98.

Ulster Med J 2009; **78 (1)** 43-50

Medical History

Thomas Wrigley Grimshaw (1839-1900). Registrar general 1879-1900.

Caoimhghín S Breathnach, John B Moynihan

Accepted 25 September 2008.

SUMMARY

Thomas Wrigley Grimshaw was born in Whitehouse, County Antrim, in 1839, and learned his medicine at the Dublin School of Medicine when its reputation was at its highest. If his teachers strayed from the art of bedside medicine into science it was into meteorology that had been revived by Thomas Sydenham, the 'English Hippocrates' in the seventeenth century. When Grimshaw was appointed Registrar General for Ireland in 1879 he diverted attention from the acute epidemics of zymotic diseases to chronic pulmonary affections that numerically were far more deadly. Cartography became an obsession with him, and he used it to show that Ireland was divided by phthisis into east and west. Koch's 'great discovery' in 1882 that tuberculosis is an infection not a 'constitutional' disease made him change his long-held views, and in the decade before his death in 1900 at Carrickmines, County Dublin, he became an active advocate of the new knowledge, distressed by the fact that thriving Belfast and its hinterland had the highest mortality from phthisis in Ireland. His concern for the health of young girls employed in large numbers in the linen factories was matched by his landmark advocacy of young ladies anxious to gain the licence to practise medicine in Great Britain and Ireland.

INTRODUCTION

Like William Wilde (1815-1876) with the intensive analyses of the Censuses that earned a knighthood, Thomas Wrigley Grimshaw was not content to compile statistics, he continually analysed them. As Registrar-General for Ireland over twenty years he reviewed new data as they arrived, and he was not afraid to change his mind – and admit that he had done so. His major contribution was to divert attention from the 'zymotic diseases' (viz. small pox, measles, 'fever' i.e. typhoid and typhus) to phthisis (tuberculosis) and diseases of the respiratory organs, death rates from which greatly exceeded those from the three 'deadly acute infections'.

BRIEF LIFE.

Thomas Wrigley Grimshaw was born on 16 November 1839 at Whitehouse, then a small town on the Antrim shore of Belfast Lough five miles north of the city[1]. His great-grandfather had migrated from Whalley in Lancashire to Greencastle, at the mouth of Carlingford Lough in County Down, and brought the calico-printing industry to Ulster. Thomas's father, Wrigley Grimshaw FRCSI, established himself as an eminent dentist in Dublin and Thomas, after schooling in Newry, Carrickfergus and Dublin's High School, attended Trinity College Dublin, graduating BA 1860, MB 1861. His postgraduate qualifications included LRCSI 1862, LRCPI and MD 1867, FRCPI 1869, and Diploma in State Medicine (TCD) 1873[1,2]. In recognition of his brilliant answering in the Diploma, the MA degree was conferred on him *stipendis condonatis*[2], that is, by simply paying the

Fig 1. Thomas Wrigley Grimshaw, from Kirkpatrick Collection, reproduced courtesy of RCPI.

School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4. Ireland.

Correspondence to Professor Breathnach

caoimhghin.breathnac@ucd.ie

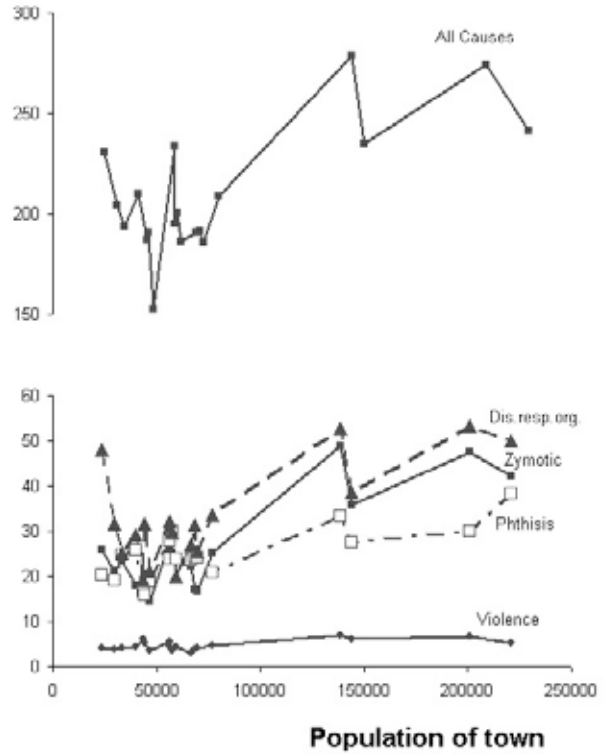


Fig 2. Mean death rates per 10,000 population in larger towns.

required fee. He was physician to Cork Street Fever Hospital and Dr Steevens' Hospital, where he lectured in succession on botany, materia medica and medicine[2]. In the autumn of 1879 he was appointed Registrar General of Ireland (based in Charlemont House, Rutland [Parnell] Square) in succession to Dr William Malachi Burke (1819-1879, a Galwayman who graduated at St. George's Hospital, London)[1] (Figure 1). Grimshaw, even though he was appointed towards the close of the decade, effected considerable improvements in the Report issued from his department for 1871-1880[1]. As part of his duty he published a *Supplement to the Seventeenth Report*: *Official Report on Births, Marriages and Deaths, Agricultural, Emigration, Banking, Criminal and Judicial Statistics, and on the Irish Census. 1871-80* in 1884[3].

He was president of the Statistical Society of Ireland (1888-90), The Dublin Sanitary Association (1885-88) and Royal College of Physicians of Ireland in 1895 and 1896. As part of the Queen's diamond jubilee he was made a Companion of the Bath in 1897[2]. He was one of the three Irish representatives at the inaugural meeting of the National Society for the Prevention of Phthisis and other forms of Tuberculosis at Marlborough House in London in 1899. Perhaps a more lasting influence was the request to grant qualification for medical registration *to all persons without discrimination of sex* made to the King's and Queen's College of Physicians of Ireland. In December 1876 during Grimshaw's presidency, John William Moore (1845-1936) successfully requested 'that permission be granted to Eliza Walker Dunbar, MD (Zurich), to be examined for the Licentiate of the College', a hurdle she successfully negotiated on the 11 January following. Thereby registration with the General Medical Council in London was opened to women through the enlightened action of the Dublin College.

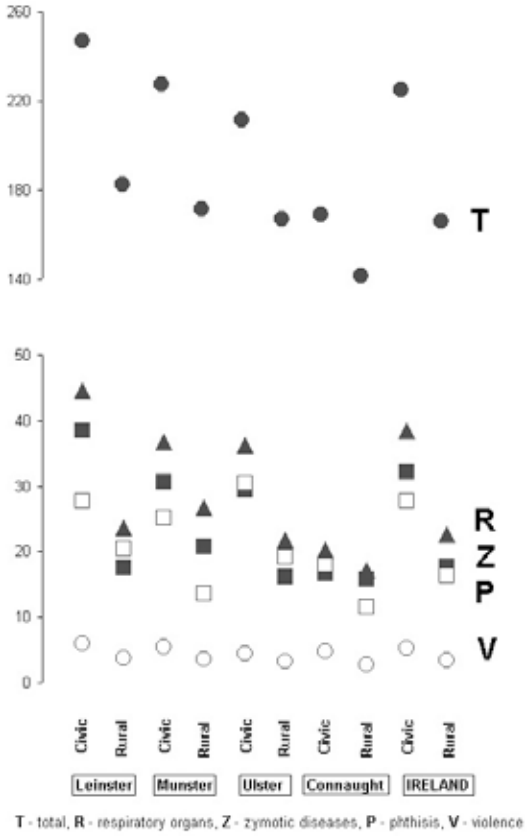


Fig 3. Death rates in civic and rural communities in the four Irish provinces. (abstracted from Grimshaw's elaborate diagram)[4].

At the early age of 26, Grimshaw married, on 11 April 1865, Sarah Elizabeth (Settie) Thomas of Broadlands, Newport, Isle of Wight. Of their twelve children, nine – seven sons and two daughters – survived their father, who died at his home at Priorsland, Carrickmines, county Dublin, on 23 January 1900[2].

REGISTRAR AND ANALYST.

The 1881 census returns gave him an opportunity to examine his view of the higher mortality among town dwellers[4]. He classified the population of Ireland into town or 'civic' populations (residing in towns of more than 10,000 inhabitants, Figure 2) and rural populations, and grouped the deaths registered according to these divisions. Although he was fully aware of the importance of the registration of diseases, he was also aware that its value was limited; 'death rates are much more exact than the statistics of disease'. Mortality and morbidity rates in town and country areas, revealed in his Tables I to IV, are summarised in Tables I and II. The contrast between civic and rural death rates stands out when demonstrated graphically (Figure 3)[4].

In the 'civic' population of 1,476,929 lung disease was the cause of death in 2.24 per 10,000, in rural districts the rate was 1.64 per 10,000 in a population of 3,816,678. The 'predominant cause of sickness and death in towns are lung diseases, not as many suppose, infectious fevers ... or the slightly greater prevalence of infectious diseases in town than in the country, but a much higher rate of mortality among affected persons'[4] (Table III). Grimshaw was struck by the

TABLE I.

Table of total deaths, and deaths from principal zymotic diseases, phthisis, and inflammatory diseases of respiratory organs, with rates per 1,000 population, in urban and rural districts.

1871 to 1880	Localities	Total deaths	rate	Zymotic diseases	rate	Phthisis	Rate	Other respir.	rate
Civic Districts		332526	22.5	47,656	3.2	40,849	2.8	56,724	3.8
Rural Districts		634219	16.6	67,391	1.8	62,688	1.6	86,267	2.3
Total Ireland		966745	18.3	115,047	2.2	103,537	2.0	142,991	2.7

TABLE II.

Death rates per 10,000 inhabitants in civic and rural districts

Respiratory illnesses	Phthisis	Diseases of Respiratory Organs	From both conditions
Civic districts	27.7	38.4	66.1
Rural districts	18.4	22.6	41.0

observation that whereas the rate for other lung diseases was lower, the death rate for phthisis in Belfast was higher than in Dublin. In concluding his 1881 Report he remarked 'the higher mortality from phthisis in Belfast must, I think, be attributed to the occupations of the people, especially among young girls, employed as factory hands' (p 403-4)[4].

In his Presidential Address to the Dublin Sanitary Association on 3 February 1887 Grimshaw had to admit that the death rate from tuberculosis in Dublin had risen slightly from 31.7 to 33.2 per 10,000, and that consumption was the 'principal cause of death in the constitutional class of diseases' (cited by Moore, p 316)[5].

In the Twenty-fourth Annual Report of the Registrar General for 1887, Grimshaw stated that consumption accounted for 21.3 deaths per 10,000 in the country as a whole, a tiny decrease on the average annual rate for the previous ten years; of the 10,329 deaths, 5,495 were of females. Of the total, 7,480 deaths or 72 per cent were of persons between 15 and 45 years of age. 'As heretofore, Leinster and Ulster yielded the highest rates, and Connaught the lowest. The rates were: Leinster 240; Ulster 219; Munster 179; Connaught 128 per 100,000.'. John William Moore contributed his usual Report on Meteorological Observations[6]. In highlighting the phthisis problem in Belfast Grimshaw was preceded by Henry MacCormac LRCPEd, MD (1832-1886) from Fairlaw, county Armagh, author of *On the Nature, Treatment, and Prevention of Pulmonary Consumption, and, incidentally, of Scrofula, with a Demonstration of the Cause of the Disease* and 'fresh air' enthusiast reputed to have broken the panes in closed sickroom windows. He retired from his post in the Belfast Medical School in 1866 to devote himself to science and philology – armed with his knowledge (so it was said) of twenty languages[7].

CARTOGRAPHY

On 19 May 1887 the Registrar General read a paper 'On the prevalence and distribution of phthisis and other diseases of the respiratory organs in Ireland' before the subsection of State Medicine of the Royal Academy of Medicine in Ireland[8]. He showed that pulmonary consumption, accounting for more than one-tenth of all deaths, was the most potent cause of death during the decade 1871-1880; it accounted for 103,528 deaths out of a total of 966,745. The countrywide death rate from phthisis was 19.6 per 10,000 annually. In towns with a population of 10,000 or more, the rate rose to 34.7. In Belmullet on the Mayo coast the annual death rate per 10,000 of the population from phthisis was 4.8; in the North Dublin Union it was 33.4, and in Belfast it was 38.2. A line drawn from Londonderry to Skibbereen divided the poverty-stricken west with little phthisis from the richer east with its phthisical towns[8]. Grimshaw improved on Wilde *a.* by contracting the social classes into four categories, and *b.* by recourse to cartography. (Figure 4, greatly simplified from the author's elaborate diagram). The four social classes in Dublin were: I. professional and independent, II. middle class III. artisan class and petty shopkeepers, and, IV. general service class[8].

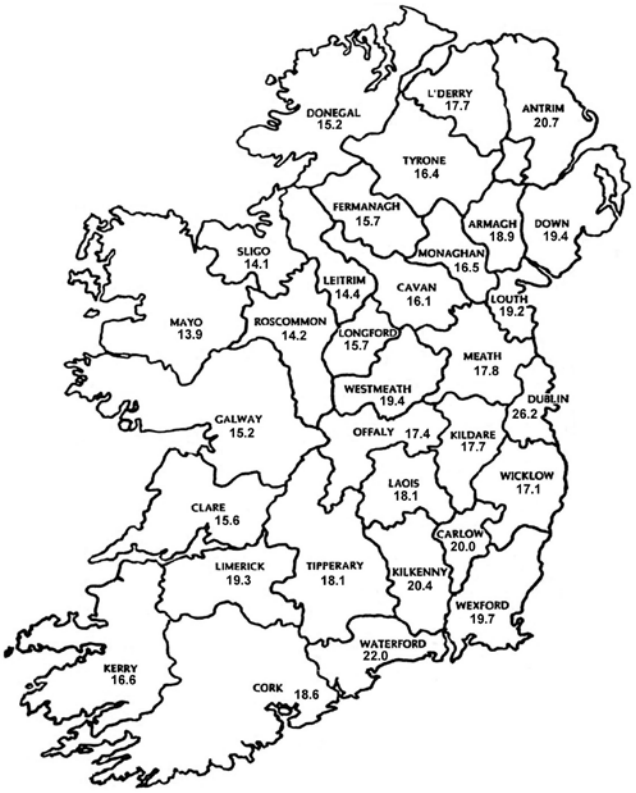


Fig 4. County death rates plotted from Grimshaw's 1881 census data[4].Grimshaw in the original map indicated by a line drawn from Londonderry to Cork (Skibbereen) the division of the west with little phthisis from the east with its phthisical towns.

Table III.

Respiratory Sickness rates in civic and rural districts.

	Civic districts No.	Sickness Rates / 10,000	Rural districts No.	Sickness Rates / 10,000
Dis Resp Organs	2,831	1.61	4,363	1.18
Phthisis	929	0.63	1,695	0.48
Total	3,760	2.24	6,058	1.66

His initial impetus to mapping phthisis and other respiratory diseases almost certainly arose from reading 'the interesting and valuable paper' by Mr Buchan and Dr Arthur Mitchell, in the *Journal of the Scottish Meteorological Society*, in July 1874 and July 1875), on the influence on mortality of different diseases and at different ages[9]. When the time came for his Presidential Address in 1887, he also had the benefit of Alfred Haviland's *Geography of Heart Disease, Cancer and Phthisis* (1875)[10] and *Consumption: its Social and Geographical Causes* (1883)[11]. Haviland's *Geography* was dedicated to, among others, William Farr (1807-1885) whose observation that the geographic distribution would lead to information stimulated him to have the map engraved on copper; and he concluded 'When once the colouring of maps is learnt, their teachings will prove to be simple and easily remembered; and I sincerely hope that what they will teach will be of service to those who consult them'. Furthermore, as Grimshaw acknowledged in the Address, Mr Buchan liberally placed his maps and tables at his disposal. (Grimshaw p 339)[8]. But he was a prisoner of Meteorology, one of the seven obstacles to be overcome in qualifying for the Diploma in State Medicine.

METEOROLOGY IN MEDICINE

Preventive medicine in these islands arose from Edwin Chadwick's *Report on the Sanitary Condition of the Labouring Population of Great Britain* (1842) and the subsequent *Public Health Act* of 1848[12]. The academic world was awakened to its responsibilities when Henry Wyndham Ramsey (1809-1876) circulated at his own expense one hundred copies of his *Essays in State Medicine* (1856), and his proposal for State Medicine received pride of place in the programme for the first meeting of the British Medical Association in Dublin in 1867[12,13]. William Stokes (1814-1878), regius professor of medicine in Dublin University, in his inaugural presidential address stressed at length the importance of Ramsey's work and of the need to introduce a certificate or diploma of competence in state medicine[13]. In February 1870 Stokes persuaded the medical professors in Trinity College to assent to the idea and they formally recommended to the Board (governing body) of the College that a qualification in state medicine be instituted. A more detailed proposal (curriculum etc.) followed. On the recommendation of the Board, the university agreed to offer a certificate in state medicine, but confined eligibility to its own graduates; quite deliberately no course of instruction was offered. The next year the General Medical Council accepted the Dublin proposal as the model to be followed, and candidacy was opened to Oxford and Cambridge graduates[13].

The details of the Qualification in State Medicine are crowded in small print on six cramped, crowded pages[14]. The subjects were 1 Law; 2 Engineering; 3 Pathology (including spread of fevers); 4 Vital and Sanitary Science, Statistics; 5 Chemistry: Air, Water, Gaseous Poisons (carbonic anhydride, coal); 6 Meteorology; 7 Medical Jurisprudence: i hygiene, ii forensic medicine. The candidates wrote nine papers, one on each of the seven subjects, together with one on hygiene as a separate subject from medical jurisprudence, and one set by the regius professor - which contained fifteen questions which were mostly epidemiological in content or concerned public health philosophy.

Meteorology disappeared from the course after Stokes's death in 1878[13]. Stokes was a lineal descendant of Sydenham, Boyle and Locke who during the seventeenth century had revived the Hippocratic importance of geographical environment in explaining the connection between fever and seasonal changes in the local weather. Stokes's climatic intransigence is best expressed in his 'Introduction' to Graves's *Physiological Essays* where at great length he argues that the French would find no difference between typhus and typhoid in Ireland, or less prosaically in 331 out of 743 deaths among physicians from typhus fever in Ireland - a mortality of 45 per cent in devotion to duty.

As Nicolaas Rupke has reminded us 'medical geography - the study of the global distribution of human diseases as a function of environmental conditions - was a largely nineteenth-century preoccupation'[15]. What Rupke has chosen to call "Humboldtian medicine" was a form of medical geography that made the new science of physical geography - synonymous with Alexander von Humboldt's (1769-1859) name - its basis, taking from it a scientific model of both explanation and representation for the global variations of health and diseases'. By shifting the burden of responsibility from the shoulders of the governing autocracies, conveniently 'Humboldtian medicine pointed the finger of accusation at nature, and not at the conditions of social deprivation'[15].

If 'a Humboldtian could be spotted by his isomaps' as Susan Cannon advised in *Science in Culture. The early Victorian period*[16], Grimshaw was certainly one. When his map was revived by the new Registrar General in 1906 the 'isomets' were removed but meteorological data collected by J W Moore now had 31 closely typed pages.

RECENSION

The winds of change struck in the final decade of the century. The bacteriological revolution was confirmed at a symposium held by the Section of State Medicine on 17 February in 1899, subsequently published in the *Transactions of the Royal*

Academy of Medicine in Ireland for 1899: the speakers and their subjects were[17]

W T Grimshaw: The prevalence of tuberculosis in Ireland, and the measures necessary for its control;

P Letters: A statistical inquiry into the distribution of tuberculosis in Ireland;

F C Martley: The death rate from tuberculosis in England; and,

E J McWeeney: The bacteriological aspect of tuberculosis.

Grimshaw sought a wider circulation for his recension by communicating his paper to the *Dublin Journal of Medical Science*[18]. The old distinction between 'zymotic' diseases of an infectious or catching nature and 'constitutional [diseases] which are caused or promoted by general unhealthy conditions, so prominent in previous papers and in the *Manual of Public Health for Ireland*, jointly written with Dr Emerson Reynolds, R O'Brien Furlong and JW Moore in 1875, had to be abandoned after 'Koch's great discovery [that tuberculosis was] of an infectious character'.

Comparative statistics impressed on him the gravity of the tuberculosis problem.

It is estimated that about 1 million deaths are annually caused by tuberculosis in Europe … In the United Kingdom the average annual deaths (1892-96) were: tabes mesenterica 8,659, tubercular meningitis 8,707, phthisis 59,015, making a total of 76,381, equivalent to 10.8 per cent of the deaths from all causes … Taking Ireland separately … the average deaths were, from tabes mesenterica 954, tubercular meningitis 928, phthisis 9,672, making a total of 11,554 and constituting 13.9 per cent of all deaths in Ireland[18].

For Dublin and its suburbs the corresponding figures were tabes mesenterica 229, tubercular meningitis 161, phthisis 1,214; total 1,604, equivalent to no less than 17.2 per cent of all deaths[18].

The unwelcome fact that phthisis had shown a tendency to increase in Ireland had to be faced. In the decade 1871-80, phthisis caused 10.7 per cent of all deaths, that is, 19.6 per 10,000 living. In the next decade the percentage rose to 11.7 and the rate to 20.9 per 10,000. During the three years 1895, 1896 and 1897 (for which detailed statistics were available) the average annual death rate was 17.3 per 10,000, for town districts 25.4 and for the rest of the country 15.2[18].

That the most lethal form, pulmonary phthisis, was well illustrated by comparing death-rates in the six large town districts. The mortality from the forms of tuberculosis other than pulmonary phthisis was the same in Dublin and Belfast, 1.8 per 1,000 of population; Londonderry 1.6; Waterford 1.21; Cork 1.1; and Limerick 0.7. For the pulmonary form, Belfast led with 3.9; to be followed by Cork 3.8. Dublin 3.3, Waterford 3.2, Limerick 3.0, and Londonderry 2.5. Phthisis caused 11.7 of all deaths in Ireland. In the rural districts the figure was 11.1 per cent – 'the proportion of deaths from pulmonary consumption is very high in the country districts'. After examining the question of tuberculosis in childhood (tabes mesenterica, tubercular meningitis, other non-pulmonary disease) he returned to the 'results [that] have taken me somewhat by surprise … the proportion of the people of adolescent and active adult ages who die of pulmonary consumption in the country districts of Ireland surpasses my worst anticipations' (p 252)[18].

Young adults were especially at risk. In the country as a whole 11.7 per cent of total deaths were due to phthisis; between the ages of 15 and 45 the percentage was 43.5; and between 15 and 35, 49.6; from 15 to 25, 52.8, more than half; from 25 to 35, 40.1; and from 35 to 45, 39.1 per cent. In the most fatal age decade (15-25) 44.6 of all deaths in Dublin was from phthisis; in Belfast, 55.4; in Cork, 54.4; in Limerick, 56.3; in Londonderry, 52.5; and, no less than 58.6 in Waterford. In the next decade of life the percentages were lower, but still close to one half of all deaths. Recorded from the most active portion of the community, these figures could not fail to excite considerable alarm[18].

Turning to the task of limiting the spread of tuberculosis from human sources, Grimshaw insisted first on general sanitary measures: cleanliness, letting in air and light at home and at work. Second came the cutting off and destruction of the contagious material itself, by isolation, and by destruction of sputum and discharges. 'Isolation' was not to be taken in the sense used for 'dangerous infective diseases'. The well-to-do with ample home accommodation could remain at home; for others, hospital isolation, in special voluntary hospitals provided by the local authority, was the only way to ensure 'the necessary conditions of safety for the healthy'. And 'the houses or rooms in which the patients had resided should be thoroughly cleansed and disinfected, so as to destroy all traces of the fatal bacillus (pp 254-5)[18].

Two incendiary questions were posed: 'How is the Sanitary Authority to become aware of cases? Is tuberculosis to be a compulsorily notifiable disease?' Compulsory notification he ruled out because it would be unpopular with physician and public, and should not be attempted because the Sanitary Authorities would simply be overwhelmed by the weight of numbers requiring isolation. Deaths from phthisis, no great cost there, 'should be brought under the notice of the Sanitary Authorities. And regional bacteriological laboratories would provide free sputum examinations[18].

'The Effect of Food derived from Tuberculous Animals on Human Health' was examined by Royal Commissions (1890, 1894, reported 1895), and a further Royal Commission (1896, reported 1898) 'was appointed to inquire into administrative procedures for controlling danger to man through the use as food of meat and milk of tuberculous animals' (p 166). The 1898 Report, quoted *in extenso*, met with Grimshaw's full concurrence, and he attested to the reliability of the tuberculin test in identifying infected animals in dairy herds. (pp 257-264)[18].

In closing he hoped he had 'said enough to convince the Academy that the great prevalence and destructiveness of tubercular disease constitute a most formidable danger to the public health, but was rather too sanguine in his hopes for the 'Movement for the Prevention of Consumption'. And, gracious in everything, he concluded by thanking Mr. P J O'Neill, Superintendent of the Statistical Branch of the General Register Office for the statistical portion of his paper and for correcting the proofs.

Table IV.

Death from Phthisis per 10,000 population in 1871-1880 and 1897[3,19].

Co.	1870	1897	+/-	Co.	1870	1897	+/-	Co.	1870	1897	+/-
Carl	20.0	17.8	-2.2	Clar	15.6	14.9	-0.5				
Dubl	26.2	30.5	+4.3	Cork	18.6	21.2	+2.6	**Ulster**			
Kild	17.7	19.1	+1.4	Kerr	16.6	16.6	0	Antr	20.7	29.9	+9.2
Kilk	20.4	18.9	-1.5	Lim	19.3	19.0	-0.3	Arm	18.9	22.7	+3.8
K'sL	18.1	17.5	-0.6	Tipp	18.1	17.6	-0.5	Cava	16.1	14.6	+1.5
Long	15.7	14.6	-1.1	Wat	22.0	20.5	-1.5	Don	15.2	14.1	+1.1
Lout	19.2	19.1	-0.1	Gal	15.2	15.7	+0.5	Dow	19.4	26.2	+6.8
Meat	17.8	20.8	+3.0	Leit	14.4	15.3	+0.9	Fer	15.7	15.6	-0.1
Q's	17.4	17.9	+0.5	May	13.9	15.8	+1.9	L'de	17.7	18.0	+0.3
Wm	19.4	18.9	-0.5	Rosc	14.2	16.0	+1.8	Mon	16.5	16.2	-0.3
Wex	19.7	21.8	+2.1	Slig	14.1	18.6	+4.5	Tyro	16.4	21.3	+4.9
Wic	17.1	17.5	+0.4								

RETROSPECT

Freeing himself from Hippocratic meteorology, Grimshaw had eventually reached Koch's discovery of the tubercle bacillus. In doing so he had overcome the hazards of meteorology and cartography, but his faith in the accuracy of the number of deaths annually registered was misplaced. In his 1885 paper he listed (but did not map) the death rates per 1,000 population in the thirty-two counties in the decade 1871-80 (p 384)[4]. The death rate in Mayo (13.9) was practically half that in Dublin (26.2). If the rates are plotted on a map of Ireland (Figure 4), a line from Londonderry to Cork will divide the low from the high county rates except for a small central nest in the north midlands.

The Births and Deaths Registration (Ireland) Act of 1863 appeared to give Ireland accurate annual statistics, but key provisions of the Public Health Acts of 1878 and 1879 which improved death certification were necessary to ensure effective notification to district registrars. It is possible, indeed probable, that reporting a death to the Registrar twenty or more miles away was not a priority among the bereaved in rural Ireland in the nineteenth century when the registration of Roman Catholic deaths was a new departure, ordained in a language foreign to the vast majority. The dead were buried in small, remote, isolated *grave*yards, where constables were no more welcome at burials than they were at Land War evictions escorting bailiffs; *church*yards were reserved for deceased members of the Protestant churches.

And deceit was not confined to the 'peasantry'; physicians did not relish annoying paying patrons by disclosing a precise diagnosis of the abhorrent phthisis – the stigma was equally loathed by rich and poor alike. At the very next meeting of the Section of State Medicine in the same Session as Grimshaw's 1885 paper, Archibald Jacob, thundering against compulsory notification, admitted openly (in relation to venereal disease) 'Concealment, such as I anticipate, from physician-notification is, in fact, practised to a great extent in death-registration, wherever there is an incentive to concealment'. And he turned to the Registrar-General's Annual Report for 1882 to provide irrefutable evidence of gross under registration[19]. The stigma of tuberculosis, with the resultant secrecy, had not abated in the twentieth century (Cyril F Warde, personal communication May 2004).

Annual returns continued to confirm the association of tuberculosis with poverty, restricted diet and poor housing, but after the discovery of the tubercle bacillus by Robert Koch in1882, slowly but surely, it became widely though not invariably acknowledged that the disease was infectious, not constitutional or hereditary. The death rate was falling steadily in England and Wales, and Scotland. Dr. Martley, from Almroth Wright's Inoculation Department in St Mary's Hospital London, revealed to the Dublin meeting in 1899 that in some districts of England and Wales the tuberculosis death rate was 32 per 10,000, away above the 24,000 for the whole country, and in other districts it was as low as 18,000 per 10,000; 'this extreme irregularity is explained – partially at all events – by how closely dependent the fatality rate is on overcrowding'[20]. His shires were selected, but so far as Ireland is concerned such a relationship is not easily assessed with any certainty because of the progressive depopulation during the second half of the century in all the provinces, affecting even the linen counties of Ulster (with the exception of the

Table V.

Mean rates of death per 10,000 from phthisis in Ulster towns.

	1871-80	1897
Armagh	24.2	36.1
Belfast	38.2	38.6
Lisburn	29.9	33.1
L'derry	24.0	25.2
Lurgan	23.5	33.7
Newry	24.3	24.2

TABLE VI.

Population Increase in Belfast during the Nineteenth Century.

Census	Population	% increase	Year	Population	% increase
1821	37,277	- -	1861	131,692	39.67
1831	53,287	42.95	1871	174,412	43.43
1841	70,447	32.20	1881	208,122	19.33
1851	87, 962	23.58	1891	266,185	22.98
			1901	349,180	36.43

baronies on the southern shore of Lough Neagh where an increase of 20 percent or more resembled that in Belfast)[21]. And Martley courageously begged to differ with his host: 'The action of climate is completely overshadowed by the social condition of the population'[20].

In contrast to the neighbouring island, the rate was rising slowly, if unsteadily, in Ireland, tuberculosis claiming 11,000 or 12,000 lives annually[5]. In 1885 Grimshaw had accepted as '*fact* that while the deaths from phthisis were 33.4 and 30.0 for the Dublin districts (North and South), and 38.2 for Belfast, the deaths from diseases of the respiratory organs were 52.9 and 52.3 in Dublin, and only 49.9 in Belfast. This would point to the tendency of pulmonary affections in Belfast to assume the phthisical type more readily than in Dublin' (pp 403-4)[4]. The confusion arose from the classification of phthisis as a *constitutional* not an infectious disease, but hindsight must also take into account the difficulty of accurate differential diagnosis: 'it is difficult to treat of phthisis and diseases of the respiratory organs separately, as they are, in *fact*, often combined in causing death, and many cases of phthisis originate in some other form of lung disease (p 387, passage already cited)[4]. Recollect that *incipient phthisis* was still a respectable diagnosis and featured prominently in the most renowned textbooks in the first quarter of the new century.

When Patrick Letters (d. 1911, physician at Valentia Island, County Kerry), who addressed the Section in February 1899 after Grimshaw, examined the returns in the 1897 Annual Report – again with the statistical help of PJ O'Neill, and the blessing of Registrar General Grimshaw - the Belfast rate exceeded Dublin's[22]. The national rate for deaths from phthisis per 10,000 population had not changed dramatically since 1871-1880 except in Ulster, where there were sizable increases in the eastern counties: Antrim 9.2, Down 6.8, Tyrone 4.9 and Armagh 3.8, while the rate dropped in Cavan, Donegal, Fermanagh and Monaghan. In Leinster increases were seen in Dublin (4.3), Meath and Wexford. Sligo (+ 4.5) stood out in Connaught, as did Cork (+ 2.6) in Munster (table IV).

Mean deaths from phthisis in the principal towns of Ulster were still rising (table V). The linen industry came to Ireland with the Huguenots in the seventeenth century but it was not until Belfast had its first flax spinning mill in 1828 that industrial prosperity came to the northeast, and the population of the city increased progressively until in the 1880s when the rate began to taper off. And then shipbuilding revived the upward trend (table 6). But industrialisation with the rapid expansion of population exacerbated the tuberculosis problem in the province[23]. Yet it is chastening to keep in mind that the mills employed just 30,000 out of a population that fell from 1,802,500 in 1871 to 1,619,814 (368,243 of them urban) in 1897. 'Kissing the shuttle' was the popular explanation among 'young girls employed as factory hands' (mentioned in Grimshaw's 1881 Report), but the moist and dusty warmth in the (crowded) mills provided an ideal environment for dissemination of infections and promotion of respiratory diseases.

The factors involved in morbidity and mortality related to exposure and environment are very complex. In the Prophit Survey of adolescent tuberculosis conducted under the auspices of the Royal College of Physicians in 1933-43, the morbidity rates for females were very slightly higher than for males among those in contact with open cases of tuberculosis. Among nurses and medical students the rates were approximately twice as high, and among controls the morbidity was four times higher for females than for males. The authors did not proffer an explanation[24].The predominance of females among adolescents continues to be striking[25]. Immunology has undergone a sea change in the meantime and the new knowledge is relevant to the plight of the young mill girls. In addition to the innate virulence of the tubercle bacillus itself, the host response to *Mycobacterium tuberculosis* plays a major role in determining the clinical manifestations and ultimate outcome in persons who encounter this pathogen[26]. Changes in the immune system without development of immunodeficiency are included in the physiological adjustments during pregnancy, and the complex signalling involved among the immunocytes is probably triggered or influenced by hormonal changes[27]. It is conceivable that the muted alterations conducted by the endocrine orchestra in dictating the normal menstrual cycle influences the immune response to tuberculosis in adolescent girls. Certainly there is evidence that steroids controlled by the hypothalamico-pituitary-adrenocortical system can influence the response of immunocytes in chronic infection[28].

Grimshaw attended the meeting in London in 1899 that set up the National Association for the Prevention of Tuberculosis (NAPT), but in so far as Ireland was concerned it remained an elitist club of Dublin, Belfast and Cork physicians. It was subsequently completely overshadowed once Lady Aberdeen's (1857-1939) Women's National Health Association (WNHA), founded in 1907, met with popular acceptance. Ironically the WNHA made skilful use of NAPT pamphlets in their own monthly magazine *Sláinte*, as indeed the Vice-Reine did of Registrar-General Reports that focussed, like Grimshaw's had done, on the dire mortality rate from tuberculosis in Ireland.

Acknowledgements: We are indebted to Robert Mills, Librarian RCPI, and Mary O'Doherty, Archivist RCSI, for invaluable help in preparing this paper. Dr Grimshaw's photograph is reproduced courtesy of RCPI.

The authors have no conflict of interest

REFERENCES

1. Cameron CA. *History of the Royal College of Surgeons in Ireland.* Dublin, Fanning. 1886. pp 595-6.
2. Moore JW. In Memoriam, Thomas Wrigley Grimshaw. *Dublin J Med Sci* 1900;**109:**157-160.
3. Grimshaw TW. *Supplement to the Seventeenth Report*: *Official Report on Births, Marriages and Deaths, Agricultural, Emigration, Banking, Criminal and Judicial Statistics, and on the Irish Census. 1871-80*. Dublin, Alex Thom. (HMSO) 1884.
4. Grimshaw TW. Observations on the relative prevalence of disease and relative death-rates in towns and country districts in Ireland. *Trans Acad Med Irel* 1885;**3:**382-404.
5. Moore JW. Tuberculosis in Ireland. *Practitioner* 1913;**90:**312-334.
6. Grimshaw TW. *Twenty fourth Annual Report of the Registrar General for 1887*. Dublin, Alex Thom. (HMSO). 1888.
7. Marshall R. The Open Window. *Ulster Med J* 1948;**17(2):**189-198.
8. Grimshaw TW. On the prevalence and distribution of phthisis and other diseases of the respiratory organs in Ireland. *Trans Royal Acad Med Irel* 1887:**5:**314-339
9. Buchan A, Mitchell A. The influence of weather on mortality from different diseases and at different ages. *J Scot Meteorol* Soc (New Series) 1876;**4:**187-265, 1878;**5:**171-188.
10. Haviland A. *Geography of Heart Disease, Cancer and Phthisis.* London, Smith, Elder and Co. 1875.
11. Haviland A. *Consumption: its Social and Geographical Causes &.* Douglas, Isle of Man, Browne and Sons.1883.
12. Acheson ED. Edwin Chadwick and the world we live in. *Lancet* 1990;**336(8729):**1482-85.
13. Acheson RM. Three regius professors, sanitary science, and state medicine; the birth of an academic discipline. *Br Med J* 1986;**293(6562):**1602-06.
14. *Dublin University Calendar* 1872. pp 101-106.
15. Rupke NA. Humboldtian medicine. *Med Hist* 1996;**40(3):**293-310.
16. Cannon S. *Science in Culture. The early Victorian period.* New York. Dawson, and Science History Publications. 1978. p 95.
17. Grimshaw TW, Letters P, Martley FC, McWeeney EJ. The prevalence of tuberculosis in Ireland, and the measures necessary for its control. *Trans Royal Acad Med Irel* 1899;**17:**530-64.
18. Grimshaw TW. The prevalence of tuberculosis in Ireland, and the measures necessary for its control, *Dublin J Med Sci* 1899;**107:**161-176, 251-265.
19. Jacob AH. Compulsory notification of infectious disease. *Trans Acad Med Irel* 1885;**3:**405-434.
20. Martley FC. The death rate from tuberculosis in England. *Trans Royal Acad Med Irel* 1899;**17:**584-587.
21. Davies KM. Population density maps in Ireland in the nineteenth century, in *A New History of Ireland* edited by TW Moody, FX Martin, FJ Byrne, Oxford, Oxford University Press, 1984, 9: pp 72,73.
22. Letters P. A statistical inquiry into the distribution of tuberculosis in Ireland. *Trans Royal Acad Med Irel* 1899;**17:**563-583.
23. Jones G. 'Captain of all these men of death'. The history of tuberculosis in nineteenth and twentieth century Ireland. 62 (Clio Medica/Wellcome Institute Series in the History of Medicine) Amsterdam, Rodopi. 2001.
24. Daniels M, Ridehalgh F, Springett VH, Hall IM. *Tuberculosis in young adults: Report of the Prophit Survey 1934 – 1944*. London, HK Lewis. 1948, pp. 147-8.
25. Donnell PR, Beyers N, and Rook GAW. Adolescent tuberculosis. *South Afr Med J* 1992;**86:**231-232.
26. Schluger NW, Rom WN. The host immune response to tuberculosis. *Am J Resp Crit Care Med* 1998;**157(3):**679-691.
27. Stirrat GM. Pregnancy and immunity. *Br Med J* 1994;**308(6941):**1385-1386.
28. Rook GAW, Onyebujoh P, Stanford JL. Th1-Th2 switch and loss of CD4 cells in chronic infections; an immuno-endocrinological hypothesis not exclusive to HIV. *Immunol Today* 1993;**14(11):**568-569.

Ulster Med J 2009; **78 (1)** 51-52

Case Report

ABCA3 Deficiency: an unusual cause of respiratory distress in the newborn

Mugilan Anandarajan, Sunil Paulraj, Richard Tubman

Accepted 6 September 2008

ABSTRACT:

Respiratory Distress Syndrome (RDS) is due to deficiency of surfactant and commonly occurs in preterm babies. We report the first confirmed case in Northern Ireland of ABCA3 transporter deficiency which is a rare but important cause of RDS in term babies.

A 38 week gestation female infant developed respiratory distress at four hours of age. Chest radiography was consistent with RDS. The baby required repeated doses of surfactant, each resulting in transient periods of decreased ventilatory requirement and improvement in blood gases, but unfortunately she did not survive.

DNA sequencing demonstrated two different mutations in the ABCA3 gene, one inherited from each parent. The baby was therefore a compound heterozygote, and both mutations were thought to be functionally significant.

ABCA3 transporter deficiency is a genetic disorder that is increasingly recognized as a cause of RDS in term babies in whom congenital deficiency of surfactant B and abnormalities of surfactant protein C have been excluded. It should be considered in mature babies who develop severe RDS.

INTRODUCTION:

Respiratory Distress Syndrome (RDS) is due to deficiency of surfactant and commonly occurs in preterm babies[1]. However, the condition can also occur in term babies and may be due to abnormalities of surfactant production. Surfactant protein B deficiency and abnormalities of protein C are recognized causes of abnormal surfactant[2]. Recent studies indicate that mutations in the ABCA3 transporter gene are a significant cause of RDS in term babies[3].We report the first confirmed case of ABCA3 transporter deficiency in Northern Ireland.

CASE REPORT:

A baby girl was born at 38 weeks gestation to non-consanguineous parents. Her mother was a primigravida whose membranes had ruptured three weeks prior to delivery. She had been treated with antibiotics for five days but was systemically well. The baby required no active resuscitation at birth but developed severe respiratory distress by four hours of age.

Initial investigations showed a high white cell count, a normal C-reactive protein and a white-out of both lung fields on chest radiograph, consistent with RDS (Figure 1). Blood cultures, respiratory viral screen, immunology profile, karyotype, ultrasound of abdomen and echocardiograph were all normal.

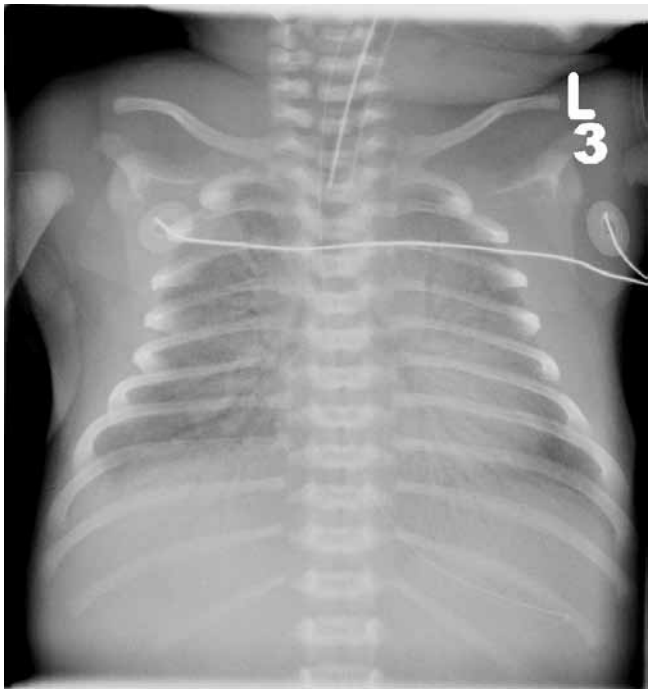


Fig 1. Chest radiograph showing severe RDS

She was treated with antibiotics and required mechanical ventilation and surfactant replacement. Her condition did not improve as expected, and she subsequently required high frequency oscillatory ventilation and multiple additional doses of surfactant. There were brief periods of decreased ventilatory requirements and improvement in blood gases following each dose of surfactant, but the effects wore off 18 to 24 hours after each treatment.

A provisional diagnosis of congenital surfactant deficiency was made. Broncho-alveolar lavage (BAL) was performed to test for surfactant proteins B and C, and blood was obtained for DNA analysis. The baby's condition continued

Royal Jubilee Maternity Hospital, Belfast HSC Trust, Belfast, BT12 6BB, United Kingdom

Correspondence to Dr Tubman

richard.tubman@belfasttrust.hscni.net

to deteriorate and on day 25 of life, after discussions with parents and family, intensive care was withdrawn and she died peacefully.

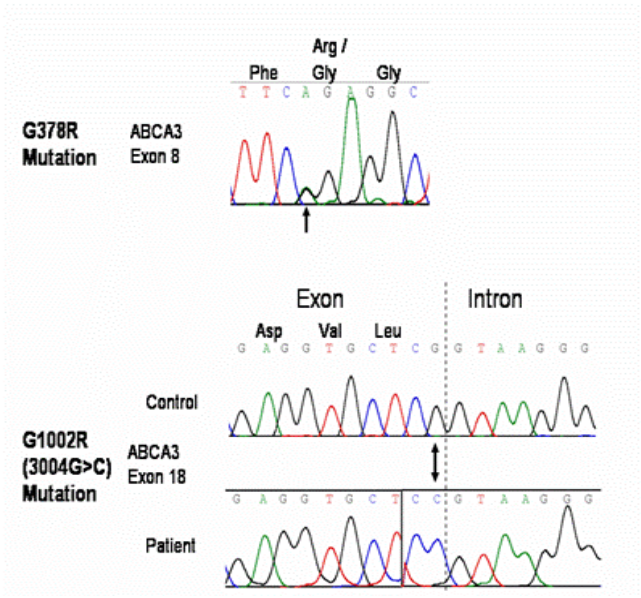


Fig 2. DNA sequencing showing two ABCA 3 mutations (arrowed)

Subsequently, surfactant protein B was detected in adequate concentrations in BAL fluid. DNA sequencing demonstrated a mutation in coding exon 8 on one allele of the baby's ABCA3 gene resulting in substitution of arginine for glycine (G378R, where G refers to Glycine and R refers to Arginine). There was a second mutation in the last base coding exon 18 that led to substitution of arginine for glycine in codon 1002 (G1002R). Both were non-conservative substitutions. One of these mutations was detected in analysis of the mother's DNA and the other mutation in the father's. Hence the baby was a compound heterozygote, with critically significant effects on her lung function (Fig 2).

DISCUSSION:

Surfactant is a complex substance containing phospholipids and four different types of surfactant proteins: hydrophilic proteins SP-A and SP-D and the hydrophobic proteins SP-B and SP-C. Surfactant is produced in the endoplasmic reticulum of the pulmonary type II alveolar cells. It is stored in the lamellar bodies and released from cells by exocytosis. After exocytosis surfactant undergoes a series of morphological changes to form a multilayered lipid rich coating at the air/ liquid interface in the alveoli.

Surfactant lowers alveolar surface tension, thereby stabilizing the lungs at the end of expiration, and preventing end-expiratory collapse. It also protects lungs against epithelial injury and provides a barrier against infection. Deficiency is common in preterm babies and results in respiratory distress syndrome, which is effectively treated with surfactant replacement. Recently, deficiency of surfactant proteins B and C, and of ABCA3 have been shown to be causes of RDS in more mature, term babies.

ABCA3 is a 1704 amino acid protein of the ATP binding cassette transporter family, whose exact function is as yet unknown. It is widely expressed in type II epithelial cells of the lung and is detected in the limiting membranes of the lamellar bodies which suggests that it is involved in the inward transport of lipids for the production of surfactant. Mutations of the ABCA3 gene may lead to the transport of abnormal lipids into these bodies leading to the production of abnormal or absent surfactant[4]. Evidence is accumulating of a range of different mutations in the ABCA3 gene[5].

The carrier rate of this condition is unknown but was thought to be extremely rare. ABCA3 transporter deficiency may be more common than originally believed[6]. The baby described here was unfortunate to have inherited two different mutations from her parents, leading to abnormal surfactant function and clinical features of severe RDS. Currently the only curative treatment available is lung transplantation without which most babies will not survive beyond 3 to 6 months of life. This treatment is however not readily available and highly problematic in very young infants.

Acknowledgements: We gratefully acknowledge the assistance of Dr Larry Nogee, Associate Professor of Paediatrics, John Hopkins Hospital, Baltimore and his staff for DNA analysis and helpful comments on the laboratory results. The authors have no conflict of interest.

REFERENCES:

1. Roberton's Textbook of Neonatology, 4th edition (Ed: J Rennie). London, Churchill Livingstone, 2005.
2. Shulenin S, Nogee LM, Annilo T, Wert SE, Whitsett JA, Dean M. ABCA3 gene mutations in newborns with fatal surfactant deficiency. *N Engl J Med* 2004;**350(13):**1296-303.
3. Whitsett, J A, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. *Hum Mol Genet* 2004;**13 (Spec No 2)**: R207-15.
4. Garmany TH, Moxley MA, White FV, Dean M, Hull WM, Whitsett JA, *et al.* Surfactant composition and function in patients with ABCA3 mutations. *Pediatr Res* 2006;**59(6):**801-5.
5. Saugstad OD, Hansen TW, Rønnestad A, Nakstad B, Tølløfsrud PA, *et al.* Novel mutations in the gene encoding ATP binding cassette protein member A3 (ABCA3) resulting in fatal neonatal lung disease. *Acta Paediatr* 2007;**96(2):**185-90.
6. Garmany TH, Wambach JA, Heins HB, Watkins-Torry JM, Wegner DJ, Bennet K, *et al.* Population and disease-based prevalence of the common mutations associated with surfactant deficiency. *Pediatr Res* 2008;**63(6):**645-9.

Ulster Med J 2009; **78 (1)** 53-55

Case Report

Mesenteric vein thrombosis associated with anti-thrombin III deficiency

Kelly-Ann Eastwood, Alison Vaughan, Kenneth H McCune

Accepted 27 August 2008

INTRODUCTION

Acute mesenteric ischaemia presents infrequently in clinical practice accounting for 1-2 cases per 1000 hospital admissions per year[1]. Of these, mesenteric vein thrombosis (MVT) is responsible for between 5% and 15% of intestinal ischaemic events[2].

Primary mesenteric vein thromboses are typically seen in patients with thrombophilias due to protein C, protein S and anti-thrombin III deficiency. Approximately 2% of primary MVT cases are caused by anti-thrombin III deficiency[3]. Secondary MVT is commonly seen post-operatively, with oral contraceptive use, trauma or in paraneoplastic syndromes.

Despite advances in diagnostic techniques and management of this disease, the prognosis remains poor with mortality rates ranging from 20% to 93%[2,4]. We describe a case of primary MVT attributable to anti-thrombin III deficiency.

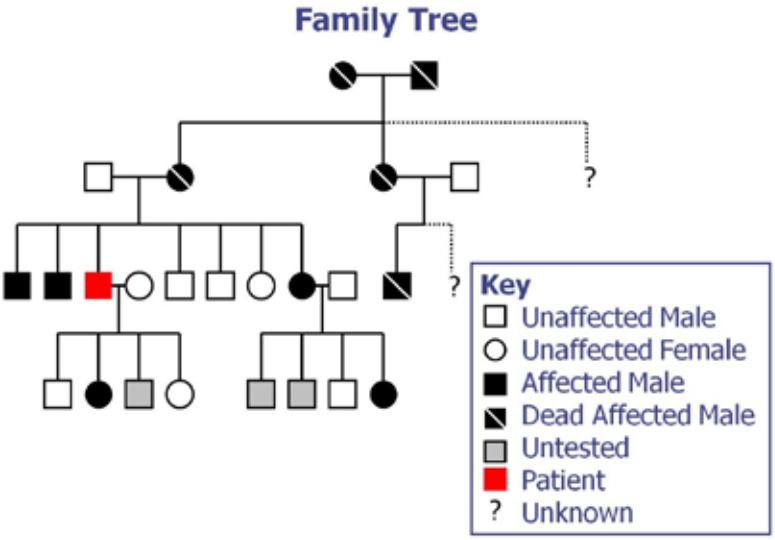


Fig 1. Anti-thrombin III deficiency in this patient's family

CASE REPORT

A 49-year-old man was admitted with a two-day history of worsening abdominal pain associated with nausea, vomiting, and constipation. His past medical history revealed a background of two proximal deep venous thromboses (DVT) and an earlier diagnosis of anti-thrombin III deficiency. He smoked over 30 cigarettes per day and consumed more than 30 units of alcohol per week. He had a family history of anti-thrombin III deficiency and many family members were already taking life long anticoagulation (figure 1). The patient had been previously warfarinised following his DVTs, but latterly had been non-compliant. On examination he was normotensive but tachycardic with abdominal distension, guarding and absent bowel sounds. The degree of subjective pain was disproportionate to his objective tenderness. Digital rectal examination was unremarkable. Initial investigations revealed a leucocytosis and elevated C-reactive protein. A plain abdominal radiograph showed dilated bowel loops in the left flank. Treatment with intravenous fluids, analgesia, anti-emetics and broad-spectrum antibiotics was commenced. An emergency computed tomograph of his abdomen was carried out in the portal venous phase; this showed thrombosis in the superior mesenteric vein extending to the portal confluence (figure 2) but the portal vein was patent. Small bowel loops were dilated and oedematous, although not clearly necrotic, and there was free fluid in abdomen and pelvis. On the basis of the clinical presentation and radiological findings, the patient was taken to theatre for a laparotomy. Intra-operatively a clearly demarcated venous infarct of the mid small bowel was found. A small bowel resection with primary anastomosis was performed. The pathology report of the resected specimen confirmed small intestinal haemorrhage and infarction with marked transmural inflammatory cell infiltrate.

Post-operatively he was transferred to the intensive care unit where he subsequently developed a severe systemic inflammatory response. Over a period of several days, his clinical and biochemical parameters suggested ongoing sepsis but the aetiology of this was unclear. He therefore underwent a second look laparotomy, but no evidence of further bowel infarction was found. Throughout his admission to the intensive care unit, the patient received full systemic support and was anti-coagulated with low molecular weight heparin.

Department of General and Vascular Surgery, Altnagelvin Area Hospital. Londonderry, United Kingdom.

Correspondence to Kenneth McCune

khmccune@msn.com

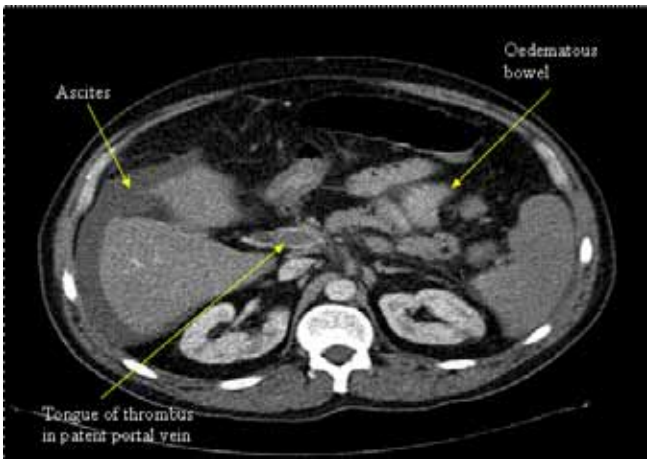


Fig 2. Abdominal CT showing tongue of thrombus extending into portal vein, bowel wall oedema and ascites.

The efficacy of anti-coagulation was monitored with factor Xa assays. Despite this, he developed multiple organ dysfunction syndrome and required increasing ventilatory support, dialysis and addition of inotropes. He also developed liver failure (although computed tomography showed no evidence of further extension of thrombus into the portal vein) and he eventually died four weeks after initial presentation.

DISCUSSION

Diagnosis of intestinal ischaemia requires a high index of suspicion, regardless of the underlying cause. Many cases of MVT do not require surgical intervention and the decision to operate is based largely on clinical grounds where there is a strong possibility of bowel infarction. Attempts can be made to refine the diagnosis by blood testing; patients may present with a raised white cell count or metabolic acidosis, but neither is sensitive nor specific enough to aid definitive diagnosis of MVT. Elevated D-dimer concentrations may also indicate bowel ischaemia, but similarly are not specific for MVT[5]. Imaging modalities such as plain abdominal radiography can demonstrate bowel wall oedema and may exclude other causes of abdominal pain. CT angiography is a more sensitive test for diagnosing thrombosis than CT or angiography alone. Magnetic resonance angiography is under review as a possible diagnostic tool for mesenteric ischaemia, but it lacks the resolution needed to diagnose non-occlusive mesenteric ischaemia or distal embolic disease.

The mainstay of medical management is anticoagulation, and immediate heparinisation has been shown to reduce recurrence and progression of the disease[6]. However, use of heparin is more complicated in the context of anti-thrombin III deficiency, as patients with reduced concentrations of anti-thrombin III are likely to be resistant to the effects of heparin and require larger doses. This may be attributable to the action of heparin, which binds to anti-thrombin, causing it to activate and inhibit thrombin. Anti-thrombin concentrate has been used effectively in patients with this deficiency and acute venous thrombosis, yet its use as an adjunctive therapy or alternative to heparin has not been studied in a controlled trial.

Thrombolysis with streptokinase, urokinase and tissue plasminogen activator (t-PA) has been used in treatment of MVT, though authors have recommended that its use be restricted to symptomatic patients with early diagnoses. Various routes for infusion of thrombolytics are described, including indirect intra-arterial infusion through the superior mesenteric artery and direct access to the portal vein with percutaneous transhepatic and transjugular-intrahepatic approaches. It is felt that trans-arterial infusions are generally safer as they avoid potential bleeding complications that can result from liver puncture during the procedure, however indirect lysis may be more unpredictable because of flow into collaterals[7]. These methods are preferred to use of systemic thrombolysis, owing to reduced haemorrhagic risk.

A further treatment option is mechanical thrombectomy, which provides a non-pharmacological alternative for treatment of MVT, particularly in patients who pose high risks for thrombolytic therapy. A combined approach using catheter-directed thrombolysis and mechanical thrombectomy has also been attempted with success though large-scale trials have not been undertaken[8].

Patients presenting with peritonitis or identifiable bowel infarction on CT require surgical management[2,9,10]. Options for surgical management of MVT include bowel resection with primary anastomosis, temporary stoma formation, thrombectomy, or a combination of these techniques. The choice of surgical management depends on the extent of bowel infarction, bowel viability and whether it is possible following bowel resection to form a stoma[2,10]. It is also often difficult to absolutely ascertain bowel viability, although it can be assessed by direct observation of colour, presence of capillary refill and bowel contractility. This can be unreliable and can lead to more bowel resection than necessary[9,10]. There remains no consensus on whether or not a primary anastomosis should be attempted or a stoma created at the time of laparotomy[10].

Open thrombectomy is rarely undertaken as not all of the thrombus can be removed[2,9,10], but its use in the treatment of acute superior mesenteric vein thrombosis when the thrombus is recently formed and restricted to the SMV may reduce the need for extensive bowel resection. Laparoscopy has been suggested as a diagnostic tool in identifying bowel ischaemia, but as it necessitates raising the intra-abdominal pressure and therefore decreasing mesenteric blood flow, it is probably best-avoided[2].

Diagnosis and management of primary MVT is complex. The condition may progress to full-blown portal vein thrombosis with more complications and a higher mortality. This case highlights the need to identify patients with MVT accurately and efficiently with clear implementation of medical and surgical management, and how, even with apparently optimal treatment, the outcome may still be fatal.

The authors have no conflict of interest to declare

REFERENCES

1. Stoney RJ, Cunningham CG. Acute mesenteric ischemia. *Surgery* 1993;**114(3)**:489-490.

2. Kumar S, Sarr MG, Kamath PS. Current concepts: mesenteric venous thrombosis. *N Engl J Med* 2001;**345(23)**:1683-8.

3. Morasch M, Ebaugh JL, Chiou AC *et al*. Mesenteric venous thrombosis: A changing clinical entity. *J Vasc Surg* 2001;**34(4)**:680-684.

4. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American gastrointestinal association *Gastroenterology* 2000;**118(5)**:954-968.

5. Acosta S, Nilsson TK, Björck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. *Br J Surg* 2001;**88(3)**:385-388.

6. Hrstic I, Kalauz M, Cukovic-Cavka S, Ostojic R, Banfic L, Vucelic B. Treatment of extensive subacute portal, mesenteric and ileocolic vein thrombosis with recombinant tissue plasminogen activator. *Blood Coagul Fibrinolysis* 2007;**18(6)**:581-583.

7. Sze D, O'Sullivan GJ, Johnson DL, Dake MD. Mesenteric and portal venous thrombosis treated by transjugular mechanical thrombolysis. *Am J Roentgenol* 2000;**175(3)**:732-734.

8. Lopera JE, Correa G, Brazzini A, Ustunsoz B, Patel S Janchai A, Castaneda-Zuniga W. Percutaneous transhepatic treatment of symptomatic mesenteric venous thrombosis. *J Vasc Surg* 2002;**36(5)**:1058-1061.

9. Clavien PA. Diagnosis and management of mesenteric infarction *Br J Surg* 1990;**77(6)**:601-603.

10. Menon NJ, Amin AM, Mohammed A, Hamilton G. Acute mesenteric ischaemia. *Acta Chir Belg* 2005;**105(4)**:344-354.

Letters

PERICARDIAL EFFUSION AND TAMPONADE COMPLICATING TREATED GRAVES' THYROTOXOCOSIS

Editor,

Pericardial effusion has been reported in Graves disease. We report a case where symptoms of cardiac failure and the development of a symptomatic pericardial effusion were the predominant manifestations of thyrotoxicosis undergoing treatment.

Case Report: A 42 year old lady was admitted with a six-week history of increasing shortness of breath. She described pleuritic chest pain and had recently noticed ankle oedema. She had no symptoms typical of thyrotoxicosis. There was no relevant past medical history. One week before hospitalisation she was found to have markedly elevated thyroid function tests with Free T4 >100 pmol/L (NR 11-21) and TSH <0.02 mU/L (NR 0.3-4.5) and had commenced treatment with Carbimazole (40 mgs od) and Propanolol (80 mgs b.d.).

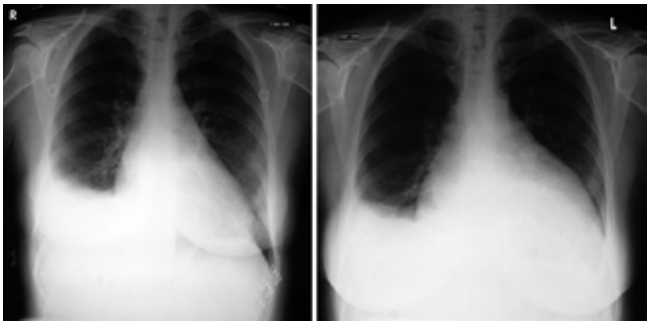


Fig 1. CXR on admission (left) showing a small pleural effusion and normal cardiac silhouette. Repeat film 2 weeks later (right) showing appearances in keeping with a pericardial effusion

On admission she was dyspnoeic at rest with a sinus tachycardia. BP was 118/62. Bilateral pitting leg oedema, a small goitre and a right pleural effusion confirmed on chest X-Ray were noted. Biochemically there was continued evidence of hyperthyroidism - FT4 34.9 and TSH <0.02 with positive anti-thyroid peroxidase antibodies; 215 IU/ml (NR 0-135). C-reactive protein (CRP) was raised at 109. An echocardiogram revealed normal left ventricular function and evidence of a small localised pericardial effusion. There was no pericardial tamponade at this time. Following continued treatment with beta-blockers and an increased dose of Carbimazole (60 mgs o.d.) and diuretics the patient's clinical condition improved and she was discharged.

Two weeks later she presented with further respiratory distress and was noted to have a raised venous pressure and a BP of 84/60. Thyroid function tests showed continued improvement. Repeat CXR revealed cardiomegaly (Figure 1). Repeat echocardiogram demonstrated a large pericardial effusion (Figure 2). The patient was transferred to the regional cardiology centre where 275mls of blood stained fluid was drained from the pericardial space with immediate improvement in dyspnoea and blood pressure. Biochemically the fluid was an exudate; culture and cytology were negative. Following this she remained well.

Conclusions: This case shows that pericardial effusion resulting in tamponade can develop in Graves thyrotoxicosis even during anti-thyroid treatment and with improving thyroid function tests.

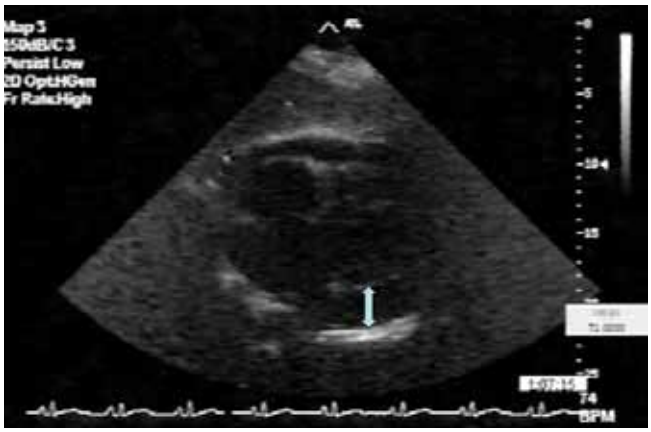


Fig 2. Repeat echocardiogram confirming large pericardial effusion (arrowed).

A Medline search over the last twenty years uncovered two other reports of similar cases in English journals with a further report in a Japanese journal[1-4]. Authors from Oxford described a series of four patients all presenting with chest pain and effusions as the predominant manifestation of otherwise occult Graves' thyrotoxocosis.[2] The most recent case report from Israel[3] describes a patient who developed a pericardial effusion despite treatment of hyperthyroidism. In this case tamponade did not develop and pericardiocentesis was not required. The aetiology of these complications is unclear although the blood stained nature of the pericardial effusion and the preceding pain and raised CRP suggests an inflammatory pericarditis. We therefore suggest it would be prudent to exclude Graves' thyrotoxicosis in any patient presenting with an unexplained pericardial effusion despite the absence of classical symptoms of thyrotoxicosis. Furthermore, in a patient with active Graves' disease, symptoms such as chest pain and dyspnoea need to be considered as potentially heralding the development of cardiac tamponade. While this complication is rare it may be rapidly fatal and thus go unrecognised and unreported.

The authors have no conflict of interest.

Emer Teague[1] *Staff Grade*

*Charles J O'Brien[1] *Consultant Physician*

Norman PS Campbell[2], *Consultant Cardiologist*

[1.] Dept of Medicine, Daisy Hill Hospital Newry, Co Down, BT35 8DR

[2.] Regional Cardiology Centre, Royal Victoria Hospital, Belfast, BT12 6BA

Charles.OBrien@southerntrust.hscni.net

REFERENCES:

1. Roffi M, Cattaneo F, Brandle M. Thyrotoxicosis and the cardiovascular system. *Minerva Endocrinol* 2005;**30(2)**:47-58.

2. Clarke NR, Banning AP, Gwilt DJ, Scott AR. Pericardial disease associated with Grave's thyrotoxicosis. *QJM* 2002;**95(3)**:188-189.

3. Ovadia S, Lyssy L, Zubkov T. Pericardial Effusion as an Expression of Thyrotoxicosis. *Tex Heart Inst J* 2007;**34(1):**88-90.

4. Nakata A, Komiya R, Ieki Y, Yoshizawa H, Hirota S, Takazakura E. A patient with Graves' disease accompanied by bloody pericardial effusion. *Internal Medicine* 2005;**44(10):**1064-1068.

PATCHY SMALL BOWEL ISCHAEMIA SECONDARY TO SEPSIS

Editor,

Insufficient blood perfusion to the small bowel may result from arterial occlusion by embolus or thrombosis, thrombosis of the venous system, or non-occlusive processes such as vasospasm or low cardiac output. Patterns of segmental, skipped, or patchy small bowel ischaemia have been reported post abdominal aortic aneurysm repair and is thought to imply that microembolisation has played an important role[1]. Microvascular thrombi in various organs can result from disseminated intravascular coagulation[2]. We present a case of patchy small bowel ischaemia in a septic patient who had developed evidence of disseminated intravascular coagulation.

Case presentation: A 50-year-old man prescribed four weeks of diclofenac for a muscular strain presented with frank haematemesis secondary to an eroding gastric ulcer measuring 7 cm in diameter. A partial gastrectomy and Roux-en-Y reconstruction was performed and a massive blood transfusion of 25 units was required peri-operatively. The patient was referred to a tertiary care centre for intensive care where on day six post operatively, he developed peritonitis as a result of a biliary leak from his duodenal stump. His blood tests at that time were suggestive of non-overt disseminated intravascular coagulation secondary to sepsis with an elevated D-dimer of 7.36 µg/ml (0.01-0.5 µg/ml). An emergency exploratory laparotomy was performed. This revealed a duodenal stump blowout and a 2 inch segment of proximal jejunum containing multiple less than 1 cm blisters in a triangular arrangement (figure 1). These were found to be necrotic areas and were resected. Histology of the specimen confirmed areas of transmural haemorrhagic ischaemic necrosis associated with a marked serosal exudate and incipient perforation. Thrombi were histologically identified within the omentum. Later in the post-operative period he developed bleeding from his duodenal stump for which he had successful radio-embolisation of the gastroduodenal artery. After a complicated postoperative period, he was discharged home. Although, patchy bowel ischaemia has been reported in past, this pattern in a mid jejunal small bowel segment containing multiple less than 1 cm areas of necrosis in a septic patient has not been reported to our knowledge.

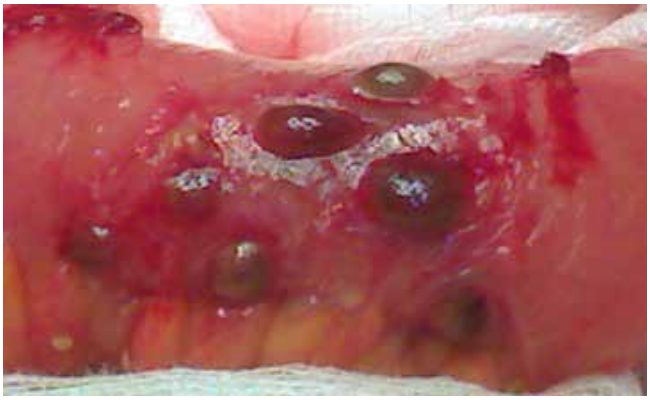


Fig 1. Proximal jejunum with multiple necrotic areas

Discussion: Patchy small bowel ischaemia has been noted in patients following abdominal aortic aneurysm repair[1]. Some of these patients have been found to have widespread microembolisation or to have pathological evidence of microemboli. As a result it has been postulated that this pattern of ischaemia is a direct consequence of microembolisation[3]. Sepsis almost invariably leads to haemostatic abnormalities. These range from the insignificant to severe disseminated intravascular coagulation. Compelling evidence from clinical and experimental studies suggests that disseminated intravascular coagulation is involved in the pathogenesis of microvascular dysfunction and that deposition of microvascular thrombi can occur[3,4]. Given the above patient had an elevated D-dimer and evidence of thrombi on histology it is our feeling that the likely mechanism behind this unusual intra-operative finding was microembolisation. With sepsis related disseminated intravascular coagulation being the most likely cause.

Conclusions: We conclude that in septic patients, the bowel should be carefully examined as missing such pathology will have serious implications for critically ill surgical patients.

The authors have no conflict of interest

*Stephen O'Neill, *F2 General Surgery*,

Arshad Malik, *SpR General Surgery*

Department of Surgery, Belfast City Hospital Trust, Belfast BT9 7AB, United Kingdom.

stephenoneill@doctors.org.uk

REFERENCES:

1. Zhang W, Kulaylat M, Anain P, Dosluoglu H, Harris L, Cherr G *et al*: Embolization as cause of bowel ischemia after endovascular abdominal aortic aneurysm repair**.** *J Vasc Surg* 2004;**40(5):**867-872.

2. Baglin T: Disseminated intravascular coagulation: diagnosis and treatment. *BMJ* 1996;**312(7032):**683-7

3. Dadian N, Ohki T, Veith FJ, Edelman M, Mehta M, Lipsitz EC *et al*: Overt colon ischemia after endovascular aneurysm repair: the importance of microembolization as an etiology. *J Vasc Surg* 2001;**34(6):**986-96.

4. Levi M, de Jonge E, van der Poll T. Sepsis and disseminated intravascular coagulation. *J Thromb Thrombolysis* 2003;**16(1-2):**43-7.

CLINICAL EXPERIENCE WITH INTRAVENOUS IMMUNOGLOBULIN AND TNF-A INHIBITOR THERAPIES FOR RECURRENT PREGNANCY LOSS

Editor,

We report on a 22 year-old non-smoking nulligravida who presented with her husband for in vitro fertilisation (IVF). She was in good general health and had five prior unsuccessful IVF treatments, all with implantation failure. While her TSH and T4 were normal, a strongly positive (1:25,600) thyroid peroxidase antibody (ATA) titre was noted. Their sixth IVF cycle included IVIG infusion x3 as had been used in the immediately preceding cycle. However, etanercept (Enbrel®;

Immunex Corp., Thousand Oaks, California USA) was added for the first time as a series of 25mg subcutaneous injections commencing four weeks before ovulation induction and continued on four-day intervals thereafter. Eight etanercept injections were given until commencement of gonadotropins, and then discontinued. Two blastocysts were transferred fresh and two were frozen at day five. Following an unremarkable obstetrical course, the patient delivered male/male twins by Caesarean at 34½ weeks' gestation. While the strongly positive ATA titre finding in our patient was concerning, we admitted that the mechanism of how ATA impacts reproductive outcome is presently unknown. ATA have been documented more often in women with recurrent pregnancy failure than controls, and a prospective clinical trial of women with "immunologic abortion" evaluating multiple autoimmune variables found ATA to be the most frequently encountered immunopathology—present in 53% of patients[1]. Our case, believed to be the first published report of its kind in Ireland, is parallel with those who have described a highly-circumscribed use of immunomodulators for refractory cases where an immune diathesis exists[2,3] and given only under closely monitored conditions. While immunomodulators are inappropriate in IVF for unselected populations and should not be regarded as first-line therapy, dampening of immune responses antagonistic to implantation and embryo development may be a derivative of IVIG + etanercept therapy. Should our patient decide to enlarge her family and return for transfer of cryopreserved embryos in future, the role of further immunomodulator treatment will require consideration.

The authors have no conflict of interest

*Eric Scott Sills[1], *Research Consultant in Reproductive Medicine*

David J Walsh[1], *Consultant*

Lyuda V Shkrobot[1], *Medical Associate*

Gianpiero D Palermo[2], *Professor & Director of Assisted Fertilization*

Anthony PH Walsh[1], *Consultant & Chairman*

drscottsills@sims.ie

1 The Sims Institute/Sims International Fertility Clinic, Rosemount Hall, Dundrum Road, Dundrum, Dublin 14 Ireland

2 Center for Reproductive Medicine & Infertility, Weill Medical College/ Cornell University, New York, New York USA

REFERENCES:

1. Stricker RB, Steinleitner A, Bookoff CN, Weckstein LN, Winger EE. Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin. *Fertil Steril.* 2000;**73(3)**:536-40.

2. Sills ES, Perloe M, Tucker MJ, Kaplan CR, Palermo GD. Successful ovulation induction, conception, and normal delivery after chronic therapy with etanercept: a recombinant fusion anti-cytokine treatment for rheumatoid arthritis. *Am J Reprod Immunol* 2001;**46(5)**:366-8.

3. Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulin (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). *J Assist Reprod Genet* 2006;**23(1)**:1-13.

Ulster Med J 2009; **78 (1)** 59-61

Abstracts

Junior Members Forum, Thursday 22 November 2007

Ulster Medical Society rooms, Whitla Medical Building, Belfast

PROGRAMME

Of the submissions, the following 5 were shortlisted for platform presentations:

1. Chronic Kidney Disease associated with mortality in Northern Ireland - Dr M Quinn
2. Metformin, Chronic Kidney Disease and Lactic Acidosis: Is metformin absolutely contraindicated? - Dr MC McCloskey
3. Folic Acid use and major congenital malformations in offspring of women with epilepsy. A prospective study from The UK Epilepsy and Pregnancy Register - Dr SJ Hunt
4. Indications for Revision Total Hip Replacement in Northern Ireland - Dr Ciara Stevenson
5. Randomised Controlled Trial to assess the vascular and biochemical effects of Cilostazol in patients with peripheral arterial disease - Mr M O'Donnell

The following 16 were shortlisted for poster presentations:

1. Transient Cardiomyopathy as presenting feature of Acute Disseminated Encephalomyelitis - Dr E Mawhinney
2. Posterior Leucoencephalopathy Syndrome in a post-partum patient - Dr KM McKnight
3. An audit of intravenous immunoglobulin use in the NI Neurology Department - Dr E Devenney
4. Usefulness of a District General Neurologist in the diagnosis of non-organic illness - Dr A Fitzpatrick
5. Octreotide scanning in the detection of metastatic renal cell carcinoma - Dr MC McCloskey
6. Carbon Monoxide Poisoning - Dr A Hammond
7. Radical Trachelectomy: a case series - Dr N Ratnavelu
8. Are alcohol related acute surgical admission rates falling? - Dr GJ Fitzmaurice
9. Improving outcomes in squint surgery - Dr MK O'Gallagher
10. Management of hypoglycaemia in Intensive Care: a prospective audit - Dr Lloyd Turbitt
11. The two-week rule help or hindrance? - Dr RS McCain
12. The documentation, interpretation and management of abnormal fetal heart rates in labour - Dr M McCauley
13. Indolent thyroid metastasis from renal cell carcinoma presenting after a remarkable 24 year latency following nephrectomy - Dr G McLean
14. Accuracy and role of ultrasonography in assessing shoulder pathology - Dr KW Chan
15. Analgesia and function following subacromial decompression - Dr J Campbell
16. The effect of modernising medical careers on junior medical doctor personality, anxiety and career choice - Mr M O'Donnell

The winner of the platform, poster and the remaining platform abstracts are published below:

PLATFORM PRESENTATION WINNER:

CHRONIC KIDNEY DISEASE ASSOCIATED WITH MORTALITY IN NORTHERN IRELAND

M Quinn[1], C Cardwell[2], G Savage[2], AP Maxwell[1], F Kee[2], D Fogarty[1]

Departments of [1]Nephrology, and [2]Public Health and Epidemiology, The Queen's University of Belfast

Introduction: We investigated the association between chronic kidney disease (CKD) and mortality in Northern Ireland (NI).

Methods: All creatinine results in NI between 1st Jan 2001 - 31st Dec 2002 were collected and linked to a patient database. Estimated glomerular filtration rates (eGFR) were calculated using the 4 variable modified diet in renal disease equation. The Registrar Generals office provided all cause and cardiovascular mortality follow up through to 31st Dec 2006.

Results: 2,065,694 creatinine results from 585,566 patients were collected. 60,209 deaths occurred. Using eGFR as time varying covariate in a Cox survival model the following association between CKD and mortality was demonstrated.

Adjusted† hazard ratios (CI 95%) for mortality		
eGFR	All cause	Cardiovascular
> 60 ml/min/1.73m^2	1.00 (Ref)	1.00 (Ref)
45 - 59 ml/min/1.73m^2	1.01 (0.99-1.03)	0.98 (0.92-1.02)
30 - 44 ml/min/1.73m^2	1.45 (1.41-1.48)	1.43 (1.38-1.45)
15 - 29 ml/min/1.73m^2	2.19 (2.11-2.27)	2.26 (2.13-2.40)
< 15 ml/min/1.73m^2	3.45 (3.23-3.68)	4.35 (3.93-4.80)
†Adjusted for Age and Sex		

Conclusions: This study demonstrates a graded association between CKD and mortality in the tested NI population. Having previously calculated the prevalence of CKD (eGFR < 60 ml/min/1.73m^2) in NI as 3.69%[1]; this work indicates the clinical and public health importance of CKD.

REFERENCE:

1. Quinn, MP, Rainey A, Cairns KJ *et al.* The practical implications of using standardized estimation equations in calculating the prevalence of chronic kidney disease. *Nephrol Dialysis Transplantation* 2008;23(2):542-548.

PLATFORM PRESENTATION RUNNERS UP:

METFORMIN, CHRONIC KIDNEY DISEASE, AND LACTIC ACIDOSIS: IS METFORMIN ABSOLUTELY CONTRAINDICATED?

MC McCloskey, J Smyth, W Marshall, N Leonard

Renal Unit, Ulster Hospital, Dundonald, Belfast, Northern Ireland

Aims: The UK prospective diabetes study showed that metformin was associated with a lower mortality from cardiovascular disease than sulphonylureas or insulin in obese patients with type 2 diabetes mellitus, as well as reduced all cause mortality. However, concerns remain about its side effects, especially the perceived risk of lactic acidosis in the presence of chronic kidney disease (CKD). This may result in many patients with type 2 diabetes being denied metformin therapy[1,2]. We aimed to assess the incidence of metformin induced lactic acidosis over a seven year period, within our hospital.

Methods: Data was retrieved from a computerised database, laboratory records and individual case note review for patients admitted over a 7-year period, from 01/01/2000 until 31/12/2006. Diagnostic codes searched included metabolic acidosis, lactic acidosis, metformin, or glucophage. Renal function at presentation, at baseline, and the presence of a clearly identified precipitating illness were recorded (N = 205 401).

Results: Three cases of lactic acidosis in patients prescribed metformin were identified. Each case had a precipitating illness; dehydration secondary to gastroenteritis in 2 cases and urinary sepsis in 1 case. Only one patient had baseline CKD (creatinine of 135mmol/l).

Discussion: The incidence of metformin induced lactic acidosis reported in this study is significantly lower than predicted in the literature, which quotes an estimated incidence of 0 – 0.09 cases per 1000 pt years[1,2].

A Cochrane review of 206 comparative trials and cohort studies in patients with type 2 diabetes who were treated with metformin and had no contraindications to its use, found no evidence of increased risk of developing fatal/non-fatal lactic acidosis in metformin treated patients. They also found no difference in lactate concentrations between metformin and non-biguanide treated patients. Several reports found that physicians have increasingly ignored contraindications to prescribing metformin and yet the incidence of lactic acidosis has remained very low. The majority of case reports relating metformin to lactic acidosis report at least one other disease/acute illness that could result in lactic acidosis[1,2]. In our analysis each case had a precipitating illness.

Metformin provides a greater degree of cardiovascular protection than expected from antihyperglycaemic actions alone, and is the drug of choice for persons with type 2 diabetes. Further studies are required in order to accurately quantify the risk, if any, of metformin induced lactic acidosis in persons with CKD[1,2].

REFERENCES:

1. Jones *et al.* Contraindications to the use of metformin. *BMJ* 2003;326(7379):4

2. Tahrani *et al*. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ* 2007;335:508-512.

FOLIC ACID USE AND MAJOR CONGENITAL MALFORMATIONS IN OFFSPRING OF WOMEN WITH EPILEPSY. A PROSPECTIVE STUDY FROM THE UK EPILEPSY AND PREGNANCY REGISTER.

SJ Hunt, AJ Russell, WH Smithson, L Parsons, I Robertson, R Waddell, B Irwin, PJ Morrison, JJ Craig, JI Morrow

Objective: In the general population folic acid supplementation during pregnancy has been demonstrated to reduce the frequency of major congenital malformations (MCMs) such as neural tube defects (NTDs). Women with epilepsy contemplating pregnancy are advised to take supplemental folic acid due to the known anti-folate effect of some anti-epileptic drugs

(AEDs). Here we aim to determine effectiveness of this practice.

Methods: Prospective, observational, registration and follow-up study. Cases are women with epilepsy who become pregnant and who are referred before outcome of the pregnancy is known. The main outcome measure is the MCM rate.

Results: In 1,935 cases reported to have received pre-conceptual folic acid, 76 MCMs (3.9%;95% C.I. 3.1 - 4.9%) and eight NTDs (0.4%; 95% C.I. 0.2 - 0.8) were identified. For 2,375 women who were reported to have received folic acid but not until later in the pregnancy (n= 1,825) or not at all (n=550) there were 53 outcomes with an MCM (2.2%; 95% C.I. 1.7 - 2.9%) and eight NTDs (0.34%; 95% C.I. 0.2 - 0.7).

Conclusions: Extrapolation from studies carried out in the general population to groups of women with epilepsy may be questionable. The increased risk of MCM recorded in this group may occur through mechanisms other than that of folic acid metabolism.

INDICATIONS FOR REVISION TOTAL HIP REPLACEMENT IN NORTHERN IRELAND

CM Stevenson, BM Hanratty, MG McAlinden

Ulster Hospital Belfast

Within Northern Ireland we have investigated the indications for revision hip procedures, carried out from April 2006 to March 2007. This was to establish our indications for revision surgery and if these are comparable to other national registers. An audit of all hospitals that perform revision surgery was carried out and the indications for revision procedures established. Revision procedures included replacement of one or both components, application of acetabular augmentation devices, and open reduction and internal fixation of peri-prosthetic fractures. 180 patients were identified in six hospitals. Revisions were performed for a peri-prosthetic fracture in 38 (21%), infection in 12 (7%), recurrent dislocation in 23(13%) and in failure of implants in 107 (59%). Six hospitals in Northern Ireland (population 1.7 million) carry out revision hip surgery. The largest body of information on revision hip surgery is the Swedish Hip Registry. Their incidence for revision hip surgery is 7%. Their indications were: aseptic loosening 71%, infection 7.5%, fracture 5.6% and dislocation 4.8%. Our data indicate a greater prevalence of revision for recurrent dislocation (13%versus 4.8%), and peri-prosthetic fractures (21% versus 5.6%) than the Swedish data. Further work should aim to identify any remediable surgical factors, which account for these differences

RANDOMISED CONTROLLED TRIAL TO ASSESS THE VASCULAR AND BIOCHEMICAL EFFECTS OF CILOSTAZOL IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

ME O'Donnell[1], SA Badger[1], MA Sharif[1], RR Makar[1], IS Young[2], LL Lau[1], B Lee[1], RJ Hannon[1], CV Soong[1].

Department of Vascular and Endovascular Surgery, Belfast City Hospital[1] and Department of Medicine, Queen's University Belfast[2], Northern Ireland.

Objectives: Cilostazol improves walking distance. The study aimed to assess vascular and biochemical effects of cilostazol in peripheral arterial disease (PAD) patients.

Methods: Patients were randomised in a double-blinded, placebo-controlled trial. Baseline clinical data were recorded following medical optimisation. Clinical assessment included ankle-brachial index (ABI), arterial compliance, peripheral trancutaneous oxygenation (TCO_2) and treadmill walking distance. Glucose homeostasis was assessed by fasting serum glucose and glycosylated haemoglobin levels along with lipid profiles. Quality of life (QoL) indices were recorded using the VascuQoL questionnaire. All tests were at baseline, 6- and 24-weeks.

Results: 106 PAD patients (M=73) were recruited from December 2004 to January 2006 (median age:66.5, range 37-86). Patients in both treatment limbs had similar baseline demographics, medical co-morbidities and walking performance. Patients who received cilostazol demonstrated a mean percentage improvement, in absolute claudication distance (77.2%vs.26.6% at 6-weeks and 161.7%vs.79.0% at 24-weeks, $p<0.05$). Arterial compliance improved at 6-weeks (-28.8%vs.-11.0%,p=0.005) and 24-weeks (-21.0%vs.-11.5%,p=0.012). There was no difference in ABI, TCO_2 or glucose homeostasis. Cilostazol reduced triglycerides at 6-and 24-weeks ($p<0.002$). Activity, symptom, pain, emotion and total VascuQoL indices improved in the cilostazol group at 24-weeks ($p<0.03$).

Conclusions: Maximal walking distance was improved by cilostazol in PAD patients with further beneficial effects in arterial compliance, lipid homeostasis and QoL.

POSTER PRESENTATION WINNER

THE "TWO-WEEK-RULE"; HELP OR HINDRANCE?

RS McCain, J Newell, SA Badger, RJ Kennedy, SJ Kirk.

Breast Surgery Unit, Ulster Hospital, Dundonald

Introduction: Breast cancer is a common malignancy. Department of Health guidelines state that all patients with suspected breast cancer should be referred urgently and seen by a specialist within two weeks of referral. The aim of this study was to assess referral patterns and clinical findings in patients referred to a specialist breast clinic within this context.

Methods: A prospective database was maintained for consecutive patients referred to a specialist breast clinic. Clinical findings in primary care and at the breast clinic were recorded and correlated with final diagnoses.

Results: Data were collected on 1098 patients. 588 (54%) were referred urgently, 285 (26%) routinely and 225 (20%) were unspecified. In many cases, referrals did not adhere to the "two-week-rule" guidelines. 86 patients (8%) were diagnosed with breast cancer. 72 (84%) of these were referred urgently, 6 (7%) routinely and 8 (9%) unspecified. Examination findings in primary and secondary care correlated in 487 (46%) patients.

Conclusions: A large number of sub-optimal referrals were made. Sensitivity and specificity of clinical examination in primary care was low. Nonetheless, with excellent examination and diagnostic skills, sensitivity of the two-week-rule could only reach 86%, suggesting that either the concept of urgent referral criteria or the criteria themselves are flawed.

Ulster Med J 2009; **78 (1)** 62-64

Abstracts

80th (Autumn) Meeting of Ulster Society of Internal Medicine, Friday 17th October 2008

Sir Samuel Irwin Lecture Theatre, Royal Victoria Hospital, Belfast.

PROGRAMME:

Chairman: Dr Kate Ritchie

2.00pm	Papers
3.00pm	Invited Abstract: 'Update on Management of type 2 Diabetes'. Prof. Patrick Bell, Royal Victoria Hospital.
3.30pm	Afternoon Tea
3.50pm	Papers
4.30pm	Presentation of prize for best abstract
4:50pm	Guest lecture: 'Occupational lung disease in the 21st century'. Dr Chris Stenton, Consultant Respiratory Physician, Newcastle-Upon-Tyne.

PAPERS

EPITHELIAL TO MESENCHYMAL TRANSITION IN SKIN – POSSIBLE IMPLICATIONS FOR SCLERODERMA

D O'Kane[1], S Kenny[1], J Tolland[2], AE Smyth[3], JS Elborn[1], DF McAuley[1], CM O'Kane[1].

[1]Respiratory Medicine Research Group, Queen's University Belfast, [2]Department of Dermatology, Ulster Hospital Dundonald, [3]Department of Rheumatology, Ulster Hospital Dundonald

Fibrogenic growth factors can force epithelial cells of the lung, kidney and liver to undergo transition to a mesenchymal phenotype – a process known as epithelial to mesenchymal transition (EMT)[1]. EMT contributes to fibrosis in these organs, and can be inhibited/reversed in animal models[2] . EMT has not been shown in fibrotic skin disorders. We hypothesised that EMT is a mechanism of dermal fibrosis and may mediate fibrosis in scleroderma and other skin lesions.

Human keratinocytes (HaCaT cells) were stimulated with TGFβ and TNFα (which occur in fibrotic skin). Cells lysates were probed by western blot for epithelial (E-cadherin) and mesenchymal (vimentin) markers. Supernatants were analysed for matrix metalloproteinases (MMP-2/-9), enzymes associated with the invasive, motile phenotype integral to EMT and CXCL8, a chemokine secreted in high quantities by activated fibroblasts. Keratinocytes stimulated with TGFβ and TNFαbecame spindle-shaped, with loss of cell-cell contact. There was a switch from epithelial to mesenchymal proteome: vimentin expression increased 3.4 fold, E-cadherin fell by 60% (p=0.02*). MMP-2 increased from 121+/-44 to 1174+/-86 relative gelatinolytic units (RGU), p<0.001*, and MMP-9 from 24 to 805+/-80 RGU, p<0.001*. CXCL8 increased from 671 to 1562pg/ml, p=0.0005*. (* t test TGFβ +TNFα vs. control)

Keratinocytes stimulated with TGFβ+TNFα (present in cutaneous scleroderma) undergo changes consistent with EMT. These novel data suggest EMT is a possible mechanism of skin fibrosis. Targeting EMT *in vivo* by inhibiting downstream regulators of TGFβ and TNFα signalling may be a novel approach to limit progression of dermal fibrosis in scleroderma / other diseases.

REFERENCES:

1. Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, et al. Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. PNAS 2006;103(35):13180-5.
2. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, et al. BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury. Nat Med 2003;9(7):964-8.

THE USE OF IMPLANTABLE CARDIOVERTER DEFIBRILLATORS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY; EXPERIENCE OF A TERTIARY REFERRAL CENTRE IN NORTHERN IRELAND.

M Sharif, V Kodoth, JR Bennett, J McOsker, M Roberts, C Wilson, E Lau, G Manoharan, PP McKeown.

The Heart Centre, Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast

Hypertrophic Cardiomyopathy (HCM) is the most common cause of sudden cardiac death (SCD) in young people[1]. The implantable cardioverter-defibrillator (ICD) has been shown to be a safe and effective therapeutic intervention in patients with HCM, both for primary and secondary prevention of SCD. We reviewed ICD data of patients with HCM to determine the indications for, efficacy, safety and complications of the device.

Out of 828 patients currently being reviewed in ICD clinic, Royal Victoria Hospital, Belfast 28 patients (4%) had HCM as primary diagnosis. Twenty four (85%) ICDs were inserted for primary prevention and 4 (15%) for secondary prevention of SCD. Pre ICD insertion the following risk factors for SCD were identified; 13 (46%) had a family history of SCD, 6 (21%) had a history of syncope, 5 (17%) had nonsustained ventricular tachycardia, 4 (14%) had ventricular tachycardia, 4 (14%) had frequent ventricular premature complex, 2 (7%) had atrial fibrillation and 2 (7%) had supraventricular tachycardia on holter monitor prior ICD insertion, 2 (7%) had an inappropriate blood pressure response to exercise and 2 (7%) had a raised left ventricular outflow tract velocity. The mean septal diameter was 22±6mm. The mean age of ICD insertion was 49.6±17years. During a mean follow up period of 32months, 9 appropriate shocks were delivered in 6 patients (21%) and 3 inappropriate shocks were delivered in 3 (10%) patients. Four patients who had appropriate shock delivered were on oral amiodarone and one patient on sotalol. Complications identified included one patients requiring ICD box replacement and one patient required lead replacement due to insulation defect of the leads.

The high rate of appropriate ICD shocks in our study is similar to published data[2]. Risk assessment for SCD should be performed in every HCM patient and ICD should be considered in high risk patients.

REFERENCES:

1. Maron BJ, Spirito P. Implantable Defibrillators and Prevention of Sudden Death in Hypertrophic Cardiomyopathy, *J Cardiovasc Electrophysiol* 2008 [Epub ahead of print].
2. Maron BJ, Spirito P, Shen WK *et al.* Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy; *JAMA* 2007;**298(4):**405-12.

BISPHOSPHONATE PRESCRIBING GUIDELINES – IS EVERYONE A LOSER?

MC McCloskey, J Smyth, W Marshall, N Leonard

Renal Unit, Ulster Hospital, Dundonald, Belfast, Northern Ireland

Osteoporotic fractures are 3 to 4 times more likely in persons with chronic kidney disease (CKD). Early menopause, previous exposure to steroids and increased risk of falls are all contributory factors[1,2]. National Institute of Clinical Excellence (NICE) guidelines on the treatment of osteoporosis do not extend to the CKD population[3] and current manufacturer guidelines do not recommend the use of bisphosphantes (BPs) in those patients with an eGFR < 30ml/min[4]. We aimed to assess compliance with precribing guidelines and to determine if BPs are underutilized across the entire spectrum of CKD.

Data was collected from a computerised data base of six-hundred and thirty seven patients with CKD currently attending our renal unit. Six point three percent (40/637) of the CKD population were prescribed a BP, 50% (20/40) of whom had an eGFR < 30ml/min. Four point four percent (28/637) had a documented diagnosis of osteoporosis (OP) or OP related fracture. However, of those with eGFR > 30 ml/min and thus eligible for BP therapy, only one third (3/9) were actually prescribed a BP. Nine point four percent (60/637) of the total population were receiving long term steroid therapy but only 50% (15/28) of those with eGFR >30 ml/min, and thus eligible, were prescribed a BP.

This study demonstrates non-adherence to bisphosphonate prescribing guidelines in persons with an eGFR <30 ml/min. However, and perhaps more importantly, we have highlighted an underutilisation of BP therapy in those with eGFR >30 ml/min. BPs have established efficacy in the treatment of OP and OP related fracture in the general population.[1,2] The underutilisation of BPs in CKD observed in this study, endorsed by both national and manufacturers' guidelines, may be explained in part by the absence of supportive data in CKD, theorotical concerns of inducing low bone turnover states, and previous reports of acute tubular necrosis with intravenous preparations.[1,2]

This study generates the following questions: Should we be extrapolating data from the general population, should we extrapolate the data and adjust the dosage, or should we wait for randomised controlled trials on BPs in CKD. As previous authors have suggested, extrapolation of data with dose adjustment seems the most practical and safe approach for the short term.

REFERENCES:

1. Hamilton DV. Osteoporosis in women undergoing chronic dialysis. *Br J Renal Med* 2007;**12(2):**19-21.

2. Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporos Rep* 2005;**2:**5-12. 3. National Institute for Health and Clinical Excellence. http://www.nice.org.uk/ 4. British National Formulary. http://www.bnf.org/bnf/

IS HYPERFILTRATION ASSOCIATED WITH THE FUTURE RISK OF DEVELOPING DIABETIC NEPHROPATHY? A META-ANALYSIS

Glynis M Magee[1], Rudy Bilous[2], Chris R Cardwell[3], Steven J Hunter[1], Frank Kee[3], Damian G Fogarty[3].

1. Regional Centre for Diabetes and Endocrinology, Royal Victoria Hospital, Belfast, UK. 2. Newcastle University and James Cook University Hospital, Middlesbrough, England. 3. Department of Epidemiology and Public Health, School of Medicine and Dentistry, Queen's University, Belfast, UK. 4. Regional Nephrology Unit, Belfast City Hospital, UK.

Aims: Glomerular hyperfiltration is well established as a phenomenon occurring early in type 1 and type 2 diabetes, however, there is no consistent answer regarding whether hyperfiltration predicts the later development of nephropathy. We performed a systematic review and meta-analysis of observational studies that compared the risk of developing diabetic nephropathy in patients with and without glomerular hyperfiltration.

Methods: A systematic review and meta - analysis was carried out. Cohort studies in type 1 and 2 diabetic participants were included if they contained data on the development of incipient or overt nephropathy with baseline measurement of glomerular filtration rate (GFR) and presence or absence of hyperfiltration.

Results: Eleven cohort studies following 830 patients were included. After a study median follow up of 7.9 years, 124 patients had developed nephropathy. Using a random effects model, the pooled odds of progression to a minimum of microalbuminuria in individuals with hyperfiltration was 2.54 (95% CI 1.25-5.17) times that of individuals with normofiltration. There was moderate heterogeneity (Heterogeneity test $p = 0.07$, $I^2 = 42\%$) and some evidence of funnel plot asymmetry, possibly due to publication bias. The pooled weighted mean difference in baseline GFR was 13.4 ml/min/1.73m^2 (95% CI 5.4-21.3) greater in the group progressing to nephropathy compared to those not progressing (Heterogeneity test $p<0.01$).

Conclusions: In published studies, individuals with glomerular hyperfiltration were at increased risk of progression to diabetic nephropathy using study level data. Further larger studies are required to explore this relationship and the role of potential confounding variables.

AUDIT OF SECONDARY PREVENTION OF OSTEOPOROSIS IN POST-MENOPAUSAL FEMALES TREATED IN A DISTRICT GENERAL HOSPITAL

I Wallace, PV Gardiner.

Department of Rheumatology, Altnagelvin Area Hospital, Western Health and Social Care Trust, Londonderry, UK.

Background: Osteoporosis may lead to significant morbidity and disability through an increased susceptibility to fracture. Post-menopausal females are a high-risk group accounting for 74% of neck of femur fractures in our unit. Appropriate treatment may reduce the risk of re-fracture in this group.

Aim: To compare current practice to guidelines contained in the National Institute for Clinical Excellence (NICE) Technology Appraisal 87.

Methods: A sample group of 100 patients was identified retrospectively using emergency department records. Female patients over 55 years of age with diagnosis of a classical osteoporotic fracture were included.

Results: 62% were aged 75 or greater. 62% sustained a fracture of neck of femur, 29% a wrist fracture and 9% a vertebral fracture. 8% underwent a DEXA scan. In the under 75 group 30 patients (of an eligible 38 (79%)) did not receive a DEXA scan. Treatment was consistent with the NICE guidelines in 41% of patients. Most (33 (80%)) were aged 75 or over and 8 (20%) were aged under 75. In the under 75 age group, treatment was commenced in 17 of 38 patients (45%). In 9 patients (24%) treatment was commenced without performing a DEXA scan. 47% of those aged 75 or over and 79% of those in the under-75 age group did not receive treatment according to NICE guidelines.

Conclusions: DEXA scanning is under-utilised, contributing to significant inconsistent treatment decisions. Adherence to the NICE guidelines is higher in the 75 and over age group, however in a significant proportion treatment is sub-optimal.

Chronic kidney disease associated with mortality in Northern Ireland

M Quinn[1], C Cardwell[2], G Savage[2], AP Maxwell[1], F Kee[2], D Fogarty[1]

[1]Department of Nephrology. [2]Department of Public Health and Epidemiology. The Queen's University of Belfast

Introduction: We sought to investigate if the increased mortality shown to be associated with chronic kidney disease (CKD) in the US population[1] is also present in Northern Ireland (NI).

Methods: All creatinine results in Northern Ireland between 1st Jan 2001 - 31st Dec 2002 were collected. Estimated glomerular filtration rates (eGFR) were then calculated using the 4 variable modified diet in renal disease (MDRD) equation. A patient level database was created and mortality follow up was provided from the Registrar Generals office up to 31st Dec 2006.

Results: 2,065,694 creatinine results from 585,566 patients were collected. Mean (Standard Deviation) duration of follow up was 3.3 (2.2) yrs. During survival follow up there were 60,209 deaths. Using eGFR as time varying covariate within a Cox proportional hazards model the following association between CKD and mortality was demonstrated.

Adjusted† hazard ratios (CI 95%) for death from any cause	
Estimated GFR	Death from any cause
> 60 ml/min/1.73m^2	1.00 (Reference)
45 - 59 ml/min/1.73m^2	1.01 (0.99-1.03)
30 - 44 ml/min/1.73m^2	1.45 (1.41-1.48)
15 - 29 ml/min/1.73m^2	2.19 (2.11-2.27)
< 15 ml/min/1.73m^2	3.45 (3.23-3.68)
†Adjusted for Age and Sex	

Conclusions: This study demonstrates a graded association between CKD and mortality in the tested NI population. The risk of death rose sharply when an estimated GFR of < 45 ml/min/1.73m^2 was recorded. Having previously calculated the prevalence of CKD (eGFR < 60 ml/min/1.73m^2) in NI as 3.69%[2]; this further work clearly indicates the clinical and public health importance of CKD.

REFERENCES:

1. Go, AS, Chertow GM, Fan D, *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Eng J Med* 2000;**351:**1296-1305.

2. Quinn MP, Rainey A, Cairns KJ, *et al.* The practical implications of using standardized estimation equations in calculating the prevalence of chronic kidney disease. *Nephrol Dialysis Transplant 2000;***23(2)**:542-548.

FATAL TRANSMISSION OF TUBERCULOSIS IN AN ACUTE MEDICAL ADMISSION UNIT (AMAU).

N McNiece, N Chapman, A John, RP Convery

Dept. of Respiratory Medicine, Craigavon Area Hospital. County Armagh. BT63 5QQ

A 33 year old male was admitted from the local Psychiatric unit with apparent pneumonia. A chronic schizophrenic and heavy smoker, he had spent some 15 years in institutional care in various facilities. He was treated with high flow humidified oxygen and nebulised bronchodilators. 48 hours later he was found to be sputum smear positive for AAFB.

He was isolated and the Infection Control Team mobilised. He turned out to have a fully sensitive M.TB organism and responded well to treatment. BTS TB guidelines were followed and all staff and patients in the same ward bay as the patient were informed and letters sent to all GPs.

One patient contact had oesophageal carcinoma and was a chronic alcoholic. He developed post operative pleural effusion (TB culture positive) some 6 months post exposure. A second contact (also alcoholic) was investigated as possible lung cancer some 30 months after exposure and was Smear positive for AAFB. Both patients died on treatment for their TB.

All 3 TB isolates were identical. The index case is alive and well. This highlights the danger of even short delays in diagnosis and appropriate isolation of TB patients. It also highlights the use of RFLP/genotyping in case series and evaluation.

Ulster Med J 2009; **78 (1)** 65-74

Abstracts

11th Meeting of the Irish Society of Human Genetics, Friday 12th September 2008

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

PROGRAMME:

10.00 – 11.00	Registration / Tea and Coffee
11.00 – 11.05	Welcome
11.05 – 12.00	Spoken Presentations: Plenary I
12.00 – 13.00	**Keynote address:** "Genes for Blood Pressure" Professor Mark Caulfield, William Harvey Research Institute, London
13.00 – 14.00	Lunch and Poster viewing
14.00 – 15.30	Spoken Presentations: Plenary II
15.30 – 16.00	Tea and coffee / Poster viewing
16.00 – 16.15	Business Meeting
16.15 – 17.15	**Keynote address**: "Amyotrophic Lateral Sclerosis: Expanded Phenotypes and Complex Genetics" Professor Orla Hardiman, National Centre for Neuroscience, Beaumont Hospital, Dublin
17.15 – 18.00	Wine reception / Presentation of Prizes / Meeting Close

SPOKEN PAPERS:

S1. BIALLELIC DELETIONS OF CHROMOSOME 13Q ARE FREQUENT AT DIAGNOSIS IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Paula Carty, Johanna Kelly, Sarah McCabe, Natasha Coen, Claire Bermingham, Thomas Morris, David Betts

National Centre of Medical Genetics, Our Lady's Children's Hospital, Dublin, Ireland

Chronic lymphocytic leukaemia (CLL) represents the most common leukaemia in the western world. The cytogenetic analysis for specific karyotypic events plays an important part in the diagnostic work up of these patients. The most frequently described aberration in CLL, in about 50% of cases, are deletions of chromosome 13q. Since 2005, 313 patients at initial diagnosis have been investigated at the NCMG using a FISH panel that identifies the common CLL-associated aberrations. One or more aberrations were identified in 238 (77.6%) patients with a deletion of 13q present in 185 (59.1%). Further analysis of the del(13q) patient subgroup showed a remarkable 53 (16.9%) with a biallelic 13q deletion population of cells. In 23/53 patients a cell population with a monoallelic deletion of 13q was also evident. The group of patients with a biallelic deletion differed from the patients with solely a monoallelic deletion in having a notably lower incidence for the presence of other aberrations [2/53 (3.8%) vs. 23/134 (17.2%)]. This latter result indicates that the occurrence of a biallelic 13q deletion arises independently of other recognized aberrations. Given the high incidence of this aberration future studies are needed to assess whether this event has an associated prognostic significance.

S2. APPLICATION OF ARRAY-CGH FOR THE DETECTION OF SUBMICROSCOPIC CHROMOSOMAL IMBALANCES IN 400 CASES OF CHILDREN WITH IDIOPATHIC MENTAL RETARDATION AND CONGENITAL MALFORMATIONS.

Freddie Sharkey[1,2], Nick Wilkie[1], Eddy Maher[1], David FitzPatrick[2]

[1] Microarray Facility, South East Scotland Cytogenetics Unit, Western General Hospital, Edinburgh EH4 2XU

[2] Medical and Developmental Genetics Section, MRC Human Genetics Unit, Edinburgh EH4 2XU

The advent of microarray technology has revolutionised molecular cytogenetics in recent times, accelerating the identification of cryptic chromosomal rearrangements. Enhanced resolution has also led to the identification of many novel new microdeletion and duplication syndromes. Detection rates for chromosome abnormalities with array-CGH in constitutional cytogenetics range from 5 - 20% in individuals with normal results from prior routine cytogenetics testing. We present BAC array-CGH data from approximately 400 cases with unexplained MR following karyotyping and subtelomere MLPA screening. We discuss the identification of novel submicroscopic rearrangements, low-level mosaicism, cryptic translocations, transmission of imbalances (1-4Mb) with no apparent phenotypic effect and the targeting of novel new microdeletion & reciprocal duplication syndromes. Large-scale array-CGH screening has also significantly increased our knowledge on the impact of copy number variants (CNVs), which represents one of the main challenges to differentiate between CNVs that are likely to be pathogenic, and CNVs that are less likely to contribute to an affected individual's clinical presentation. With continual resolution changes, array-CGH will facilitate the identification of novel loci involved in MR and / or malformation syndromes and will provide important insights into the flexibility and plasticity of the human genome.

S3. STUDY OF THE KNOWLEDGE OF INHERITED METABOLIC DISORDERS AMONG PATIENTS AND THEIR FAMILIES IN THE IRISH POPULATION.

Rosie O'Shea[1], Eileen Treacy[2], Anne Marie Murphy[2], Sally Ann Lynch[3], Deborah Lambert[2,3].

[1] Department of Medical Genetics, Cardiff University,

[2] Children's University Hospital, Temple Street, Dublin

[3] National Centre for Medical Genetics, Dublin.

Galactosaemia and Maple Syrup Urine Disease (MSUD) are recessively inherited conditions detected by newborn screening in Ireland. Patients are treated at one centre and genetic information is provided by the specialist team. We assessed knowledge among parents and patients to see whether referral for formal genetic counselling would be beneficial, using a questionnaire including 4 demographic, 8 knowledge, 2 information and 5 disease impact questions. 27 families with galactosaemia and 10 with MSUD were interviewed in clinic. All parents of children with galactosaemia and MSUD answered >75% of questions correctly, but there were misunderstandings about the risk or implications of carrier status. There was a significant difference in knowledge between ethnicities. Adult patients with galactosaemia had more misunderstandings in relation to inheritance, recurrence risks and carrier status than their parents. 83% of study participants requested more information about their condition and its transmission. 40% of affected adults with galactosaemia identified a need to meet others with the same condition. While parents of children with MSUD or galactosaemia are well informed, the majority expressed a wish to be referred for genetic counselling. Adult patients with galactosaemia and parents from an Irish Travelling background could especially benefit.

S4. SHOULD A FAMILY HAVE TO FACE A UV DILEMMA?

Claire W Kirk, Patrick J Morrison.

Northern Ireland Regional Genetics Centre, Belfast Health and Social Care Trust, A Floor, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

With the advancement of high-throughput technologies for mutation screening, unclassified variants (UV; non-informative mutations for which the pathogenic effect is unclear) are increasingly being discovered in the BRCA1 and BRCA2 genes. There are a number of ways to try to establish the pathogenicity of a UV, including testing to see if the UV co-segregates with the disease in a family, checking a number of control samples to exclude its presence in the general population, and accessing websites designed for protein modelling and in silico functional analysis.

In those cases where pathogenicity cannot be established with certainty, there are issues around counselling and management of patients and their families. Genetic centres differ in their reporting policies, with some centres reporting all UVs to patients and others operating on a case-by-case basis. There does seem to be a general consensus that family history remains central to risk assessment and management of family members and that presymptomatic testing using UVs of uncertain clinical significance should not be offered. Here we present a case where a BRCA1 UV was found in a family member affected with breast cancer and discuss our decision regarding disclosure of the result and future management of the family.

S5. A CLOSER LOOK AT MISSINGNESS: THE IMPLICATIONS OF NON-RANDOM MISSINGNESS ON FALSE POSITIVE ASSOCIATION IN GENOTYPE CALLING APPROACHES FOR GENOME WIDE ASSOCIATION DATA.

Richard Anney, Elaine Kenny, Colm O'Dushlaine, Jessica Su, Barbara Franke, Ben Neale, Steven Faraone, Michael Gill.

Department of Psychiatry, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine & Trinity College Dublin, Ireland.

The considerable data-handling requirements for genome wide association studies (GWAS) prohibit individual calling of genotypes and create a reliance on sophisticated "genotype-calling algorithms". Despite their obvious utility, the current genotyping platforms and calling-algorithms used are not without their limitations. Specifically, some genotypes are not called due to the ambiguity of the data. Any bias in the missing data could create spurious results. Using data from the Perlegen 600K Array - Genetic Analysis Information Network (GAIN) data - we observed that missing genotypes are not randomly distributed throughout the homozygous and heterozygous groups. Using simulation, we examined whether the level and type of missingness observed might influence deviation from the null-hypothesis under common case-control and family-based statistical approaches. Under a case-control model, where missingness is present in a case group but not the controls, we observed bias giving rise to genome-wide significant type-I error for missingness as low as 3%. The family-based association simulations show close to nominal type-I error at 4% genotype missingness. These findings have important implications to study design, quality-control procedures and reporting of findings in GWAS.

S6. GENOME-WIDE ASSOCIATION STUDY USED POOLED DNA SAMPLES AND ITS APPLICATION IN CORONARY HEART DISEASE.

W Meng[1], A Hughes[1], CC Patterson[1], C Belton[1], F Kee[1], PP McKeown[1,2].

[1] Centre for Clinical and Population Sciences, Queen's University Belfast, Institute of Clinical Science, Grosvenor Road, Belfast, BT12 6BJ, Northern Ireland, UK.

[2] Regional Medical Cardiology Centre, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BA, Northern Ireland, UK.

Background: Genome-wide association studies have been successful in identifying susceptibility loci for common diseases. DNA pooling is a practical way to reduce the huge cost of large-scale genotyping.

Methods: In the first stage, our work focused on the use of 330k / 550k SNP chips, using pooled DNA samples from up to 50 cases or controls. The cases were male patients with early-onset (<55yr) coronary heart disease. The control individuals (age > 68yr) were identified from the PRIME study. We then selected SNPs with differences of allele frequencies between 5% and 13%, combined with a 'cluster' method. In the second stage, replication was undertaken using independent DNA samples from a family-based study (1494 individuals from 580 families with probands having early-onset coronary heart disease).

Results: Among 9 regions, SNPs in 2 chromosomal regions were successfully replicated in the second stage. The P values for SNPs in the DNAJC6 gene, rs501691, rs1325607, rs4325172 were 0.03, 0.03, and 0.004, respectively. Another SNP on chromosome 15, rs3825877 was also positive (P=0.009).

Conclusion: Genome-wide association studies using pooled DNA samples are feasible and may be a cost-effective way to detect genes for complex diseases. DNAJC6 gene may be associated with early-onset coronary heart disease.

S7. POLYMORPHISMS IN THE OXYTOCIN RECEPTOR GENE AND AUTISM: ASSOCIATION AND FUNCTIONAL STUDIES.

Katherine Tansey [1], Matthew Hill, Richard Anney, Michael Gill & Louise Gallagher.

Department of Psychiatry, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine & Trinity College Dublin, Ireland.

The neuropeptide oxytocin has recently been implicated in the aetiology of autism. We examined 20 markers in oxytocin receptor gene (OXTR) for association in 179 simplex families from the Irish Autism Study. We followed up genetic association studies with allelic expression imbalance (AEI) testing for alterations in expression of the OXTR gene. Using lymphoblast cell lines from the CEU HapMap collection, we examined the influence of common variation and different levels of β-Estradiol and Progesterone on AEI.

We found associations between 3 SNPs in OXTR and autism (rs11720238 p=0.031; rs7632287 p=0.0076; rs4564970 p=0.0091). Two SNPs showed association with a high functioning subset of individuals (rs11720238 p-corrected= 0.025; rs7632287 p-corrected=0.0042). We observed AEI in OXTR. The variation in AEI was driven, in part, by a SNP in intron 3 of OXTR (rs237897; p=0.0265). rs237897 was not associated with autism in our sample. The addition of hormones did not appear to alter AEI significantly from the baseline.

These results confirm the importance of OXTR in the aetiology of autism and identify a SNP involved in differential gene expression.

S8. MODELLING ABERRANT SPLICING IN MUTANT GENES.

CE Willoughby, D O'Prey, DAC Simpson.

Centre for Vision Science, Queen's University Belfast, Belfast, United Kingdom.

Purpose: Up to 50% of all point mutations responsible for genetic diseases cause aberrant splicing. The aim of this study was to model the pathological impact of known mutations on the splicing process in genes associated with Bardet-Biedl syndrome (BBS: MIM 209900). Methods: Computational methods were applied 'in-silico' to prioritise and direct subsequent laboratory workup of mutations in BBS genes to establish which, if any, might have a pathogenic effect on splicing. Splice site score was calculated on 190 exons in 12 BBS genes using web-based servers and correlated with EST evidence. Computational predictions of aberrant splicing were validated in vitro using a minigene system. Results: 290 mutations were modelled and 21% identified 'in-silico' as potential mis-splicing mutations. BBS9, BBS10 and BBS5 genes contained the greatest percentage of possible splicing mutations with 75%, 33% and 33% respectively. A number of predicted aberrant splicing events were modelled with a minigene system in HEK293 cell lines to validate predictions. Conclusions: Traditionally, mutation screening is based on genomic DNA analysis and the effect of a mutation on the mRNA or protein is usually predicted from the primary genomic sequence, as opposed to direct experimental evaluation by determining mRNA expression and splicing patterns. Here, we present an approach to predict and model aberrant splicing in mutant genes.

S9. FUNCTIONAL ANALYSIS OF POLYMORPHISMS IN GENES IMPLICATED IN PSYCHIATRIC DISORDERS.

Matthew Hill, Richard Anney, Michael Gill.

Department of Psychiatry, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine & Trinity College Dublin, Ireland.

Introduction: Psychiatric diseases such as autism, ADHD and schizophrenia are highly heritable. Past years have seen the identification of a handful of susceptibility genes via traditional candidate gene testing. With the advent genome-wide associations novel susceptibility genes are being rapidly identified. In order to elucidate the molecular mechanisms giving rise to disease susceptibility it is necessary to identify and characterise functional genetic variation. To this end we sought to identify cis acting variation in 'traditional' candidate genes and novel susceptibility genes using allelic expression imbalance (AEI).

Methods: HapMap CEU lymphoblast cell lines were used as a source of mRNA for measuring AEI for the nine selected genes; three monoaminergic genes, a recent schizophrenia susceptibility gene and five novel ADHD susceptibility genes were tested. AEI was determined using TaqMan SNP

genotyping assays.

Results: Significant AEI was observed for 7/9 genes. Only COMT and TRUB1 did not show AEI. A SNP in CHI3L1, rs4950928, previously associated with schizophrenia was strongly associated with AEI.

Conclusion: We have identified cis acting regulatory events in multiple psychiatric disease susceptibility genes. These data will aid in both the future refinement of the association signal and elucidation of the molecular mechanisms underlying susceptibility.

S10. DEVELOPMENT OF GENE THERAPIES FOR DOMINANT DYSTROPHIC EPIDERMOLYSIS BULLOSA.

CP Morgan, D Allen, PF Kenna, P Humphries, GJ Farrar.

Smurfit Institute of Genetics, Trinity College Dublin

Epidermolysis Bullosa comprises a group of rare and heritable human blistering skin diseases, affecting up to 1 in 17,000 live births. The dominant dystrophic form of EB (dDEB) is characterised by mutations of the COL7A1 gene, resulting in production of mutant type VII collagen protein. Any potential dDEB therapeutic would require suppression of expression of the mutant gene. Continuing advances in the field of gene therapy have led to the discovery of potential therapeutics for dominantly inherited human disorders: the method of RNA interference (RNAi) represents one such molecular tool for suppression of COL7A1 expression. RNAi is based on the sequence specific binding of synthetic RNA molecules to endogenous mRNA transcripts, causing their subsequent degradation. This study involved such suppression in human epidermal keratinocytes, using microRNA vectors expressing short hairpin RNAs targeting COL7A1. Subsequent evaluation of COL7A1 mRNA levels by real time rtPCR showed significant COL7A1 suppression. Additionally, the expression levels of three interferon stimulated genes were evaluated in cells transfected with the COL7A1-targeting constructs. It was found that delivery of these potential therapeutics does not result in an interferon type-1 response. The results obtained thus far represent an important step in the progression towards a suitable therapy for dDEB.

POSTER PRESENTATIONS:

P1. INVESTIGATING PROMOTER HYPERMETHYLATION OF APOPTOTIC GENES IN PROSTATE CANCER.

TM Murphy[1], AS Perry[1] L O'Connor[1], M Lawler.[1]

[1]Prostate Cancer Research Group, Institute of Molecular Medicine, Trinity Centre for Health Sciences, St. James Hospital, Dublin 8, Ireland.

It is now well established that cancer cells exhibit a number of genetic defects in the machinery that governs programmed cell death and that sabotage of apoptosis is one of the principal factors aiding in the evolution of the carcinogenic phenotype. A number of studies have implicated aberrant DNA methylation as a key survival mechanism in cancer, whereby promoter hypermethylation silences genes essential for many processes including apoptosis. To date, studies on the methylation profile of apoptotic genes have largely focused on cancers of the breast, colon and stomach, with only limited data available on prostate cancer. The aim of this study was to profile methylation of apoptotic-related genes in order to generate a prostate cancer "apoptotic methylation signature". This in turn could play a role in the early detection and prognosis of prostate cancer and may help elucidate novel therapeutic targets. An in silico approach was first applied to generate a list of apoptotic genes. Relevant genes were identified based on the following criteria: 1) biological role in apoptosis, 2) the presence of a 5' CpG Island 3) susceptibility to promoter hypermethylation in other cancer types and 4) down-regulation in prostate cancer. Under these criteria, 22 apoptotic-related genes were identified as possible targets of methylation in prostate cancer. PCR assays were designed to amplify whole CpG islands in these gene promoters. Genes will be screened for CpG methylation in a panel of prostate cancer cell lines (LNCaP, DU145, PC-3, 22RV1, RC58) using an automated Denaturing High Performance Liquid Chromatography (DHPLC) instrument (WAVE®, Transgenomic Inc). To date, DHPLC results suggest that the CpG promoter region of TMS1, C-FLIP and BNIP3 are fully or partially methylated in the five cell lines examined, while APAF1, CASP8 and CASP3 show no evidence of CpG promoter methylation. Currently we are screening BIK, DR4 and DR5 for promoter hypermethylation.

Genes of interest will be further validated through bisulfite sequencing and methylation levels quantified using quantitative methylation specific PCR in a prostate cancer biorepository that we have generated in Ireland, representing prostate cancer, normal adjacent prostate and benign prostatic hyperplasia.

P2. ANALYZING ILLUMINA HUMAN 1M SNP DATA FOR CNVS USING RAW BEAD-LEVEL DATA.

Naisha Shah[1], Judith Conroy[2], Regina Regan[2], Sean Ennis[2,3], Denis C Shields[1]

[1] UCD Conway Institute and UCD Complex and Adaptive Systems Laboratory, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland,

[2] Health Science, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland,

[3] National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Dublin, Ireland

With the advent of high-throughput genotyping chips, whole genome association studies are undertaken to determine potential candidate loci by linking common SNPs and copy number variations to human disorders like autism. Illumina's Human 1M SNP beadchip is one of the high-throughput genotyping chips popularly used. The genotype reproducibility for Human 1M SNP chips is 99.99%. However, standard existing methods for prediction of CNVs from the normalized intensity data, generated by Illumina's proprietary software BeadStudio, have between 15-60% reproducible on experimental replicates depending on the algorithm used. We are developing improvements in the pre-processing and normalization of raw intensity bead-level data with respect to improving the CNV reproducibility of experimental replicates. In addition, we are optimizing the normalization of the SNP chip data to recover CNVs predicted using other experimental platforms. Applications to large clinical datasets of probands and parents as well as to HapMap datasets will be presented.

P3. A FUNCTIONAL PROMOTER POLYMORPHISM WITHIN MTHFD1 MAY INCREASE NEURAL TUBE DEFECT RISK IN THE IRISH POPULATION THROUGH AN INTERACTION WITH THE R653Q POLYMORPHISM.

Nicola Carroll[1], Faith Pangilinan[2], Anne M. Molloy[3], James Troendle[4], James L. Mills[4], Peadar N. Kirke[5], Lawrence C. Brody[2], John M. Scott[6], Anne Parle-McDermott[1].

[1] Nutritional Genomics Group, School of Biotechnology, Dublin City University, Dublin 9, Ireland.

[2] Molecular Pathogenesis Section, Genome Technology Branch, National Human Genome Research Institute, Building 50, Room 5306, 50 South Drive, MSC 8004, Bethesda, MD 20892-8004, USA.

[3] School of Medicine, Trinity College Dublin, Dublin 2, Ireland.

[4] Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA. [5]Child Health Epidemiology Division, Health Research Board, Dublin, Ireland. [6] School of Biochemistry & Immunology, Trinity College Dublin, Dublin 2, Ireland.

Genetic variants in MTHFD1 (5, 10-methylenetetrahydrofolate dehydrogenase/ 5, 10-methenyltetrahydrofolate cyclohydrolase/ 10-formyltetrahydrofolate synthetase), a key folate metabolic enzyme, are associated with a number of pregnancy complications, including neural tube defects (NTDs). We have previously reported that a common polymorphism (dbSNP ID: rs1076991 C→T), present in the core promoter region of the MTHFD1 gene, has a negative effect on gene transcription in vitro (ISHG meeting, 2006). We have since investigated this SNP as a potential risk factor for NTDs and report here that it is not an independent NTD risk factor in the Irish population, nor does it influence red cell folate or homocysteine levels. However, SNP-SNP interaction analysis with the previously identified disease-associated SNP rs2236225 G→A (R653Q polymorphism) in the MTHFD1 gene revealed a highly significant association with NTD risk in both case and maternal groups ($P < 0.001$ and 0.01, respectively). These two SNPs are not in linkage disequilibrium and, therefore, the identified interaction cannot be attributed to simple co-segregation. Thus, although not an independent risk factor for NTDs, this SNP is relevant to elucidating the genetic component of common diseases through its interaction with the disease-associated R653Q polymorphism.

P4. ABSTRACT: FUNCTIONAL ASSESSMENT OF S100B AS A SUSCEPTIBILITY GENE FOR PSYCHOTIC BIPOLAR DISORDER.

E Dagdan[1], P McKeon[2,3], S Roche[1,2]

[1] Smurfit Institute of Genetics, Trinity College, Dublin, Ireland;

[2] Department of Psychiatry, Trinity College, Dublin, Ireland;

[3] St. Patrick's Hospital, Dublin, Ireland.

Introduction: The glial cell-derived neurotrophic factor, S100B, is implicated in the pathology of bipolar affective disorder (BPAD) and schizophrenia. S100B protein levels are elevated in serum of patients with both disorders

and S100B variants are associated with schizophrenia. We previously reported association of a SNP in the promoter of S100B, rs3788266, with a psychotic form of BPAD (P=0.088). The disease-associated C allele disrupts a Trex/MEF3 consensus recognition, which is bound by Six-family transcription factors, suggesting that it could affect S100B expression.

Methods: The functional effect of rs3788266 on S100B promoter activity was determined using the luciferase reporter system. Promoter fragments containing the T or C alleles of rs3788266 were subcloned into the pGL4.23 minimal promoter-luciferase vector and were assayed for activity in U373MG glioblastoma cells. We also measured S100B RNA levels in post-mortem brain tissue and protein levels in serum to test for possible genotypic effects in vivo.

Results: Luciferase reporter gene expression was significantly increased in the presence of the T compared to C allele (t= 4.151, P=0.001). However, preliminary data indicate that BPAD individuals with the TT genotype have lower mean serum S100B levels compared to those with the TC or CC genotypes (ANOVA: F=5.093, P=0.01). A similar pattern was observed at the RNA level but was not significant.

Discussion: The disease-associated C allele is associated with reduced promoter activity in U373MG glial cells and increased protein levels in serum. SNP rs3788266 may represent a functional susceptibility variant that contributes to the increased S100B levels observed in BPAD patients.

P5. FOUR CASES OF MOWAT-WILSON SYNDROME.

L Bradley, AJ Green, SA Lynch

National Centre for Medical Genetics, OLCHC, Dublin 12

Mowat-Wilson is a recently described multiple congenital anomaly condition with Hirschsprung disease as a hallmark feature. ZEB2 is the causative gene. We report 4 cases of Mowat-Wilson syndrome. Their age ranged from 22 months to 5 years and 2 months. They all presented developmental delay, microcephaly, typical facial features and absent speech. Interestingly, none had Hirschsprung disease and only one had constipation.¾ had epilepsy which was well controlled and all of these also had congenital heart defects with 2 requiring heart surgery. ¾ had brain imaging with no structural abnormalities were noted. 2/4 had ocular findings, 1 astigmatism and the other a strabismus. All had the typical affable personality. Their developmental delay was in the moderate to severe range.

All 4 were found to have de novo mutations in the ZEB2 gene. Three were novel mutations with 2 being frameshift and the other a nonsense mutation. The fourth mutation had previously been described and was also a nonsense mutation.

P6. VARIANTS IN THE NESTIN GENE AND CORONARY HEART DISEASE.

W Meng[1], A Hughes[1], CC Patterson[1], C Belton[1], PP McKeown[1,2].

[1] Centre for Clinical and Population Sciences, Queen's University Belfast, Institute of Clinical Science, Grosvenor Road, Belfast, BT12 6BJ, Northern Ireland, UK.

[2] Regional Medical Cardiology Centre, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BA, Northern Ireland, UK.

Background: There is evidence that the intermediate filament protein, nestin, may play a role in tissue regeneration and nestin expression has been detected in coronary atherosclerotic plaques. However, to date, no population-based studies concerning the role of the nestin gene in coronary heart disease (CHD) have been reported.

Methods: We evaluated 3 SNPs in the nestin gene amongst 1494 individuals in 580 Irish families with at least one member prematurely affected with coronary heart disease. Genotypes were determined by multiplex SNaPshot technology.

Results: Using the TDT/S-TDT test, we found that rs11582300 and rs3748570 were associated with early-onset CHD (P=0.04 and P=0.02).

Conclusion: We found that nestin gene variants were associated with early-onset CHD. These findings emphasise the importance of further research to explore the role of nestin in atherosclerosis.

P7. INVESTIGATION OF THE PUTATIVE FUNCTIONAL EFFECT OF THE 19BP DELETION POLYMORPHISM WITHIN INTRON 1 OF THE DIHYDROFOLATE REDUCTASE (DHFR) GENE.

Alan Magee, Kirsty O'Brien, Anne Parle-McDermott.

Nutritional Genomics Group, School of Biotechnology, Dublin City University, Ireland.

DHFR is an important folate metabolising enzyme that catalyses the conversion of dihydrofolate to tetrahydrofolate. Folate genes are considered candidates for association with neural tube defects (NTDs) such as spina bifida due to the preventative effect of periconceptional maternal supplementation with folic acid. Investigation of an intronic 19bp deletion polymorphism within the DHFR gene found a significant protective effect in mothers of NTD cases when present in one (Relative Risk 0.59 (95% CI: 0.39-0.89), p= 0.01) or two copies (Relative Risk 0.52 (95% CI: 0.32-0.86), p= 0.01). Analysis of mRNA levels revealed a small increase in expression (~1.5 fold) associated with the 19bp intronic deletion polymorphism, but this was not significant (Parle-McDermott *et al., Am J Med Genet* 2007;**143(11):**1174-1180).

We sought to further investigate the potential impact of the DHFR 19bp intronic deletion polymorphism on gene expression by employing a recombinant dual luciferase system in HEK293 cells. The results of these experiments showed that the 19bp deletion showed a modest increase in reporter gene expression in agreement with the mRNA data. It is proposed that the sequence of the 19bp deletion harbours an Sp2 binding site that acts as a repressor of transcription. Mobility shift assays are being employed to directly test whether this polymorphism results in loss of an Sp2 binding site.

P8. UNCOMMON PRESENTATION FEATURES OF THE T(8;14)(Q11.2;Q32) TRANSLOCATION IN ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL).

Johanna Kelly[1], Claire Bermingham[1], Paula Carty[1], Aengus O'Marcaigh[2], Helen Enright[3], David Betts[1]

[1] National Centre of Medical Genetics, Our Lady's Children's Hospital, Dublin, Ireland,

[2] Department of Haematology and Oncology, Our Lady's Children's Hospital, Dublin, Ireland,

[3] Adelaide and Meath Hospital, Dublin, Ireland

The t(8;14)(q11.2;q32) translocation represents a rare but non-random event in ALL that results in a rearrangement of IGH on 14q32. Almost 50% of reported cases occur in either Down syndrome (DS) associated or t(9;22)-positive disease. From a series of over 400 cases of ALL analysed at presentation by G-banding and/or FISH two were found to contain a t(8;14)(q11.2;q32) translocation in either balanced or unbalanced form. Case 1 was an 18-year-old DS female who presented with a der(14)t(8;14) as the sole clonal aberration. The second case was a 49-year-old female who presented with t(9;22)-only as the minor stemline clone and a major sideline clone containing a t(8;14) in which the der(8) had a p arm deletion. Subsequent analysis of this case demonstrated only the presence of the t(9;22) stemline clone. This report further reinforces the association of the t(8;14)(q11.2;q32) with both t(9;22) and DS-associated ALL. As the standard der(8) was absent in both cases we speculate whether other cases with this translocation exist but were not fully characterised. The persistence of leukaemia without the rearrangement questions the importance of the event in the disease process. Further cases are needed to understand its potential relevance to the disease process and prognosis.

P9. AN APPROACH TO IDENTIFY NOVEL HUMAN FOLATE RESPONSIVE GENES.

Christian Fiedler, Anne Parle-McDermott.

Nutritional Genomics Group, School of Biotechnology, Dublin City University, Dublin 9, Ireland.

The molecular details of how low folate status increases the risk of a range of common diseases such as neural tube defects, cardiovascular disease and colorectal cancer remains to be elucidated. In a bid to begin to understand the molecular response of cells to a restricted supply of folate that is physiologically meaningful; an in vitro cell culture model of folate deficiency was employed in combination with gene expression profiling. The nature of the experimental design ensures that the group of genes that initially respond to folate deficiency would be identified.

A Coriell® lymphoblast cell line that was homozygous wildtype for the MTHFR 677C>T polymorphism (CC) was grown in folate sufficient or folate deficient media over a 12 day period. The folate deficient cells were grown in the presence of hypoxanthine and thymidine throughout the 12 day period to ensure the cells maintained a similar proliferation rate to the folate sufficient cells. The hypoxanthine and thymidine were removed several hours prior to harvest on day 12. Each condition was carried out in replicates of 5 yielding

a total of 10 RNA samples for subsequent transcriptome profiling. Each RNA sample was hybridisation to an individual Affymetrix Human Genome U133 Plus 2.0 array. These arrays are one of the most comprehensive whole genome expression arrays; consisting of probe sets that represent over 47,000 transcripts.

The resulting data signals were normalized and sufficient and deficient expression profiles were compared. A total of two gene lists were generated; each subjected to stringent or less-stringent statistical parameters and represent genes that showed a consistent differential gene expression pattern across the replicate samples. The stringent list consists of 4 down-regulated genes and 288 up-regulated genes. The less-stringent list consists of 324 down-regulated genes and 597 up-regulated genes. Based on the experimental design; these genes are likely to represent the initial cellular response to a depleted folate supply. Further bioinformatics analysis and confirmation of expression differences by Quantitative RT-PCR are currently being performed.

In conclusion, our approach has identified a list of novel folate responsive genes under conditions of relatively mild folate deficiency. These genes/pathways are likely to represent the initial response of a cell to low folate status. These results will ultimately lead to a better understanding of how an individual's folate status influences their disease risk.

P10. MOLECULAR ANALYSIS OF KERATOCONUS IN NORTHERN IRELAND.

DP Dash[1], Sonia George[3], G Silvestri[1,3], J Jackson[3], D Frazer[3], AE Hughes[2], CE Willoughby[1,3]

Centre for Vision Sciences[1], Medical Genetics[2], Queen's University & Royal Victoria Hospital[3], Belfast.

Purpose: Keratoconus (KC; MIM#148300) is the commonest reason for corneal transplantation in the Western world. Mutations in the visual system homeobox gene 1 (VSX-1; MIM#605020) and superoxide dismutase 1 (SOD1; MIM#147450) have been reported in KC. The purpose of this study was to perform a comprehensive screening of VSX-1 and SOD1 in KC patients and further molecular analysis of the chr15q22 linked to a Northern Irish family we mapped previously.

Method: Index cases with KC were recruited and mutational analysis of VSX1 and SOD1 gene was carried out. Further candidate gene analysis was performed in chr15q22 interval and the region was analysed for copy number variations (CNV).

Results: Four VSX1 sequence variants c.432C>G (p.D144E), c.479G>A (p.G160D), c.789C>T (p.S263S) were not seen in 100 healthy controls. Segregation was not detected for p.D144E and also for an intronic changes, c.844-13T>A. Although predicted to alter VSX1 splicing p.S263S had no effect on transcript processing. A silent mutation in SOD1 was detected in a familial KC patient and absent from 100 controls. Till date no pathogenic mutations and no CNV detected within the linkage region chr15q22.

Conclusions: VSX1 and SOD1 play a minor role in keratoconus pathogenesis. The identification of the genetic basis of the chr15q22 KC family is ongoing.

P11. VITAMIN D RECEPTOR POLYMORPHISMS FOK 1 AND APA 1 HAVE NO ASSOCIATION WITH SKIN CANCER IN RENAL TRANSPLANT PATIENTS.

ME Laing, P Dicker, PJ Conlon, D Shields, GM Murphy.

Beaumont Hospital, Dublin 9

Vitamin D has potent anti-tumour properties. Calcitriol (1,25(OH)2D3), the hormonal derivative of vitamin D3, is an antiproliferative and prodifferentiation factor for several cell types, including human squamous cells of the head and neck. Several polymorphisms of the vitamin D receptor have been described, including Fok 1, Taq 1, Apa 1 and Bsm. These polymorphisms have been reported to be associated with the occurrence and outcome of malignant melanoma[1]. Bsm BB genotype is associated with increased squamous cell carcinoma risk [2]. We have examined the frequency of FokI and ApaI polymorphisms in 401 renal transplant patients and measured the association with squamous cell carcinoma, basal cell carcinoma, melanoma and also renal allograft survival. There was no association between patients with the polymorphism and the development of SCC, BCC or melanoma. There was however significantly improved graft survival at 3, 5 and 10 years for heterozygotes and homozygotes for the T allele (p=0.03) of Fok 1 Vitamin D polymorphism. This is the first time that the Fok I polymorphism has been associated with improved renal allograft survival. The finding is in keeping with a number of other related studies. In a retrospective study patients receiving $1,25(OH)_2D_3$ along with standard immunosuppression had improved graft survival. There is also animal data showing prevention of chronic allograft rejection with use of Vitamin D receptor agonists. Any risk for skin cancer would be compounded for by the longer graft survival and is therefore a true negative association.

1. Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? *Br J Dermatol* 2002;**147(2):**197-224.
2. Han J, Colditz GA, Hunter DJ. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. *Carcinogenesis* 2007;**28(2):**390-397

P12. PHENOTYPIC VARIANTS IN MELAS.

Deirdre Donnelly, Shane McKee

Belfast City Hospital, Belfast BT9 7AB.

MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, is one of the commonest mitochondrial disorders. The incidence is estimated to be around 1 in 15,000, but may be higher. The age of presentation and symptomatology vary widely, making under-diagnosis likely. Early-onset stroke is the commonest presentation in adulthood. Presentation in childhood is more unpredictable and non-specific. Early cardiac changes generally begin in childhood but are asymptomatic. We report the case of an individual who was diagnosed following early-onset stroke and epilepsy. The pedigree showed a brother with diabetes mellitus and a sister who died of cardiomyopathy. Testing shows all family members to have a mt3243A>G mutation, the commonest mutation found in MELAS. All have had mutational load measurements in blood and urine. Mutational load may influence prognosis, but does not always correlate with phenotype due to tissue heteroplasmy. This family will be followed up closely, and will have mutational load measured annually. Our patient is currently being treated with anti-epileptic medication, along with aspirin, L-arginine and thiamine. This family illustrates some of the many complexities in dealing with mitochondrial disorders.

P13. A FAMILIAL T(2;9)(Q37.3;Q12) TRANSLOCATION: AN ILLUSTRATION OF THE POTENTIAL LIMITATIONS OF COMMERCIALLY AVAILABLE FISH PROBES.

Adam Dunlop, Andrew Green, Gillian Clarke, David Betts

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

The importance of cytogenetic family studies following the identification of either an inherited or de novo unbalanced chromosome abnormality is well documented. Conventional G-band analysis was performed on a 2 day old girl with dysmorphic features, frontal bossing and low set ears. The result indicated the presence of an additional chromosome, identified as del(9)(q12), "trisomy 9p", a recognised syndrome that is typically considered to arise de novo and was consistent with her phenotypic features. G-band chromosome analysis was performed on both parents and showed a maternal reciprocal translocation t(2;9)(q37.3;q12). In an attempt to delineate the translocation further, FISH analysis with subtelomere probes mapping to 2q and 9q (TelVysion, Vysis) was undertaken. Unexpectedly, the 2q subtelomere region had not been translocated to the der(9). Given the breakpoints involved in this case, if only FISH and some molecular based studies were performed, the potential for a familial t(2;9) translocation would have remained unsuspected with significant consequences for this family.

P14. ABNORMALITIES OF 3Q26 IN MYELOID MALIGNANCY: THE BELFAST EXPERIENCE.

SE McNerlan, P McGrattan, A Logan, M Humphreys

Northern Ireland Regional Cytogenetics Laboratory, Belfast Trust.

Rearrangements of chromosome 3q26, although well recognised in myeloid disease, are still relatively rare. They have been reported in AML, MDS, CML and other MPDs. They tend to be associated with tri-lineage dysplasia, prior treatment with alkylating agents, shorter survival time, poor response to treatment and abnormal expression of the EVI1 gene. However, in the majority of patients demonstrating abnormal EVI1 expression, 3q26 rearrangements are generally not detected cytogenetically.

Since 1990 the Northern Ireland Regional Cytogenetics lab has investigated 11 patients with 3q26 rearrangements. These patients (6 females and 5 males) suffered from a range of myeloid conditions including AML of various subtypes, MDS and transforming CML. Age of diagnosis ranged from 55 to 86 years. Survival data was available for 7 patients and ranged from <1 to 21 months post diagnosis.

Our experience therefore confirms the poor survival generally associated

with 3q26 rearrangements and enforces the importance of establishing their presence at disease diagnosis and during treatment. Technical difficulties have precluded the development of satisfactory FISH tests in the past, however, new molecular technologies are now available. Considering the poor prognosis, routine introduction of these techniques for cultures that fail to grow or patients with a normal karyotype should therefore be considered.

P15. AN ATTENUATED FORM OF MORQUIO DISEASE SEEN IN NORTHERN IRELAND.

Fiona Stewart[1] Karen Tylee[2] Aoife Bradley[1] Alan Cooper[2]

[1] Northern Ireland Regional Genetics Service, Belfast City Hospital,

[2] Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester.

Morquio disease (mucopolysaccharidosis type IV) is a lysosomal storage disorder causing predominantly skeletal manifestations. It is caused by a deficiency of galactosamine-6-sulphate sulphatase. In the classical form of Morquio disease there is extreme short stature with average height being between 90 and 120 cm. There are marked skeletal deformities and many affected individuals require surgery to stabilise their cervical spine. We have identified 6 individuals in Northern Ireland who have an attenuated form of the disease – two sets of siblings and two single cases. Ages ranged from 27 years to 38 years. Height ranged from 142 cm to 160cm. This form of the disease was initially considered relatively benign. However it is now clear that affected individuals have major problems with their joints and 5/6 patients have had at least one major joint replaced with two having had 3 joints replaced. Our patients have also shown evidence of osteoporosis. We will present biochemical and molecular data on the cases.

These patients were all initially considered to have spondyloepiphyseal dysplasia before the correct diagnosis of MPS IV was made.

P16. MULTIPLEX MASSARRAY SPECTROMETRY (IPLEX) PRODUCES A FAST AND ECONOMICAL TEST FOR THE DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA.

William T Wright[a], Pádraig J Hart[a], Shirley V Heggarty[b], Ian S Young[c], D Paul Nicholls[c], Colin A Graham[a]

[a] Northern Ireland Regional Genetics Centre, Belfast.

[b] Genomic Core Technology Unit, Queen's University, Belfast.

[c] Regional Lipid Clinic, Belfast.

An iPLEX™ assay that includes 57 mutations in the LDLR, APOB and PCSK9 genes, gives a 75% detection rate for definite Familial Hypercholesterolaemia (FH) and was tested to determine if this technology was applicable to routine genetic diagnostics. The iPLEX™ MassARRAY platform (Sequenom GmbH) utilizes single base extension of mass modified terminators using MALDI-TOF mass spectrometry to analyse primer extension products, determining SNPs accurately, rapidly and economically.

The iPLEX™ test was verified by analyzing 150 FH samples with a previously characterized mutation and 96 no-mutation control samples. Mutations were identified in all 150 FH mutation-positive samples using the iPLEX™ assay, with 96% directly called by the software. The false positive rate was 0.015%, and the overall specific mutation assay failure rate was 2.1%.

116 hyperlipidaemia patients with elevated cholesterol levels were tested by the FH iPLEX™ assay, with 21 (18%) having mutations identified. This pick-up rate would be significantly increased were the patients to be selected using the Simon Broome criteria. The FH iPLEX™ system chip can test up to 86 patients in approximately two days at a cost of less than €10 per sample, and so provides a useful and efficient first-line screen for FH.

P17. CHALLENGES IN GENETIC COUNSELLING ARISING FROM THE RISK OF MULTIPLE GENETIC CONDITIONS IN A SINGLE FAMILY.

Alana Ward, Cliona deBaroid, Sally-Ann Lynch.

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

During a Genetics consultation ascertaining a family history can be a delicate process. Three families in whom several separate genetic risks were present and the complexity of the counselling required are discussed. Family 1 were referred due to a child born with Trisomy 21. The couple also had a family history of SMA and CF and advanced maternal age was also a consideration. Family 2 were referred due to a history of X-linked Adrenoleukodystrophy. A child had also died neonatally due to SMA. Family 3 were referred due to a diagnosis of Fragile X. Further exploration showed a relative affected with Huntington Disease and a neonatal death which revealed, although was unexplained by, a Robertsonian translocation.

Each of these families came to the Genetics clinic with a single genetic condition as their primary focus. Introducing the concept of additional significant yet diverse risks in a clear and understandable manner presented a number of practical counselling challenges particularly with regard to communicating burden of risk.

P18. NON-MOSAIC TRISOMY 22 IN A LIVE-BORN MALE.

Alex Magee[1], A Beckett[2], M Humphreys[2], A Harper[3], F Casey[4], F Stewart[1]

[1] Regional Genetics Service, Belfast City Hospital, Belfast BT9 7AB.

[2] Regional Genetics Laboratories, Belfast City Hospital, BT9 7AB.

[3] Royal Jubilee Maternity Hospital, Belfast BT12 6 BE.

[4] Paediatric Cardiology Service, Royal Belfast Hospital for Sick Children, Belfast BT12 6BE

Non-mosaic trisomy 22 is recognised as a common cause of first trimester miscarriage; survival beyond this is rare.

In this case, a baby boy was delivered at 39 weeks by caesarean section to a 39 year-old mother, and survived approx 60 minutes. She had 2 first trimester miscarriages, a daughter with multiple problems including microcephaly, septo-optic dysplasia and severe epilepsy (46,XX), and a healthy 23 year-old daughter from a previous relationship. Scan at 14 weeks was normal, but rescan at 26 weeks showed IUGR. Further assessment at 27 weeks identified abdominal left isomerism; biventricular AV connection, large VSD, single outlet right ventricle; oligohydramnios and severe IUGR. Amniocentesis was declined.

Birth weight was 1390g. He was dysmorphic, with dolicocephaly, hypertelorism, epicanthic folds and an open mouth. The palate was narrow and high, with thickened gums. He had very low set ears; the right ear was rudimentary and the left dysplastic with a preauricular tag. The anus was posteriorly placed and imperforate. Post-mortem was declined. A blood sample was taken for karyotyping and non-mosaic trisomy 22 confirmed.

Survival to term and significant life expectancy in trisomy 22 is usually associated with mosaicism. Identification of non-mosaic cases, and recognition of the poor prognosis, is important to allow clinicians and parents to plan appropriate management.

P19. DOES NOGGIN CAUSE TWINNING?

Miriam Russell[1], Sally Ann Lynch[1]

[1] National Centre for Medical Genetics, OLCHC, Crumlin, Dublin 12.

Human monozygotic twins account for 1 in 250 live births and are considered genetically identical. The origin of MZ twins is attributed to two or more daughter cells of a single zygote undergoing independent mitotic divisions, leading to independent development and births. To date, the cause of monozygotic twins remains unknown. Human beings and armadillos are the only mammals where monozygosity occurs.

We have previously reported two unrelated sets of monozygotic twins from spontaneous dizygotic triplet pregnancies, with a clinical phenotype of facio audio symphalagism (FAS). The dizygotic sibling of each triplet set has a normal phenotype. Spontaneuosly conceived triplet pregnancies occur in 1 in 6500 births in the Republic of Ireland. Noggin mutations occur in approximately 1 in 10000 births. The probability of FAS recurring in monozygotic twins from a triplet pregnancy is therefore highly unlikely.

A nonsense mutation in the Noggin (NOG) gene located on chromosome 17 q22 has been implicated as a causative factor in FAS. Mutations in GDF5 on chromosome 20q11.2 have also been identified in this syndrome.

We examine the correlataion between the phenotype of FAS and Noggin and monozygosity to detemine if a Noggin mutaion predisposes to twinning or indeed if there is an underlying mechanism that might cause noggin to influence monozygotic twinning. It is documented that monozygotic twins show DNA methylation disturbance, for example, Beckwith Weideman Syndrome (BWS) show excess of monozygotic twins (often discordant for BWS) more than by chance. Methylation disturbance has been shown to be the causative factor. As there is a CpG island present in the Noggin gene, one possibility would be to explore the methylation status of Noggin to determine if there are methylation irregularities that may play a role in twinning.

The coding region of Noggin was amplified in two overlapping segments. Sequencing was carried out using the ABI Prism BigDye Terminator Sequencing Kit. Both sets of twins returned normal results at the Noggin

DNA sequencing level. GDF5 sequencing is currently ongoing. Monozygosity of twins was confirmed using the Promega PowerPlex 16 kit.

DNA methylation is currently being assesed in both sets of monzygotic twins and, where available, unaffected siblings, by using both methylaytion microarray chip and BiSulphite modification PCR.

We propose to examine the methylation irregularities of Noggin, and to determine if there is a correlation between noggin methylation and twinning.

P20. THE DESIGN OF A THERAPEUTIC STRATEGY FOR DOMINANTLY INHERITED RETINITIS PIGMENTOSA FOR USE IN LARGER ANIMAL MODELS.

CA Kilty, M O'Reilly, S Millington-Ward, PF Kenna, N Chadderton, A Palfi, P Humphries, GJ Farrar.

Smurfit Institute of Genetics, Trinity College Dublin

Retinitis Pigmentosa (RP) represents a group of retinal disorders that results in progressive loss of vision due to photoreceptor cell death. Over 100 mutations have been identified in the rhodopsin gene that gives rise to autosomal dominant (ad) RP. One therapeutic approach which has been suggested for adRP, utilises suppression and replacement. Both wild-type and mutant rhodopsin alleles are suppressed and simultaneously a replacement gene, refractory to the suppression agent is delivered. This strategy has previously been employed in our laboratory using RNA interference (RNAi) as the suppression agent. In this study we decided to design a strategy for use in a porcine model of RP. Two siRNA molecules were designed to target both human and porcine rhodopsin. Initially these were tested in vitro in HeLa cells and one of these siRNAs was found to suppress rhodopsin significantly both at the RNA and protein levels. We are currently converting this siRNA into both shRNA and miRNA formats in order to test suppression in vivo in a mouse RP model carrying a mutant porcine rhodopsin transgene.

P21. WITHDRAWN

P22. AAV-MEDIATED CHRONIC OVER-EXPRESSION OF SNAP-25 IN ADULT RAT DORSAL HIPPOCAMPUS INCREASES EXTRACELLULAR GLUTAMATE AND IMPAIRS SPATIAL LEARNING.

Alex G McKee[1], Niamh C O'Sullivan[2], Naomi Chadderton[1], Jennifer S Loscher[2], Sean O'Shea[2], Mary Moran[2], Olive McCabe[2], Alfonso Blanco Fernández[3], Menelas N Pangalos[3], Ciaran M Regan[2], William T O'Connor[2§], Peter Humphries[1], G Jane Farrar[1,5], Keith J Murphy[2,5]

[1] Applied Neurotherapeutics Research Group, Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland.

[2] Applied Neurotherapeutics Research Group, UCD School of Biomolecular and Biomedical Science &

[3] Flow Cytometry Core Facilities, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland.

[4] Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543, USA.

[5] These authors contributed equally to this work § Present address: Graduate School of Medicine, University of Limerick, Limerick, Ireland

Long-term memory is formed by alterations in glutamate-dependent excitatory synaptic transmission, which is in turn regulated by SNAP-25, a key component of the SNARE complex essential for exocytosis of neurotransmitter-filled synaptic vesicles. Both reduced and excessive SNAP-25 activity has been implicated in various disease states that involve cognitive dysfunctions such as ADHD, schizophrenia and Alzheimer's disease. Here we provide evidence that over-expression of SNAP-25 in the adult rat dorsal hippocampus, achieved by infusion of a recombinant AAV vector, causes selective impairment in spatial memory acquisition in the water maze task. This effect was accompanied by a specific and significant increase in the levels of extracellular glutamate detectable by microdialysis. These results suggest that chronic high expression of SNAP-25 in a significant proportion of the glutamatergic hippocampal neurons creates a high background transmission state that obscures the spatial memory trace and prevents accurate synapse selection during the consolidation phase.

P23. A 5Q DELETION WITH A CRYPTIC ETV6/RUNX1 IN A CASE OF CHILDHOOD ALL.

SE McNerlan[1], P McGrattan[1], C Cairns[2], SI Dempsey[2], MW Humphreys[1].

Regional Genetics Service, Belfast City Hospital, Belfast BT9 7AB

Department of Haematology, Royal Belfast Hospital for Sick Children, Belfast BT12 6BE

A 7year old girl presented with pallor, puffy face and pain in her foot. Haematological findings showed a WCC of $43.8x10^9$/l, platelets $31x10^9$/l, haemoglobin 5.2g/dl, with 87% blasts. Bone marrow revealed an L1 FAB type with flow cytometric results in keeping with precursor B-ALL (common ALL).

Cytogenetic analysis showed del(5q) and del(12p) in 6/20 (30%) cells analysed. Interphase FISH analysis revealed the presence of ETV6/RUNX1 rearrangement in 193/201 (96%) cells, and of these 161 (80%) showed a deletion of the non-translocated chromosome 12 homologue. FISH using an EGR1 probe for 5q31 showed a del(5q) in 96/200 (48%) of cells examined.

The ETV6/RUNX1 rearrangement is a recurrent finding in childhood ALL, and is associated with a favourable prognosis. Deletions of 12p are a common secondary finding in childhood ALL, however, deletions of 5q are more commonly associated with myeloid disease and have only rarely been reported in ALL.

As the percentage of cells containing the t(12;21) (96%) was so much higher than those containing del(5q) (48%) and also slightly higher than those containing del 12p (80%), this might suggest that the del 5q, and possibly the del(12p), represent secondary abnormalities in this patient. Secondary abnormalities are generally associated with disease progression and therefore influence disease prognosis. The significance of this finding in this particular case remains to be determined.

P24. DEVELOPMENT OF A RETINITIS PIGMENTOSA (RP) GENOTYPING MICROARRAY AND DETECTION OF KNOWN AND NOVEL MUTATIONS IN A COHORT OF NORTHERN IRISH RP PATIENTS.

GR Clark, D Muszynska, S Alexander, P Crowe, J O'Neill, GJ McKay, G Silvestri, DAC Simpson

Centre for Vision Science, Queen's University Belfast, Northern Ireland

The inherited retinal disease Retinitis Pigmentosa (RP) is extremely genetically heterogeneous, with 20 genes implicated in non-syndromic recessive RP to date. However, it is very difficult to identify the causative mutation when a new patient presents. Therefore, we have developed an Affymetrix customseq microarray capable of resequencing reported mutations and the exons within which they are found. In total 30 kbp from 22 genes were tiled on the array. Approximately 100 amplicons spanning the regions of interest were amplified from 35 DNA samples from recessive or sporadic RP patients. These were pooled, fragmented, labelled and hybridised to the genechip according to the manufacturer's protocol. Results were analysed using the GeneChip DNA Analysis Software (GDAS, Affymetrix). An average call rate of 91% was achieved for all the sequences analysed. A total of eleven known mutations in RGR, USH2A and CRB1 and a number of novel sequence variants were detected. This microarray platform is therefore a rapid and effective screen for RP mutations and provides a new tool to include in screening strategies. It is anticipated that the improved detection of RP mutations will facilitate genotype : phenotype correlations, better prognosis and application of therapeutic interventions such as gene therapy.

P25. DETECTION OF A 12P13 CHROMOSOME ANOMALY INVOLVING ETV6 AT RELAPSE IN AN ADOLESCENT PRESENTING WITH CYTOGENETICALLY NORMAL, FLT3-ITD$^+$, TYPE A NPM1$^+$ DE NOVO AML (M5 FAB-TYPE).

P McGrattan[1], MW Humphreys[1], KI Mills[2], AF Gilkes[3] MF McMullin[4]

[1] Department of Medical Genetics, Belfast City Hospital, Belfast Health & Social Care Trust, Lisburn Road, Belfast, Northern Ireland, BT9 7AB.

[2] Centre for Cancer Research and Cell Biology, Queen's University of Belfast, School of Biomedical Sciences, 97 Lisburn Road, Northern Ireland, BT9 7BL

[3] Department of Haematology, School of Medicine, Cardiff University, Wales, CF14 4XN.

[4] Department of Haematology, Belfast City Hospital, Belfast Health & Social Care Trust, Lisburn Road, Belfast, BT9 7AB, Northern Ireland.

Although pre-treatment MRC AML 10 cytogenetic data has been extremely useful for predicting initial response to chemotherapy, remission duration and overall survival in AML, several studies now indicate that cytogenetically normal AML (CN-AML) is in fact represented by underlying molecular mutations. The clinical impact of NPM1$^+$ (favourable) and FLT3 (adverse) mutations in younger de novo CN-AML adults is now well established.

12p13 chromosomal rearrangements associated with treatment related AML have only been reported in 6 cases and are generally associated a poor median survival (~4 months). To our knowledge, all 6 patients had 12p13 rearrangements resulting from translocations in which a 5'ETV6-3'partner fusion gene was generated.

We describe a CN-AML (M5 FAB-type) 16 year old presenting with two FLT3-ITD mutations and an NPM1 (Type A) mutation. She received intensive chemotherapy but relapsed after 10 months. Despite being FLT3-ITD$^-$, NPM1$^+$, a pericentric inversion of one chromosome 12 homologue was detected with breakpoints at 12p13 and 12q13. Metaphase FISH studies confirmed ETV6 gene involvement.

To our knowledge, this is the first reported case of a 12p13 rearrangement resulting from a pericentric inversion of chromosome 12 at relapse appearing with a persistent NPM1 mutation and loss of FLT3-ITD.

P26. GENOME-WIDE ASSOCIATION (GWA) STUDY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER-COMBINED TYPE (ADHD-CT); ADJUSTMENT FOR GENETIC HETEROGENEITY IN LARGE MULTICENTRE STUDIES.

Richard Anney, Matthew Hill, Colm O'Dushlaine, Elaine Kenny, the IMAGE Consortium, Michael Gill.

Department of Psychiatry, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine & Trinity College Dublin, Ireland.

As modern humans have spread throughout the world, allele frequencies and linkage disequilibrium (LD) have become more varied between populations. Population admixture is a major source of bias in the case-control study design. Family-based designs, such as the Transmission Disequilibrium Test, have been used to limit this phenomenon. However, the power of the TDT to detect disease susceptibility loci (DSL) can be influenced by population admixture through its impact on the degree of LD between the genetic marker and the DSL.

We have examined the population clustering of a large multicentre study of approximately 950 simplex ADHD-CT families collected from a white-European population. We have applied selection criteria to reduce heterogeneity at the clinical and genetic level.

We present data from this pre-cleaning step and discuss the implications to large multicentre studies. Moreover, we present the results of the application of this data to GWA data using data generated from the IMAGE ADHD-CT study. These data are examined at the marker, gene and hypothesis-free and hypothesis-driven gene-network analysis. Moreover, we examine the functional variation of genes tagged by associated SNP markers.

P27. PARTIAL TRISOMY FOR THE 17Q SUBTELOMERE REGION: FIRST CASE REPORT AND REVIEW OF THE LITERATURE.

V McConnell, G Smith, S McCullough

Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast Health and Social Care Trust, Northern Ireland.

Complex and isolated partial trisomy 17q subtelomere patients have rarely been reported in the literature. We report a patient with an isolated partial trisomy of the 17q subtelomere region. The patient first presented for genetics assessment aged 13 months with abnormal head shape, subtle dysmorphism and normal development. Cranial radiology was normal. Reassessment at 8 years and 9 months showed the patient to have a specific learning disability, mild truncal hypotonia, gross and fine motor skills delay, atrial septal defect, trigonocephaly with prominent metopic ridge and dysmorphism. There is a history of similar learning difficulties and motor delay in an older sister. Chromosome analysis and 22q11 and 2q37 FISH deletion studies were normal. Subtelomere testing using multiplex ligation-dependent probe amplification showed a duplication of the 17q subtelomere probe region. Further FISH testing demonstrated that the patient had an unbalanced translocation between chromosomes 13p and 17q resulting in a partial trisomy for the 17q subtelomere region. Parental chromosomes were normal. To our knowledge, this is the first reported patient with an isolated partial trisomy of 17q subtelomere. It also demonstrates the value of reassessment of patients in light of new technology.

P28. NOVEL SPLICE SITE MUTATIONS AS THE CAUSE OF FAP-RELATED CANCER IN TWO FAMILIES.

K Sweet, B McIlhatton, V McConnell, P Logan, C Graham

Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast Health and Social Care Trust, Northern Ireland.

Familial Adenomatous Polyposis (FAP) is an autosomal dominant inherited disease which is characterized by the presence of adenomatous polyps in the colon and rectum. Here we describe two novel mutations in the adenomatous polyposis coli (APC) gene in two separate families which have been shown to affect RNA splicing and be the cause of the FAP-related cancer.

In one family, a 62-year old woman diagnosed with Attenuated FAP was referred for testing. DNA sequencing of the APC gene revealed a recently identified mutation c.423G>T (p.R141S) in exon 4. The mutation was subsequently found in the proband's sister, niece and nephew. In the second family, a 51-year old male diagnosed with an adenocarcinoma of the right colon and the presence of multiple polyps (50+) in the whole colon was tested. DNA sequencing of APC gene revealed a c.1409-5A>G (p.G470VfsX15) mutation at the intron/exon boundary of exon 11. Reverse transcriptase-PCR demonstrated at the RNA level that both mutations affected the splice site. One mutation resulted in deletion of exon 4 of APC gene and the other mutation created an alternative splice acceptor site at the 5' end of exon 11.

P29. A ROLE FOR GENETIC VARIATION AT HOMER2 IN SCHIZOPHRENIA: FURTHER EVIDENCE FROM IRISH AND OTHER EUROPEAN POPULATIONS.

William P Gilks[1], Emma Allott[1], Michael Gill[1], Aiden P Corvin[1], Derek W Morris[1] and the International Schizophrenia Consortium.

[1] Neuropsychiatric Genetics Research Group, IMM and Dept. of Psychiatry, Trinity College Dublin, Ireland.

Schizophrenia (SZ) is a complex disorder of uncertain aetiology but which may involve dysfunction at glutamatergic synapses of the brain. Based-on linkage and gene expression data we identified HOMER2 (OMIM 604799) as a plausible candidate gene for SZ. Homer2 is enriched at excitatory synapses where it links glutamate receptors to the cytoskeleton. We previously reported allelic and haplotype evidence of association at HOMER2 in a sample of 375 cases and 812 cases from Ireland (Gilks *et al. Ulster Med J* 2008;**77(1):**66[S7]). The best result was at rs869498 (p=0.016, OR 1.39)

The International Schizophrenia Consortium conducted a genome-wide association study of schizophrenia using 3,380 cases and 3,593 controls from Europe (Affymetrix 5.0 and 6.0 platforms). Across HOMER2, 44 SNPs were genotyped of which 11 were associated with disease status at $p<0.05$. Of our four previous LD-independent associations, two (at rs2306428 and rs869498) were reproduced by proxy (rs17158194, p=0.001, OR 1.15 and rs17158155, p=0.02, OR 1.27 respectively). We have also found evidence for association with genes regulated by HOMER2 in this dataset. These data support a role for HOMER2 in SZ susceptibility and further genetic and functional studies are warranted to investigate molecular pathways involving HOMER2 in SZ.

P30. ALLELIC EXPRESSION IMBALANCE ANALYSIS OF PSYCHOSIS SUSCEPTIBILITY GENES.

Emma Quinn, Matthew Hill, Richard Anney, Michael Gill, Derek Morris, Aiden Corvin.

Neuropsychiatric Genetics Research Group, Dept. of Psychiatry and Institute of Molecular Medicine, Trinity College Dublin, Ireland.

Schizophrenia and bipolar disorder are complex psychiatric disorders affecting approximately 1-2% of the population worldwide. Evidence from twin and family studies indicate that both disorders are highly heritable. However, identifying candidate genes associated with the disorders has proved difficult due their complex genetic aetiology. The advent of genome wide association studies (GWAS) has made is possible to rapidly identifying potential candidate genes associated with common disorders. It now remains to further investigate these regions to elucidate the putative functional roles of susceptibility variants. As part of international consortia for schizophrenia and bipolar disorder research we are investigating several genes (ZNF804A, CACNAC1 and ANK3) that have been significantly associated in GWAS for possible functional variants. Genetic variants that have a regulatory role in gene expression can be investigated by measuring Allelic Expression Imbalance (AEI), whereby the expression levels of two alleles from a marker SNP can be compared in heterozygous individuals. The presence of AEI indicates cis acting factors that influence gene transcription or processing. Heritable differences in gene expression are thought to contribute to the susceptibly of many complex diseases and could potentially influence an individuals susceptibility to schizophrenia.

P31. LARGE SCALE PATHWAY-BASED ANALYSIS OF GENOME-WIDE ASSOCIATION STUDY DATA: IMPLICATIONS AND APPLICATIONS.

Elaine Kenny, Colm T O'Dushlaine, Derek W Morris, Richard JL Anney, Michael Gill, Aiden P Corvin.

Neuropsychiatric Genetics Research Group, IMM and Dept. of Psychiatry, Trinity College Dublin, Ireland.

With the advent of whole genome association studies, listing of all results for up to 1 million SNPs is not feasible and usually only the top associated SNPs are listed/ analysed in-depth. Such focused analysis may hide the biology behind disease.

To overcome this problem we have designed a novel SNP ratio test (SRT) to look at all significant SNPs in a biologically relevant format. The SRT analyses the significant SNPs that lie within genes in KEGG pathways, and looks for enrichment of significant to non-significant signal in one pathway compared to all other pathways.

We applied this method to 7 whole genome association studies testing which pathways were significantly enriched for association signal in the different datasets. The association data was sourced from the Wellcome Trust Case Control Consortium that carried out a joint whole genome association study examining 2,000 individuals for each of 7 major diseases using a shared set of 3,000 controls.

It is striking to note that obvious pathway candidates for certain diseases e.g. Type I diabetes mellitus pathway and Type II diabetes mellitus pathway were both found to be significant in the Type I diabetes and Type II diabetes datasets respectively.

P32. NOVEL GENOMIC PATHWAY ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES: IDENTIFICATION OF ERBB SIGNALLING AS A SUSCEPTIBILITY PATHWAY IN PARKINSON'S DISEASE

Colm T O'Dushlaine, Elaine Kenny, Carlos Pinto, William P Gilks, Michael Gill, Derek W Morris, Aiden Corvin.

Neuropsychiatric Genetics Research Group, IMM and Dept. of Psychiatry, Trinity College Dublin, Ireland.

Background: Systems-based approaches to mining complex genome-wide association study (GWAS) data have recently gained prominence. We have developed, and evaluate the performance of a novel SNP ratio test (SRT), which compares observed to expected ratios of significant to non-significant SNPs within versus outside pathways, in two Parkinson's disease (PD) GWAS datasets.

Results: In both PD datasets the SRT identified significant evidence for involvement of the "ErbB signalling pathway" in PD aetiology. Comparison with an alternative method of pathway analysis, genomic pathway mining (GPM), provided convergent statistical support for involvement of this pathway in PD. The erbB signalling pathway performs multiple neuronal functions and has been linked to many neuropsychiatric disorders including Alzheimer's disease, schizophrenia and PD.

Conclusions: We identify the SRT as a valuable method of rapidly identifying pathway signals in GWAS data, which can be followed up using more detailed pathway modelling to identify the relative contributions of different SNPs to susceptibility. This approach may be particularly valuable for complex genetic disorders of uncertain aetiology and is applicable to any available pathway resources. In PD, further replication and characterisation of involvement of erbB signalling pathways is warranted in larger, more densely genotyped datasets.

P33. NO EVIDENCE OF ASSOCIATION BETWEEN POLYMORPHISMS IN A 2P25 GENE-CLUSTER WITH VARIATION IN BONE MINERAL DENSITY

KG Hegarty[1,2], M Daly[1], F Shanahan[1], MG Molloy[1].

[1] Department of Rheumatology and Sports Medicine, National University of Ireland, Cork, Ireland.

[2] Department of Medicine, National University of Ireland, Cork, Ireland.

[3] Alimentary Pharmabiotic Center, National University of Ireland, Cork, Ireland.

Osteoporosis is a complex skeletal disease, under strong genetic influence, that alters the mineral composition of bone resulting in a loss of bone mineral density (BMD), variation in bone strength and elasticity which leads to an increase in non-traumatic fractures. We chose to fine map a gene-cluster at 2p25 to elucidate potential genetic associations with BMD variation. The potential candidate genes in this 387.6kb region are the development and differentiation enhancing factor 2 (DDEF2), integrin beta 1 binding protein 1 (ITGB1BP1) and a disintegrin and metalloproteinase domain 17 (ADAM17). Haploview was used to determine the gene-cluster linkage disequilibrium structure and select tagSNPs. The Kbioscience Genotyping service was employed to determine the SNP genotypes in 552 individuals from 251 families (192 pedigrees) ascertained through probands with low BMD (T<-1.5). Sixteen tagSNPs captured 70.0% of the HapMap validated variation across the gene-cluster region. None of the SNPs significantly deviated from HWE. Age, height, weight and sex were included as covariates in all subsequent statistical analysis. There was no evidence of population stratification, linkage or association observed between these tagSNPs or haplotypes and the BMD phenotypes tested. Denser SNP genotyping and replication in an independent study is required to support these results.

P34. EPIGENETIC SUPPRESSION OF CTNNA3 AND ITS NESTED GENE LRRTM3 IN UROTHELIAL CARCINOMA OF THE BLADDER (UCB).

Maria Meehan[1], Jenny Watson,[1] Emma Gallagher[1], Alo Mc Goldrick[1], Michèle Harrison[2], Elaine Kay[3], John Fitzpatrick[4], Peter Dervan[2] Amanda Mc Cann[1].

[1] UCD School of Medicine and Medical Sciences (SMMS), College of Life Sciences, UCD Conway Institute of Biomolecular and Biomedical Research, Belfield, Dublin 4.

[2] Department of Pathology Mater Misericordiae Hospital, Eccles Street, Dublin 7.

[3] Department of Pathology, Royal College of Surgeons in Ireland, Beaumont Hospital Dublin 9.

[4] Department of Surgery, Mater Misericordiae Hospital, Eccles Street, Dublin 7.

LRRTM3 is normally neuronally expressed and is located within the largest intron of CTNNA3 suggesting co-evolution of these two genes. LRRTM3 is entirely located within CTNNA3, but is transcribed in the opposite direction and is therefore a nested gene. Moreover, CTNNA3 is a developmentally imprinted gene, with preferential expression of the maternal allele, while LRRTM3 is not imprinted.

Taqman® QRTPCR employing the relative quantity method was used to determine the mRNA levels of CTNNA3 and LRRTM3 in a series of UCB cell lines (HT1376, RT4, T24, TCCSUP, RT112, CAL29). The demethyl transferase inhibitor 5-aza-2'deoxycytidine (DAC) was used for the chromatin modifying treatments of TCCSUP.

We demonstrate that CTNNA3 and LRRTM3 are co-ordinately expressed in these UCB cell lines. In TCCSUP, mRNA levels of CTNNA3 and LRRTM3 are minimal. However, following DAC treatment, CTNNA3 and LRTMM3 demonstrated increased mRNA expression by 4 and 7 fold respectively. Two CpG islands identified in the promoter region of CTNNA3 (MethPrimer) show no evidence of DNA methylation following sodium bisulphite modification and sequencing. Therefore, the increased expression of CTNNA3 following DAC treatment suggests indirect effects of this drug on this region such as the demethylation of transcription factors or transcription factor binding sites common to both genes.

P35. RET VARIATION IN THE AETIOLOGY OF VESICOURETERIC REFLUX.

Niamh HN Molloy, John M Darlow, Andrew J Green , Prem Puri, David E Barton

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

Vesicoureteric reflux (VUR) is the retrograde flow of urine from the bladder towards the kidneys and is a major cause of renal failure and hypertension. Primary VUR is a developmental anomaly of the vesicoureteric valves and commonly occurs along with other developmental anomalies of the urinary tract in the same individual or other members of the same family. The cause of VUR is unknown but it often runs in families and may be inherited as an autosomal dominant in most cases. Some of the genes already known to be involved in urinary tract development are also involved in other developmental processes and therefore their mutation is liable to cause multiple anomalies and is unlikely to result in isolated VUR. RET is such a gene. Some mutations of RET result in multiple endocrine neoplasia, and others in Hirschsprung disease (defective intestinal innervation). However, a group in Quebec found that a single nucleotide polymorphism (SNP) in RET, which changes an amino-acid (p.Gly691Ser), is greatly increased in VUR, with a heterozygote frequency of 69% as against 29% in the healthy Quebec population. We present the results of a study of this SNP in VUR patients and

healthy controls in the Irish population and discuss the implications.

P36. THE SEARCH FOR GENES INVOLVED IN VESICOURETERIC REFLUX.

Wei San Wong, Claire McGuinness, John M Darlow, Andrew J Green, Prem Puri, David E Barton

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

Vesicoureteric reflux (VUR) is the retrograde flow of urine from the bladder towards the kidneys. It is common in young children and is a major cause of renal failure and hypertension, though the condition resolves in some as they grow. Primary VUR is a developmental anomaly of the vesicoureteric valves and is part of a spectrum of developmental anomalies of the urinary tract. Though a few genes are known whose mutation causes VUR in addition to defects of other organs (such as renal-coloboma syndrome, and branchio-oto-renal syndrome), the cause of isolated VUR is unknown, but genetic studies so far suggest that it is highly genetically heterogeneous. A genome scan that we performed on 129 Irish families highlighted 10-15 regions of the genome that appeared to show linkage to the disorder, including 2 regions yielding non-parametric lod scores >2.5. We investigated the genes and non-coding regulatory elements in these regions to develop a priority list of places in which to search for possible pathogenic mutations, and present the results of our search so far.

P37. PHENOTYPE AND GENOTYPE ANALYSIS OF FAMILIAL PERIODIC PARALYSIS IN IRISH FAMILIES.

SB Kelly[1], NA Parfrey[2], AM Ryan[1], CK Hand[2].

[1] Department of Neurology, Cork University Hospital,

[2] UCC Department of Pathology

The familial periodic paralyses are caused by autosomal dominant mutations of skeletal muscle ion channels leading to altered membrane excitability. The disorders are characterised by episodes of limb weakness and paralysis lasting minutes to hours. Hyperkalaemic periodic paralysis (Hyper PP) is caused by missense mutations in the skeletal muscle sodium channel gene, SCN4A. Hypokalaemic periodic paralysis (HypoPP) is due to mutations in the calcium channel gene CACNA1S (HypoPP1) and mutations in SCN4A (HypoPP2).

We aimed to identify patients and families with periodic paralysis in an Irish population and characterise them clinically and genetically.

Patients were recruited through a neurology tertiary referral centre. Detailed clinical and family history, physical examination and specialised neurophysiologic examination were performed in each case. Genomic DNA was extracted and screening was performed for known and novel gene mutations.

To date we have identified 4 families with HyperPP and 1 with HypoPP (genetically confirmed elsewhere). All of the HyperPP families have the same SCNA4 Met1592Val mutation, but are phenotypically heterogeneous. One is a four-generation pedigree with an unusually prolonged attack duration. The HypoPP patient has a de novo but previously reported SCNA4 mutation.

P38. IL18 AND IL2 POLYMORPHISM IN PSORIASIS SUSCEPTIBILITY IN THE IRISH POPULATION.

Anthony W Ryan[1], Kutaiba Al-Jubury[1], Graham Turner[1], Phil Gallagher[2], Alan Irvine[1], Oliver Fitzgerald[2], Brian Kirby[2], Ross McManus[1]

[1] Department of Clinical Medicine and Institute of Molecular Medicine, Trinity College, Dublin, Ireland.

[2] St Vincent's University Hospital, University College, Dublin, Ireland

Psoriasis is an inflammatory disease of the skin and joints with a prevalence of up to 2% in European populations. IL18 is a pro-inflammatory cytokine, which promotes Th1 T-cell development by inducing γ-interferon. Genetic variation in this gene has been implicated in the pathogenesis of several autoimmune conditions, including inflammatory bowel disease, type 1 diabetes, atopic eczema and asthma. There is some evidence that IL18 may play a role in psoriasis. rs6840968 is a single nucleotide polymorphism (SNP) within the IL2/IL21 region of chromosome 4q27, which has recently been associated with Type I Diabetes, Rheumatoid Arthritis, Graves' Disease and Celiac Disease. The functional relevance of the IL2 and IL21 genes in inflammatory and autoimmune conditions is highlighted by the role of these cytokines in T-cell activation and development. We have genotyped IL18 rs187238 (IL18-137) and IL2/IL21 rs6840968 in 231 ethnically uniform Irish patients with psoriasis and 871 Irish controls. Both loci conformed to HWE in both populations. Both loci showed evidence of association with psoriasis in this population (IL18 rs187238, Odds Ratio 0.61 [0.44 – 0.86], $\chi^2 = 8.99$, P = 0.0027; IL2/IL21 rs6840978, Odds Ratio 0.67 [0.48 – 0.92], $\chi^2 = 6.41$, P = 0.01134, for carrier status of the minor allele in both cases). This latter value for IL2/IL21 rs6840978 is similar to a recent study of psoriasis susceptibility for the same SNP in UK and US populations (OR = 0.77 [0.62 – 0.95] and OR = 0.81 [0.68 – 0.96], respectively), for the same allele and direction, substantiating existing evidence that the IL2/IL21 haplotype block represents a risk factor for the development of psoriasis.

P39. A RETROSPECTIVE AUDIT OF AUTISM REFERRALS TO THE NORTHERN IRELAND REGIONAL GENETICS SERVICE BETWEEN 1988-2008.

C Harris, V McConnell

NI. Regional Genetics Service, Belfast City Hospital, Belfast Health and Social Care Trust

Autistic spectrum disorder (ASD) comprises impairment in the three core domains of social interaction, language development and behaviour. Prevalence has increased fourfold in the past ten years, likely due to heightened awareness and broader diagnostic criteria. Aetiology is primarily unknown with neurological, metabolic and genetic factors responsible for 5-10%.

Due to the significant increase in ASD referrals to the Genetics Service a retrospective audit of ASD referrals over the last 20 years was completed to develop guidelines for referrers. Referral details, genetic investigations completed, presence of a family history and confirmation of ASD diagnosis were some of the features analysed in the referral, in addition to the outcome of the genetic assessment.

Of the cohort, 60% were familial, 15% isolated and 25% associated with congenital abnormality and or learning disability in the referral letter. 32% had genetic investigation prior to referral. After genetic assessment, 47% were familial, 14% genetic, 39% of unknown aetiology.

We recommend that ASD referrals to the Genetics Service should have the following criteria (1) confirmation of the ASD phenotype (2) completion of chromosomal analysis and Fragile X studies (3) positive family history of learning disability / ASD and /or (4) dysmorphic features / other congenital abnormality.

Book Reviews

MRSA in Practice. Ian Gould. The Royal Society of Medicine Press. November 2006. Paperback, 140pp. £18.95. ISBN 978-1-85315-687-8

Health care associated infections, HCAI, have recently raised the concerns of both the public and politicians because of their significant socioeconomic burden. MRSA is a big player in the aetiology of HCAI and constitutes a major public threat presenting both therapeutic and infection control challenges in both the hospital setting and the community. This book, which consists of 16 chapters written by a group of international experts on MRSA, comes at important crossroads. The book starts with a summary chapter written by Ian Gould, the editor.

MRSA was first isolated in the United Kingdom in 1961, two years after the introduction of Methicillin, although there is evidence that it was there before that. Chapter 3 describes the evolution of MRSA since then and explains how the recent molecular techniques helped to understand that. However, there are other molecular advances which added to the understanding of MRSA such as VNTR, spa sequencing, toxin gene profiling and DNA arrays which are currently used in Colindale laboratories to type MRSA.

The distribution of MRSA is quite patchy and there is huge variation within the individual countries. This may reflect variations in surveillance, sampling, screening programmes and how strict the infection control measures are. There is a great difficulty in dividing MRSA acquisition to community and hospital, so most recently it is divided to community acquired, community onset and hospital acquired; Chapter four and five explains this very well.

The relationship between *Staphylococcus aureus* / MRSA and its human host start with colonisation, going through local inflammatory response, to severe invasive disease. Chapter two sketches the various virulence factors and their associated host responses in simple comprehensive way without unnecessary details. I personally recommend following with reading chapter nine which explains the different clinical presentations of MRSA infections with totally devoted chapter, 8, for CAMRSA.

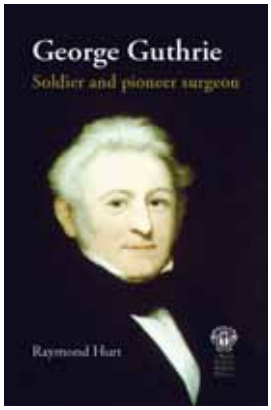
Since 1961, when MRSA was first isolated until now, there are huge advances in the laboratory diagnosis of MRSA. For better infection control purposes we need timely identification, but how rapid? Rapid identification is a real challenge for most of the microbiological labs. Chapter 6 explores the debates about the currently available laboratory diagnostic methods and explains the real difficulties we face when dealing with MRSA isolates.

Treatment of MRSA has been complicated by the development of resistance to the different anti-staphylococcus drugs including the newly introduced agents (chapter 10 &7). The new anti-MRSA drugs, apart from Linezolid, should be used intravenously which limits their use in the community. My only comment is, there is very little mentioned about the classical oral treatment which we usually prescribe for treating simple uncomplicated urinary tract and soft tissue infections. Natural alternative treatments have been also suggested, but unless there is clear evidence that they work without causing significant toxic effects, it is very early to consider these options.

Chapters 16, 11, 13, 14 and 15 deal with MRSA surveillance and infection control challenges. There is no clear evidence that decolonisation, environmental cleaning (unless it is terminal cleaning) and isolation/ cohorting (unless it is done right) do or do not work. Also, there is no clear consensus as to which practice is of most value in preventing transmission of MRSA. Most of the infection control specialists believe that package of measures that work most.

I enjoyed reading "MRSA in Practice" and I recommend this book for those who are interested in furthering their knowledge about MRSA infections. I would also like to commend on further readings' section which follows most of the chapters, giving chances for those who would like more details. I think, apart from the feeling that the chapters may need to be arranged differently, to maintain a more streamlined reading, and unavoidable duplication of information, "MRSA in Practice" is a very useful up to date comprehensive review.

Wesam Elbaz



George Guthrie – Soldier and Pioneer Surgeon

Raymond Hurt. The Royal Society of Medicine Press. June 2008, Hardback, 294pp. £24.95. ISBN: 978-1-85315-765-3

This little book is an excellent personal history of a renowned soldier and surgeon of the 19th Century and a wonderful commentary on the times in which he lived and worked. It is written by Raymond Hurt, a Cardiothoracic Surgeon in London. It is full of insightful commentary on the surgery pertaining to George Guthrie and his times.

This book, in essence, is in two parts. The first is a description of Guthrie's life and work, especially his remarkable surgery in the Peninsular Wars of the 19th Century. His life and times have been researched in a meticulous fashion by the author. George Guthrie clearly was remarkable. During the years of the Peninsular Campaign, he operated almost constantly, treating almost 20,000 wounds. He served at the Battle of Waterloo, performing perhaps the first successful amputation of the hip recorded. Following his wartime experience he wrote a number of textbooks, lectured widely, and gave a Hunterian Lecture which is detailed in the second part of this

beautifully written little book.

The second part of the book details many of Guthrie's lectures and writings. Following his wartime experiences, he specialised in ophthalmic surgery and wrote three textbooks on eye surgery. He progressed to become President of the Royal College of Surgeons of England on three separate occasions. He enabled the end of "body snatching" by the Anatomy Act of 1832. This remarkable man was multi-lingual in Spanish, French and Portuguese and was also an outstanding orator. He was offered a Knighthood after the Battle of Waterloo, which he declined, although he did later accept the honour. He died in 1856, age 71 years, from cardiac failure.

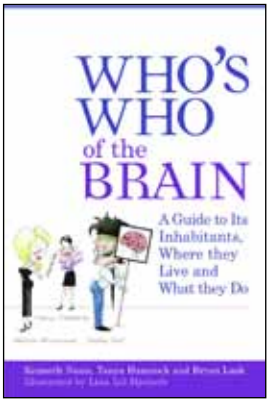
This book will be of interest to many readers. It is beautifully researched and is a wonderful description and commentary of the life of an outstanding surgeon and soldier and his times. The book will be of interest to serious students of medical history, students of military history, and will also be of interest to doctors of all grades and specialties. I would recommend it also as browsing material for undergraduate students.

Surgeons in particular will enjoy reading the case studies in the last one-third of the book, including the survival of the patient who had the successful removal of a darning needle from his heart. In addition to this remarkable man's experience of trauma, he also treated 1084 cases of primary syphilis in the York Hospital at Chelsea. His trial of mercury treatment confirmed that mercury was a dangerous and useless treatment for syphilis!!

This book is a remarkable read. I can recommend it both for serious study and for the reader who wishes to dip in and out of the work of an outstanding soldier and surgeon of the 19th Century.

Professor Roy AJ Spence

Who's Who of the Brain. A Guide to Its Inhabitants, Where They Live and What They Do



Kenneth Nunn, Tanya Hanstock and Bryan Lask. Jessica Kingsley Publishers. May 2008.

Paperback. 272pp. £13.99. ISBN: 978-1-84310-470-4

Did you ever wish you had paid more attention in your neuroanatomy classes at Medical School? Or did you just find the subject too difficult and complicated? Have you now come to regret this, as you realise that, actually, the subject is of real and practical importance in your day to day clinical practice? If so, this book may just be the answer.

'Who's Who of the Brain' is a rather light hearted guide to the anatomy, function and dysfunction of what has been described as the most complex structure in the universe, in fact so complex that it is beyond the ability of the human brain to understand.

The authors discuss in some detail the structures of the brain explaining their connection and their functions. They do this by creating an allegorical district and community which they call 'Cephalton-upon-Ridge'. Within this community of Cephalton-upon-Ridge there live a number of residents. Each of these key characters offers a dramatis personae representing the area of brain in which they reside. The authors describe each of these characters in terms of their place of domicile, their relationship to their neighbours, their appearance and their personality, followed by a more formal explanation of the analogous brain structure.

For example; the inhabitants of Cephalton-upon-ridge reside in one of three residential areas, Uptown, Midtown and Downtown. Among the uptown inhabitants there live such colourful characters as: Dudley Doit, a fitness fanatic. Representing the motor cortex, he is responsible for planning movement, initiating movement and monitoring and maintaining movement. Dudley works in close harmony with Cherry Chatterley (broca's area), who is the main newsreader, and who is responsible for communication and sending information, and also with Maurice Mappley (the parietal lobe) who is a major landholder, mathematician and a lover of maps and all things environmental.

In midtown Cephalton resides Christopher Crosstalk (the corpus callosum) whose property is described as joining Eastern and Western Cephalton and is responsible for communication between both halves of the brain, ...er,sorry,.. town. Corrie O'Graphie (the basal ganglia) is described as a world famous dancer. It is she who is responsible for implementing movement routines, remembering skills and maintaining muscle tone.

In downtown Cephalton resides Frank Finesse (the cerebellum), Fay Faceandear and Sam Swallowtalk (the pons and the medulla). They are responsible for more basic functions such as balance, regulating heart beat, breathing, sleep and waking as well as being responsible for acting as a conduit for messages from the cortex to the body.

Each of the characters portrayed provides a memorable and easy way to understand the characteristics, the functions and the relationships that each part plays in the making of the whole 'community'.

If there is a weakness in the book then it lies within the illustrative case histories that are included and are utilized to illustrate dysfunction of the area under current description. Given the substantial advances in Neurology over recent years with the advent of MRI, functional MRI and PET scanning, which undoubtedly have led to more precise anatomical diagnosis in explaining clinical symptoms and signs, then some of the case histories provided in the book might be considered somewhat weak and even speculative.

Despite the above reservation, I am sure this will prove a popular book among those who have some familiarity, no matter how little, of the brain and its functions, whatever their professional background, and even for those who are an expert in the area. All may well enjoy the conceptualisation of the areas, the connections and functions of this, the most complex of all organs.

Jim Morrow

The History of Medicine, Money, and Politics: Riding the Rollercoaster of State Medicine.

Paul R. Goddard. Clinical Press Ltd. July 2008. Paperback, 270pp. £25.00. ISBN: 978-1-85457-050-5

This work essentially represents two parts of a whole. Part one is a medical chronology and the reader is taken on an odyssey, as we chart the evolution of medicine from prehistoric times, through the ancient world, the middle ages, and into our modern world. Goddard writes with impressive authority, and reveals a deep love for learning, not just about medicine, but civilization. The author also invites us to consider the huge intellectual contributions of the Roman, Greek, Chinese and Islamic worlds.

Part one of the book concludes with a consideration of medicine in the Early Modern Period, the genesis of the National Health Service, and that most audacious scheme, the Welfare State. Goddard reminds us how difficult it is for contemporary citizens to imagine health care prior to its inception. Interestingly, he invites comparison with the legal system, "when only the rich and poor have access to the courts," to remind us what the rest of us, with poor health, faced before 1948.

Part two charts the time course of the National Health Service, or as Professor Goddard entitles it, "The Decline of the National Health Service." In great detail, Harold Shipman, the Bristol Cardiac Scandal, and the Organ Retention investigation are all considered. Professor Goddard, a working consultant in Bristol at the time, was well-placed to appreciate the misery and suffering that these events created, both within and without the medical community.

It is clear that Goddard is not a dispassionate bystander in all of this. Passionate is what he is. The second section pulsates with moral outrage and righteous indignation. His other conviction is that of patient advocacy. The author feels that permeating our physicianly core is duty to our patients. Their advocacy is our responsibility.

A younger readership, reared on tall skinny lattes, MP3 players, and fashion credibility will recoil at the description of numbing on-calls rotas, crippling visceral fatigue, and cynical fiscal exploitation. Older readers will remember, shudder and sob quietly.

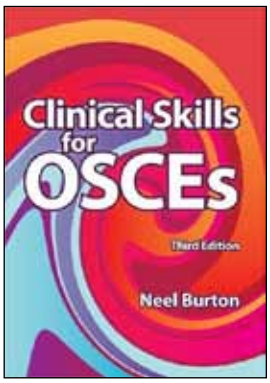
It is to Professor Goddard's great credit that he does not trade on his international reputation as a radiologist, or a pioneer of Magnetic Resonance Imaging. In fact, his specialty is barely alluded to. Instead he is everyman's Virgil, guiding the reader through a medical timeline.

To paraphrase Clive James, Paul Goddard's book affirms the truism that some of us are different from the rest of us. But so are the rest of us.

This book will be of great interest to many: students beginning, and practitioners enjoying or enduring their practice. It is also likely to be relevant to medical historians, as it charts one particular small step for mankind.

Barry Kelly

Clinical Skills for OSCEs (Third Edition)



Neel Burton. Scion Publishing Ltd. September 2008. Paperback, 350pp. £24.99. ISBN: 978-1-904842-59-0

This small book should be excellent preparation for medical students undertaking examinations which are now mostly OSCE-based. This book is well laid out, with excellent use of contrasting colours for the different sections. From my own experience, all the major topics normally used in OSCEs are covered in excellent detail and presentation. The book is up to date, having been published for the 2009 market.

The book is well laid out in sections including General Skills, Cardiovascular and Respiratory Medicine, ENT, Opthalmology, Dermatology, Psychiatry, Orthopaedics, Obstetrics and much more. The section on communication skills, which are now so important and are a frequent content of the modern OSCE examination, is also well laid out and all the common topics are presented. The authors have included topics such as death certificate completion and data interpretation, so frequently asked.

However, the text is spoiled by major printing errors – after page 115, comes page 84 (duplicated from previously), then pages 118, 119, followed by page 88, then 122, 123, followed by 92, 93, then 126, 127, followed by 96, 97, and so on until page 146; there are many pages inserted out of sync which spoils the entire book. The publishers need to immediately withdraw this print run and correct. If it was not for this major, distracting printing error, this would be an excellent text. More minor critiques are that some photographs lack definition – Fig. 19, page 49, Fig. 38, page 112. On page 48, the addition of a diagram showing laparoscopic incisions would be helpful, e.g. laparoscopic cholecystectomy.

This potentially useful book is spoiled by printing errors. If the printing mistakes are corrected, the content is sound and it would be a useful little book for revision purposes in those anxious few days before the final MB OSCE examination.

Prof Roy A J Spence

THE ULSTER MEDICAL JOURNAL

Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. United Kingdom
www.ums.ac.uk

NOTICE TO CONTRIBUTORS

1. Editorial communications should be sent direct to the Editor (who will be pleased to advise on the preparation of manuscripts if requested): Prof PJ Morrison, Department of Medical Genetics, A Floor, Belfast City Hospital Trust, Belfast, BT9 7AB Northern Ireland. All manuscripts are independently refereed. Manuscripts should be accompanied by a covering letter signed by all the authors agreeing to publication and stating that the work has not been published elsewhere; and stating that they have been actively involved in the preparation of the paper. Any conflict of interest should be declared. Appropriate consent for identifiable patient details should be obtained prior to submission.

2. Articles submitted for the editor's consideration should be typewritten in single spacing, with wide margins, preferably in Times Roman 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 are currently no charge for colour reproduction. **Electronic copies of images and tables should be attached as separate high resolution .jpg or .tif files and NOT embedded in the Word manuscript file.**

3. For full or short papers, the text should indicate the purpose of the paper, and should include an abstract, introduction, sections on methods, results, and a discussion relevant to the findings. For case reports, these should be novel or particularly important cases with a new finding not previously described and not just good teaching points, with a maximum of 10 references and appropriate patient consent for publication of photographs. Letters to the editor should be less than 500 words with up to 5 references and 1 table and / or figure.

4. Scientific measurements should be in SI units (DN Baron. *Units, Symbols and Abbreviations. A Guide for Medical and Scientific Authors*. 5th ed. London: Royal Society of Medicine, 1994). Blood pressure may be expressed in mmHg and haemoglobin concentration as g/dl.

5. References should be restricted to those really necessary and useful. This journal uses the "Vancouver" style. See www.icmje.org. for full details and advice. Text references are numerical and each article reference should include:
   i) a list of all authors when six or less (when seven or more only the first six should be listed followed by *et al*).
   ii) the title of the article.
   iii) the title of the journal in *italics* (abbreviated to the form published by Index Medicus).
   iv) the year.
   v) volume number and issue number (in brackets) in **bold**
   vi) first and last pages.

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

   Book references should give the author, title, edition, town of publication, name of publisher, year of publication, and, where appropriate, volume and page numbers.

6. Ten offprints of each article will be forwarded free of charge to the corresponding author. Further reprints can be obtained from the printers, Messrs Dorman & Sons Ltd, Unit 2, 2A Apollo Road, Boucher Road, Belfast BT12 6HP, Telephone (+44) 028 9066 6700, Email info@dormans-print.co.uk who should be approached directly. For reprint information in the United States contact: International Reprint Corporation (IRC), 287 East H Street, Benecia, California, 94590 USA. Telephone (707) 746-8740, Fax (707) 746-1643.

7. Fellows and Members of the Ulster Medical Society receive the journal free. Individuals may subscribe directly (see back page). The journal contents are covered by *Current Contents/Clinical Practice, Index Medicus, Excerpta Medica PubMed Central, Index Copernicus*, and *Science Citation Index*. The journal is available in 16mm and 35mm microfilm and 105mm microfiche from UMI, 300 North Zeeb Road, PO Box 1346, Ann Arbor, MI 48106-1346, USA.

Volume 78 No. 1 **January 2009**
ISSN 0041-6193

Cover legend: Whins (photograph by Paul Hackney). See paper on page 26