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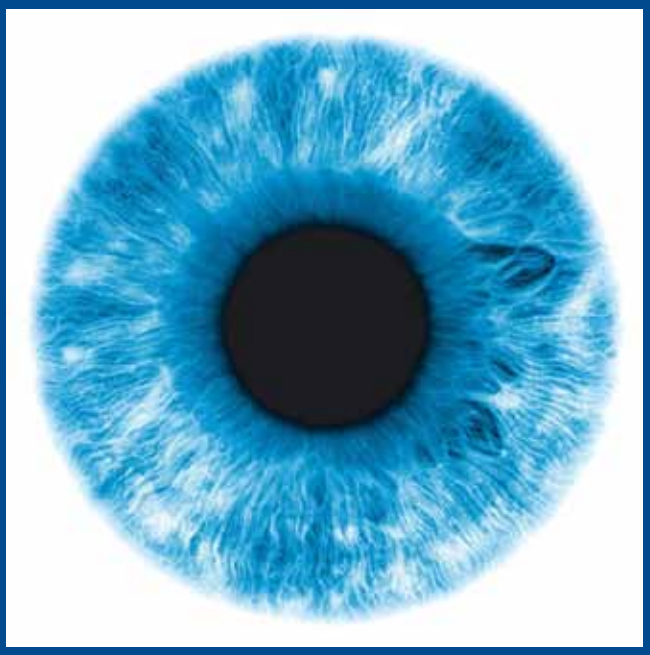

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CONTENTS

Ulster Med J 2010;**79(1):**1-2

Editorial

Forging Ahead

'All I know,' wrote Seamus Heaney, 'is a door into the dark[1].' Me too. The world of radiology is figuratively and perhaps, on occasion, literally just that. Our game is the image, not the written word. Pretty pictures. Yet, now we increasingly find ourselves integral to the medical paradigm. This, clearly, is no reflection on us, but underpins the requirement, primacy, and accessibility of the increasingly dazzling image for so much of what we do. If that picture paints a thousand words, and I find myself at this helm, perhaps, paraphrasing, the least that I can do is to make those words and pictures rhyme[2].

Patrick Morrison assured me that the editorial process was so smooth a timepiece that it would be the work of a few moments to maintain its bejewelled movements. Well, certainly, the indefatigable Mrs Marie Murphy in the UMJ office provides stellar advice and wise counsel. It quickly became evident, however, that the smooth editorial process resulted largely from Patrick's diligent hand being ever present on the tiller, carefully, quietly, meticulously working: 'the unpredictable fantail of sparks[1]' in the editorial office, forging resolutely ahead.

On behalf of the editorial board, I would like to thank Professor Morrison for his consummate professionalism and diligence towards the Journal. In addition, I owe him a huge personal debt for his unfailing patience and courtesy to me, often in the face of my significant provocation. This is one of the last Medical Schools in these islands with an associated Journal. Part of my job description therefore has to include not breaking it!

Continuing Medical Education is, I would contend, a good thing (and in both upper and lower case characters). Professor Ian Roddie, Dunville Professor of Physiology, in 1971 considered the lot of the mature practitioner. 'Returning to Physiology after some years is like going back to a city after a long absence[3].' Ideas change. Science evolves. To me it seemed that medical specialties, like that road in the yellow wood, have diverged. Some, like mine, have become instantly accessible: one thinks of 4D obstetric ultrasound, or brain MR imaging. Others though, have contracted into a cloistered world, thinly inhabited by its expert practitioners. In some arenas, the concepts have become so intricate, and the lexicon so rarefied, that it remains inaccessible to the generalist.

So, in the spirit of Professor Roddie, it occurred to me that it might be time to revisit this theme. Over successive issues, the Journal hopes to publish reviews which I hope will be of interest to the middle-aged practitioner (like me), and which might permit us to read further. I am delighted therefore, that our editor emeritus, has readily agreed to deliver the first of these. Professor Morrison's review of the iris follows on page 3.

Coaxing reviewers, cajoling authors and currying favour generally: such is the life of any editorial board. Never more so than in these straitened times. To them all, I add my heartfelt appreciation. My thanks also, to the tireless Ms Mary Crickard, for her patient and forensic sub editing.

I hope that you find something of interest within these pages, and that you continue to send in your good papers.

Barry E Kelly, Honorary Editor

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2. Heaney S. *The Cure at Troy*. London. Faber and Faber; 2002.
3. Roddie IC. *Physiology for Practitioners*. Edinburgh and London. Churchill Livingstone; 1971.

LIST OF REFEREES FOR 2009

We pass on our sincere thanks to all of our referees for 2009.

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Ulster Med J 2010;**79(1):**3-5

Review

The iris – a window into the genetics of common and rare eye diseases

Patrick J Morrison

Accepted 11 November 2009

ABSTRACT

Visual examination, without instruments, of the eye allows inspection of the iris, sclera, cornea and, through the iris, some abnormalities of the lens and retina. Several hereditary disorders can easily be recognised by characteristic iris changes. This review discusses changes in the iris, visible lens anomalies, and changes in the cornea surrounding the iris. A genetic diagnosis can help with management of diseases. Some conditions are single gene disorders, some are chromosomal rearrangements, and some are abnormalities of fetal development.

INTRODUCTION

When NHS evidence (www.evidence.nhs.uk) was being set up last year, the logo chosen was a picture of a normal iris (figure 1). At the meeting of the board where the logo was presented for discussion and approval, Sir Michael Rawlins, the chairman of NICE, asked "how do we know is it a normal iris?" I mentioned that we could say there were at least 25 genetic disorders that the person probably did not have, although we could not necessarily say the iris was normal. The result, having been asked to name them, was a presentation to the board on the disorders, and now this paper. Several genetic conditions can be detected by just looking at the iris or the overlying cornea or intervening lens, and I use this article to illustrate how recognition of some common and some rare diseases that can be identified by direct visualisation in the outpatient clinic or GP surgery, can lead to prevention and management of underlying complications.

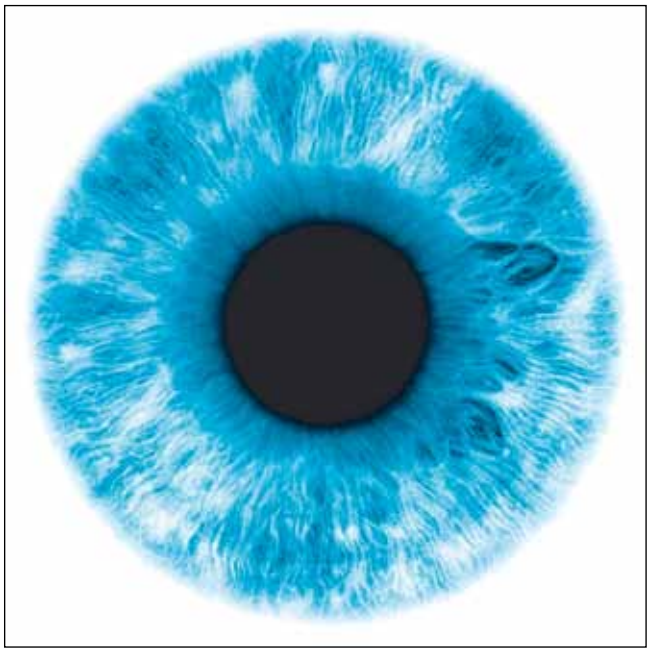

Fig 1. NHS evidence 'normal' iris.

Figs 2-10. From left to right, abnormal irides – see text for diagnoses.

GENERAL IRIS DISORDERS.

Glaucoma, uveitis, conjunctivitis and iritis may all be discernable by ocular examination. Most of these disorders are caused by common somatic disease, often caused by infection or trauma, and usually are not heritable. Glaucoma does occur in some autosomal dominant families. Pupillary anomalies may also give a clue to the diagnosis (a dilated iris occurs naturally with death or with drugs such as mydriatics or cocaine) Similarly pupillary constriction can be a marker of heroin and other drug use, or other neurological abnormalities. The list is too long to deal with in this review.

CHROMOSOMAL ANOMALIES

Humans have 23 pairs of chromosomes, most of which have a clearly defined short (p) and a long (q) arm. Cytogenetic

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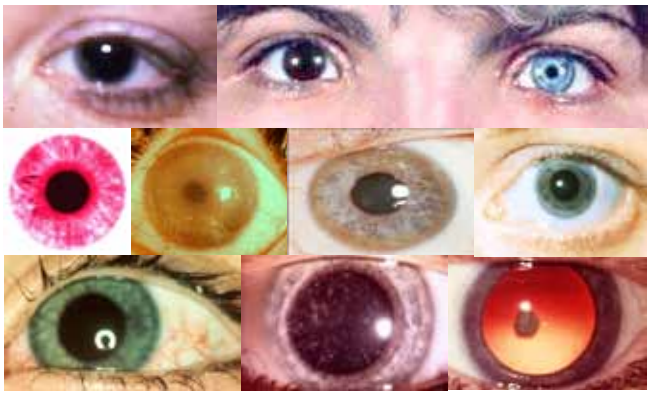

Figs 11-19. From left to right, abnormal irides – see text for diagnoses.

analysis has improved over the last few years with small duplicated or deleted segments now being more easily detected by automated karyotyping techniques. Some chromosome disorders have characteristic iris findings including trisomy 21 (Down syndrome) where Brushfield spots may occur (figure 2), and Williams syndrome – a condition caused by a missing segment (deletion) at chromosome 7q11.23 (deletion is on chromosome seven on the long arm, at segment 11, sub-band 23) . Affected individuals have a characteristic phenotype including a recognisable facial appearance, and typical behavioural traits (including moderate learning difficulties), along with hypercalcaemia in childhood. The Williams syndrome iris is described as 'stellate' lace-like appearance (figure 3). A coloboma (small missing segment) of the iris may be present sporadically, or due to a developmental anomaly, or be a marker of an underlying chromosome disorder (figure 4) such as 'cat-eye' syndrome (caused by an extra segment of chromosome 22, and having ocular coloboma and anal atresia). Such abnormalities should prompt investigations for a chromosome karyotype and a thorough ophthalmic examination as the coloboma may extend into the retina. Severe cyclopia may occur as a developmental or chromosomal abnormality (figure 5) with fusion of the two optic globes and a single iris.

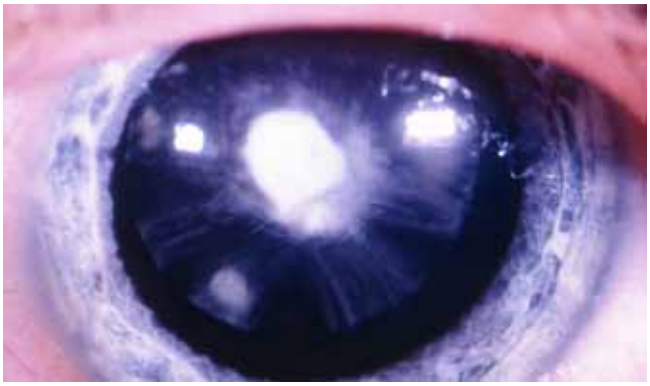

Fig 20. X-linked cataract.

SINGLE GENE DISORDERS

The twenty-three sets of chromosomes carry DNA wrapped carefully in a compact form. 'Unwinding' the DNA into its double helix allows analysis of genes, where mutations (changes in a small segment of DNA base pairs) can change the structure and function of a particular amino acid and thus inactivate or change the expression of a gene product – usually a protein or enzyme. Several genetic disorders have clearly autosomal dominant or autosomal recessive inheritance. Some have recognisable iris signs.

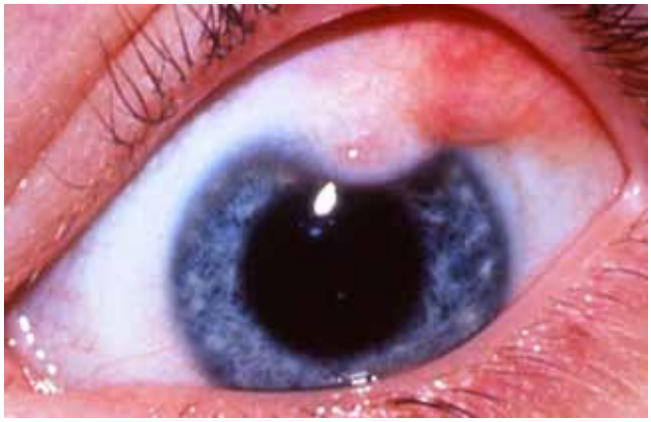

Fig 21. Epibulbar dermoid overlying the iris.

Autosomal Dominant.

Autosomal dominant disorders generally require a mutation in one of the two sets of genes, and often code for proteins. Such protein abnormalities make take time to build up or process within cells, and unlike recessive disorders where often an enzyme is the gene product and thus present early in life, dominant disorders are often not present until adulthood. One example is Marfan syndrome, a disorder of connective tissue with abnormalities in the fibrillin protein, causing hyperelasticity of fibrillin and a propensity to aortic dissection. Patients can have a series of eye abnormalities, the most easily recognisable is a dislocated lens (figure 6). Dislocation occurs because the zonules holding the lens in place are weaker and careful examination by an ophthalmologist is helpful. Other dominant causes of dislocated or abnormal lens include familial ectopia lentis, and Weill-Marchesani syndrome.

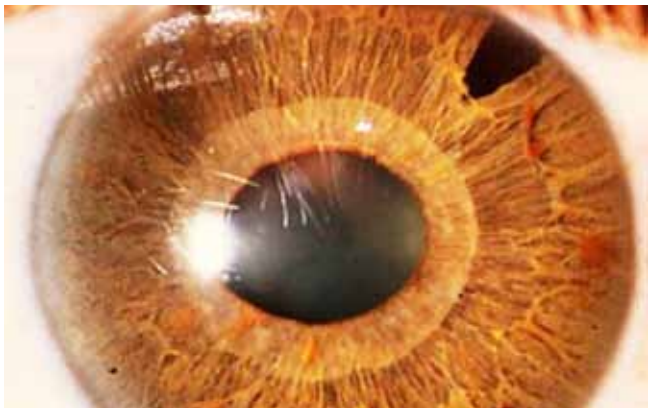

Fig 22. Rieger anomaly.

Neurofibromatosis type I, a neurocutaneous disorder causing pigmentation of the skin (café au lait spots, and skin neurofibromas), may exhibit clumps of pigment (Lisch nodules) within the iris (Figure 7). Some patients may develop optic nerve compression, and females are at moderate risk of breast cancer. Markers of systemic disease such as raised cholesterol may be familial – dominant familial hypercholesterolaemia may cause cholesterol and lipid

deposits – arcus senilis - around the iris (Figure 8). Autosomal dominant cataract may be familial or isolated (figure 9) or part of other disorders including Myotonic dystrophy. Virtually all modes of inheritance have been recognised for hereditary cataract including recessive and X-linked types. Occasionally some cancers may be hereditary and retinoblastoma (figure 10) and Wilms' tumour (hypernephroma, figure 11) are examples of tumour suppressor genes that may fail to normally function if one of the pair is abnormal, and can occur in early childhood. These may present in autosomal dominant familial forms with a white retinal reflex and aniridia respectively. Curious differences in the colour of the iris (heterochromia) are found normally in the population, but may be inherited (figure 12) as autosomal dominant, and more rarely in syndromic forms such as Waardenburg syndrome with underlying hearing loss and a white forelock being characteristic. The pop star David Bowie is said to have heterochromia.

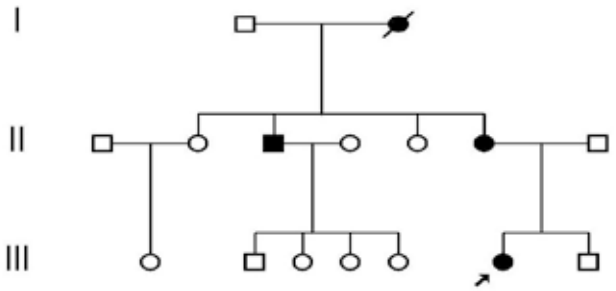

Fig 23. Autosomal dominant family tree. Affected cases are shaded.

Autosomal recessive.

Albinism – lack of melanin pigment, may manifest as a pink coloured iris (figure 13). Several metabolic diseases produce characteristic iris findings with the mucopolysaccharidoses producing a build up of mucopolysaccharide within the cornea making the iris appear cloudy (figure 14). Enzyme replacement therapy started early will improve lifespan. Cystinosis may cause crystals to build up in the overlying layers, as does Wilson disease with abnormal copper metabolism. Characteristic Kayser-Fleischer rings (figure 15) may be detectable and treatment initiated. Patients with osteogenesis imperfecta (brittle bone disease) may have thin sclerae and this may show around the iris (figure 16), particularly in the more severe autosomal recessive types, or sometimes in the more common later onset autosomal dominant type. The rare ataxia disorder ataxia-telangiectasia – causing early unsteadiness with radiosensitivity, and immune problems, may present with childhood unsteadiness, and telangiectasia around the iris (figure 17), rather than just hyperaemic blood vessels at the periphery of the eye as may be normal or due to irritation or trauma. Iris hypoplasia may occur in a syndrome of immunodeficiency and autoimmunity associated with STIM1 mutations.

X-Linked (Sex-linked recessive)

Sex linked recessive disorders usually only affect males as females have two X chromosomes (46XX karyotype) and males one X chromosome and one Y chromosome (46XY). Mutations involving one X chromosome therefore are masked by the corresponding normal X in most females so the majority of female carriers may have no or markedly reduced signs, unlike males who have no normal X as the Y chromosome generally has different genes from the X chromosome. Lowe syndrome – (oculocerebrorenal syndrome) – a disorder causing renal abnormalities and lenticular cataract in males (figure 18, and minor lens opacities in carrier females, shows the variation in X-linked disorders (figure 19). Similarly X-linked cataract is more severe in males with minor lens opacities sometimes visible in female carriers on close ophthalmic investigation (figure 20).

DEVELOPMENTAL DISORDERS

Some conditions may have a genetic basis not yet recognised. Epibulbar dermoids – white-grey fleshy overgrowths on the cornea - may occur in Goldenhar syndrome (oculoauriculovertebral dysplasia – heart, skeletal and facial abnormalities) and overgrow the lens (figure 21). Similarly a pterygium may occur with excess sun exposure or may be a feature of some rare genetic diseases. Rieger anomaly - a small outer segmental iris defect caused by abnormal cleavage of the anterior chamber, is mainly sporadic (figure 22), but autosomal dominant and chromosomal anomalies may be a cause. Teratogens may cause abnormal development of the eye during pregnancy, and include infections causes such as fetal varicella, and drug exposure such as anti-epileptic drugs, and also alcohol. Careful examination of an infant may give a clue to the cause of problems in a baby, and may also reveal undisclosed drugs taken during the pregnancy.

DIAGNOSIS AND MANAGEMENT

Genetic testing for mutations in the appropriate gene can be carried out in an affected case and if a mutation found, will allow predictive (presymptomatic) gene testing for single gene disorders for autosomal dominant disorders, or for carrier testing in autosomal recessive or X-linked diseases. This can help patients determine the exact risk and seek early diagnosis which may assist in treatment or prevention of complications in other organ systems. For example in the pedigree in figure 23, the shaded members are affected with medullary thyroid cancer. The arrowed proband (the first family member that draws the family to the attention of the clinician – often an affected member) was tested for mutations in the RET gene causing medullary thyroid cancer in which the rare type 2B can manifest with tongue neuromas and prominent corneal nerves on close ocular examination. Having identified the mutation, other at risk family members can be offered genetic testing and either given definitive reassurance if normal, or appropriate preventative surgical treatment such as early thyroidectomy or biochemical screening using serum calcitonin if mutation carriers wish.

CONCLUSIONS

Early clinical diagnosis of genetic disorders can allow accurate advice to be given to families and molecular genetic testing may allow better management and treatment options in patients. A brief examination of the iris may give a clue to diagnosis.

Acknowledgements.

I thank Sir Michael Rawlins for his encouragement in writing this article, and Dr Gillian Leng, CEO of NHS evidence, for enduring the board presentation, and permission to use the NHS evidence iris logo.

The author has no conflict of interest.

Ulster Med J 2010;**79(1):**6-11

Paper

Are Alcohol-Related Acute Surgical Admission Rates Falling?

Gerard J. Fitzmaurice[1], Susim Kumar[1], Robin Brown1, Atiq Hussain[1], Mark E. O'Donnell[1&2]

Accepted 3 December 2009

ABSTRACT:

Background: Alcohol-related admissions (ARA) represent a significant burden on hospital resources. The study objectives were to assess alcohol-related acute surgical admissions to a District General Hospital over a 5-year period, to determine the cost of these admissions and to consider strategies to affect future admission rates.

Methods: A prospective observational study was completed from October 2007 to March 2008. A daily review of acute surgical admissions determined whether alcohol was a factor for patients admitted. Data recorded included patient demographics, clinical presentation, investigations and final outcomes. This data was then compared with a previously completed prospective study between November 2002 and March 2003.

Results: Overall emergency surgical admissions during the study period were 1,125 (10.4%) compared to 838 (11.02%) in 2002. There was a 1.1% reduction in ARA from 9.5% (80/838) in 2002 to 8.4% (94/1,125) in 2007. The majority of ARA were male (82.8%) and 59.8% of ARA were under 40 years of age. ARA secondary to road traffic collisions (RTC) were reduced in 2007 compared to 2002 (12.5% to 8.5%). However, head injuries (30.0% to 48.9%) and pancreatitis (3.8% to 19.1%) secondary to alcohol had increased (p=0.27). 79.3% of admissions occurred out of hours. Although use of plain x-rays had decreased (70% to 54.3%, p=0.018), CT imaging (11.3% to 20.2%, p=0.67) and upper GI endoscopy had increased (2.5% to 7.4%, p=0.82). Blood alcohol levels increased with 83.0% of patients in 2007 compared to 60.9% in 2002 admitted with a level greater than 151mg/100mls (p=0.10). The overall cost of ARA over one year was calculated at £341,796.

Conclusion: Alcohol-related admissions have reduced at this District General Hospital. However, despite recent government initiatives it still remains unclear how these factors affected ARA, as blood alcohol levels, alcohol-related head injuries and pancreatitis admissions all increased. Our findings highlight the relevance of the implementation of an inpatient alcohol policy combined with the availability of an alcohol liaison nurse in all acute surgical units.

INTRODUCTION

Alcohol-related problems are commonplace in society and pose significant resource implications for their management by healthcare providers [1, 2]. In the emergency setting, alcohol remains a major factor for many hospital attendances ranging from simple accidents to violence and assault, major trauma and the sequelae of acute end-organ failure [3, 4].

Within the National Health Service (NHS), the effects of alcohol have become a significant resource and financial burden accounting for over 811,000 admissions to NHS hospitals in England alone in 2006/2007 – a rise of more than 15% annually [5]. These figures were mirrored in Ireland where there were 133,962 alcohol-related admissions (ARA), which accounted for 841,161 bed days, over a 10-year period from 1995-2004 [6]. Indeed the age standardised rate of ARA in the Irish population increased by almost 60% from 144.3 to 238.3 per 100,000 people between 1997 and 2001 [6]. Over a similar time period the National Cancer Registry reported that liver cancer had the greatest increase in occurrence compared to other cancers with a 7.4% and 10.7% increase in males and females respectively [7]. Within the NHS, it is estimated that 1 in 16 hospital admissions are alcohol-related and that alcohol-related diseases account for 1 in 8 bed days (approx. 2 million), 1 in 8 day cases (approx. 40,000 cases), and up to 35% of all accident and emergency attendances [8]. The estimated annual cost of alcohol misuse to the NHS in 2006/2007 was approximately £2.7 billion [9].

Recent reports suggest that ARA account for between 7% and 11% of all surgical admissions [1, 10]. ARA rates vary according to the type of hospital (tertiary or district general) and location (urban or rural). Trauma associated with alcohol tends to involve more severe injuries, necessitating longer hospitalisation [11]. Williams *et al* (1994) assessed alcohol-related head injuries and identified that 3.2% had a delay in discharge due to alcohol withdrawal [12]. These factors have direct implications for patient care and service provision.

Government initiatives to curb alcohol-related problems include local and national strategies to target pro-alcohol influences. Dring and Hope (2001) assessed the impact of advertising alcohol products on a teenage population in Ireland and identified that alcohol adverts appeared to be targeted at this population, where alcohol consumption was

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associated with social and sexual success [13]. A report from the Academy of Medical Sciences (2004) identified a direct correlation between the level of expenditure on alcohol advertising and alcohol consumption between 11-15 year olds in the UK [14]. This prompted a revision of alcohol advertising rules in 2005 whereby alcohol advertising must not appeal to those under 18-years of age and should not imply social or sexual success or glamorise over consumption of alcohol and anti-social behaviour [15]. Similar rules have been enforced in Ireland since 2007.

Within Northern Ireland, the government has introduced a "New strategic direction for alcohol and drugs 2006-2011". The aim of this policy was to improve community based services for people with alcohol and drug problems; to provide better education about alcohol for young people; and to implement better enforcement of current legislation [16]. A UK and Ireland wide consultation is also ongoing regarding the possibility of lowering the legal blood alcohol limit for driving from 80 mgs to 50 mgs of alcohol per 100 mls of blood which has been estimated to potentially save up to 50 lives and up to 1,500 injuries per year [17].

OBJECTIVE

The aim of this study was to assess alcohol-related acute surgical admissions in a District General Hospital and to compare patient demographics, admission aetiology, clinical presentation, and surgical outcome between two different time periods. We then evaluated the financial implications these admissions placed on our unit, the possible treatment course, future patient management options, and whether recent changes in government policy have affected the trend of these alcohol related admissions within our unit compared to national and international reports. This was possible as at the time of both studies there were no hospital-based alcohol policies within Daisy Hill Hospital.

METHODS

A prospective observational study was completed over an 18-week period from 29th October 2007 to 1st March 2008. All acute patients admitted surgically over this period were included and details of those admitted with alcohol-related problems were recorded. Alcohol-related admissions were identified through history, clinical signs, and blood alcohol levels and defined as any person admitted with a condition that was attributable to alcohol. They were then divided broadly within four categories: 1) patients in whom alcohol was the primary reason for admission, e.g. head injury while intoxicated; 2) patients in whom alcohol was the secondary reason for admission, e.g. road traffic collision caused by drunk driving or an assault by a drunk assailant; 3) known alcoholics who were admitted to the surgical ward with chronic alcohol related disease such as pancreatitis; and 4) known alcoholics who were admitted to the surgical ward for social reasons. A review of the patient discharge system using the keyword "alcohol" was also completed at the end of this period to ensure that all patients had been identified.

Demographical data, date of admission, diagnosis, blood alcohol level, in-patient investigations, date of discharge, and the number of previous alcohol-related admissions were recorded. All aspects of patient data were collected in tandem by two members of the surgical team to facilitate concordance with admission aetiology. A prospective study had been previously completed using similar methodology over a 13-week period from 29th November 2002 to 1st March 2003. The results of each study were then compared to published national and international data to enable trend comparison.

A cost analysis for all patient admissions was performed using data provided by *The Southern Hospitals Trust Finance Directorate* using costings from the 2001-2002 and 2005-2006 financial years respectively. The stated cost per admission was based on medical, nursing, administrative, as well as miscellaneous overheads and expenses. However, these figures did not include the cost of additional investigative modalities. The overall cost of an ARA per day was therefore calculated at £328.28 for 2002-2003 and £469.50 for 2006-2007.

Recent national government policy decisions were accessed through The Department of Health, the Office of Communications, and the Cabinet Office websites while local policy decisions were accessed through The Department of Health, Social Services, and Public Safety Northern Ireland website [5,8,9,15,16]. National trends in alcohol use including policy papers were accessed through The Institute of Alcohol Studies, The National Cancer Registry Ireland, and the NHS Information Centre websites [7, 17-19]. Other relevant articles and papers were accessed through Pubmed using keywords acute, alcohol, cost and surgery.

STATISTICAL ANALYSIS:

Descriptive statistics for baseline variables such as patient demographics were calculated as the mean and standard error of the mean (SEM) or the median and interquartile ranges (IQR). The independent samples T-Test was used to compare differences between the two time periods. All statistical tests were 2-sided and differences were considered significant if the p-value was <0.05. Statistical analysis was performed using the SPSS statistical package (Version 12 SPSS®inc. Chicago, USA).

RESULTS

Patient Demographics

There were a total of 10,810 attendances at the accident and emergency (A&E) department over the 18-week period between October 29th 2007 and 1st March 2008, which was a 2.5% increase on the 13-week period for 2002/2003 (a total of 7,602 attendances at A&E between November 29th 2002 and 1st March 2003). There were a total of 838 admissions in the first study period and 1,125 admissions during the second. In the 2002 period, 80 (9.5%) emergency admissions to the general surgical ward were related to alcohol whilst in the 2007 period, 94 (8.4%) were related to alcohol (**Table 1**). With regard to overall attendances at A&E, 11.02% were surgical admissions in 2002 with 1.05% being alcohol-related, which compared to 10.40% in 2007 with 0.87% being alcohol-related.

Of the 80 patients admitted in 2002, 62 (77.5%) were male which compared with 82 (87.2%) male in 2007. The median age was 37.3 years in 2002 (range 14-79) and 38.4 years (range 18-78) in 2007. 50 (62.5%) patients were under 40 years and 30 (37.5%) over 40 years in 2002, which compared with 54 (57.5%) patients under 40 years and 40 (42.5%) over 40 years in 2007 (Figure 1).

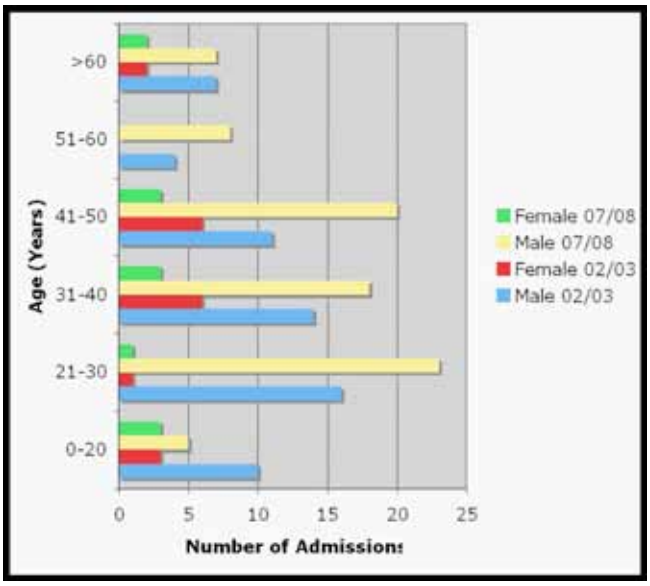

Fig 1. Patient age range vs. gender in all acute surgical admissions where alcohol was a predisposing factor to admission.

The majority of admissions occurred out-of-hours, which was defined as any admission between the hours of 5pm and 9am Monday to Friday and all of Saturday and Sunday. In the 2002 period, 40.0% of admissions occurred on Saturday and Sunday as compared with 47.8% of admissions in the 2007 period. During the 2002 period, there were 12 admissions (15.0%) between 9am-5pm Monday to Friday while 65 admissions (81.3%) were out-of-hours. This compared with the 2007 period, during which time 20 admissions (21.3%) were between 9am-5pm Monday to Friday and 73 admissions (77.7%) were out of hours. In particular, 29.8% of admissions occurred on a Sunday in the 2007 period (22.5% in the 2002 period) and the most common time overall for admissions was between 12am and 4am – 33.8% in 2002 and 25.5% in 2007. The time of admission was not documented for one patient in 2007 and for three patients in 2002 (Figure 2).

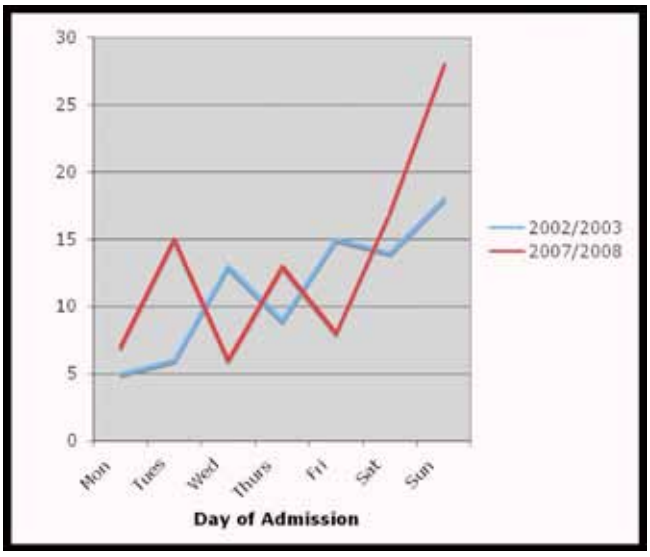

Fig 2. A breakdown of the day of admission in all acute surgical admissions where alcohol was a predisposing factor.

The number of admissions in category 1 had increased between 2002 and 2007 from 30 (37.5%) to 55 (58.5%) patients respectively. However, ARA from category 2 had reduced from 21 (26.3%) to 9 (9.6%) patients, while ARA from category 3 remained static (29 to 30 patients) (p=0.064). There were no admissions in Category 4 during either period (Table 1).

TABLE 1

Comparison of total number of surgical admissions and alcohol related admissions in 2002-2003 vs. 2007-2008.

	2002-2003	2007-2008
Total number of surgical admissions	838 (770 patients)	1,125 (1,049 patients)
Total number of admissions related to alcohol	80 (9.5%)	94 (8.4%)
Category 1	30 (37.5%)	55 (58.5%)
Category 2	21 (26.25%)	9 (9.6%)
Category 3	29 (36.25%)	30 (31.9%)
Category 4	0 (0%)	0 (0%)
Average number of admissions per month	27	24
Average number of admissions per week	7	5.2

The majority of patients were admitted following a head injury (24 vs. 46). Pancreatitis increased from 3 patients in 2002 to 18 in 2007. In contrast, the level of ARA with generalised abdominal pain, fractures, and as a consequence of road traffic collisions (RTCs) decreased. The decrease in ARA following RTCs is particularly pertinent as it represented a reduction from 12.5% (n=10) in 2002 to 8.5% (n=8) in 2007. However, these shifts in admission aetiology were not statistically significant between the two time points (p=0.27) (Table 2).

Although the use of plain x-rays had reduced from 70.0%

TABLE 2

The diagnosis on discharge of patients admitted to the surgical ward with an alcohol related admission.

DIAGNOSIS	2002-2003	2007-2008
Head Injury	24 (30.0%)	46 (48.9%)
Abdominal Pain	16 (20.0%)	1 (1.0%)
Fracture	8 (10.0%)	6 (6.4%)
Epigastric Pain	6 (7.5%)	0 (0%)
Laceration (not head)	4 (5.0%)	1 (1.0%)
Pancreatitis	3 (3.8%)	18 (19.1%)
Liver Cirrhosis	3 (3.8%)	0 (0%)
Haematemesis	3 (3.8%)	0 (0%)
Other	13 (16.3%)	22 (23.4%)

TABLE 3

The number and type of investigations performed on alcohol related acute surgical admissions during 2002-2003 vs. 2007-2008.

INVESTIGATION	2002-2003	2007-2008
X-ray	56 (70.0%)	51 (54.3%)
Computed Tomography (CT) Scan	9 (11.3%)	19 (20.2%)
Ultrasound	8 (10.0%)	13 (13.8%)
Oesphageogastroduodenoscopy (OGD)	2 (2.5%)	7 (7.4%)
Full Blood Count (FBC)	48 (60.0%)	74 (78.7%)
Urea & Electrolytes (U+E)	48 (60.0%)	79 (84.0%)
Liver Function Tests (LFTs)	23 (28.8%)	55 (58.5%)
Coagulation	14 (17.5%)	23 (24.5%)
Other	35 (43.8%)	65 (69.1%)

to 54.3% (p=0.018), a corresponding increase in computed tomography scans had occurred between the two time points (11.3% to 20.2%, p=0.67). Upper gastrointestinal endoscopies increased with 7 performed in 2007 compared to 2 in 2002 (p=0.82) (Table 3). During the 2002 period, 46 patients (57.5% of admissions) had their blood alcohol level checked and 28 of these patients had a blood alcohol level greater than 151 mg of alcohol/100 mls. The highest level detected was 449 mg of alcohol/100 mls. In the 2007 period, 53 patients (56.4% of admissions) had their blood alcohol level checked and 44 patients had a level greater than 151 mg of alcohol/100 mls. The highest level detected was 411 mg of alcohol/100 mls (Figure 3). These figures represent an increase in elevated blood alcohol levels with 83.0% of patients admitted with a level greater than 151 mg of alcohol/100mls in 2007 compared to 60.9% in 2002 (p=0.10).

55.0% of patients were discharged within 24 hours after admission in 2002 compared to 51.0% in 2007. However, 7.5% (n=6) of patients remained in hospital for greater than 7 days after admission in 2002, which is comparable to a 9.6% (n=9) rate in 2007. An increase in recurrent admissions was demonstrated in both time points where 31.3% and 42.6% of admissions were recurrent for the 2002 and 2007 time periods respectively.

FINANCIAL IMPLICATIONS

The average bed day cost in 2001/2002 was £328.28. During the 13-week period assessed in 2002-2003 the total cost of alcohol-related surgical admissions based on these figures was £69,923.64. This extrapolates to £279,695 over a period of one year. In 2005/2006, the cost of a general surgical bed day had increased to £469.50. During the 18-week period assessed in 2007-2008 the total cost of alcohol-related surgical admissions based on these figures was £118,314.00. This extrapolates to £341,796 over a period of one year and an annual increase of £62,101 compared to 2002. This figure is for bed days only and does not include the cost of the numerous investigations or therapeutic procedures performed on ARAs.

DISCUSSION

In Canada, ARA account for over 1.2 million hospital days in acute care at a cost of nearly Can$1.5 billion in 2002 [2]. Lost productivity due to alcohol was also estimated as Can$7 billion per year with the cost to Irish business estimated at €1.5 billion per year [20, 21]. The fall of 1.1% in ARA in this study stands in contrast with reports from England, which report a 15% increase in ARA in 2006/2007 accounting for over 811,000 patient episodes [5]. More recent data from England documents a doubling of ARA over the last 10-years [18]. These figures correlate with experiences in Ireland where alcohol-related discharges increased by 92% between 1995 and 2002 [6].

Previously, Taylor *et al* (1986) found that 70% of alcohol related admissions were male [1,22,23]. We identified a similar male predominance for ARA of 82.8%. A younger patient age was also shown to be an important factor where Taylor *et al* (1986) identified that 42% of their male admissions were aged 40 years or less [1]. In our study, 48.9% of male admissions were aged 40 years or less, implying similar epidemiological trends previously identified in 1986. This data highlights the target population for possible intervention but also the failure in the intervening period to accomplish positive change amongst this age group.

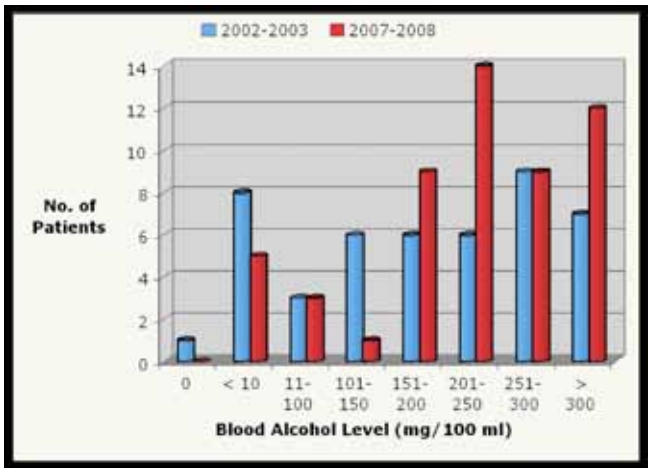

Fig 3. Blood alcohol levels on acute surgical admissions where alcohol was a predisposing factor in 2002-2003 and 2007-2008.

Concerningly, a marked rise in primary ARA (category 1) was demonstrated between the two time periods. This contrasted with a fall in category 2 admissions while category 3 admissions remained almost static. There were no category 4 admissions during either time period. It is unclear why there was a fall in category 2 admissions. However, it was expected that category 3 admissions would remain static as chronic alcohol-related pathologies often have a lag-period before clinical presentation. The absence of category 4 admissions probably relates to alcohol-related social admissions being directed to the medical team.

Although an important reduction in ARA following RTC was demonstrated, most other conditions experienced an increase in ARA rates and this was against a backdrop of an 11% increase in attendances at the accident and emergency

department between the study periods. 48.9% of ARAs were now due to a head injury, an increase of 18.9% over the intervening 5-year period. As a district general surgical unit, Daisy Hill Hospital still manages head injury patients similar to other general surgical units within the UK and Ireland [12]. Williams *et al* (1994) reported that 51.0% of head injury admissions to their acute general surgical ward in a central London teaching hospital were intoxicated. Following a similar increase over the last five years, our figures are now approaching this rate [12].

The incidence of alcohol-related pancreatitis increased dramatically over the 5-year period. This parallels O'Farrell *et al* (2007), who reported an increased incidence of acute pancreatitis from 17.5 per 100,000 population in 1997 to 23.6 per 100,000 population in 2004 [24]. This increase was associated with alcohol ingestion rather than biliary tract related conditions [24]. Despite these shifts in admission aetiology between the time-periods, there was no actual statistical difference in condition rates between the time-periods (p=0.27).

A particularly worrying finding was the level of alcohol consumption. We identified that 83.0% of those patients admitted had a blood alcohol level greater than 151mg/100mls, representing a 22.1% increase from 60.9% from 2002. The National Audit Office recently reported that more than 10 million people in England are regularly drinking above the recommended guidelines [25]. However, the influence of public health schemes has not affected those admitted to hospital. Indeed, the Statistics on Alcohol: England 2008 study found that while 69% of people in Great Britain had heard of the government's guidelines on alcohol consumption, only 40% knew the recommendations [18]. Therefore the delivery of such concepts for responsible alcohol consumption may require modification.

The influence of admission times highlighted a resource factor, where 79.3% of ARA occurred out-of-hours during periods of reduced staffing levels. Subsequent investigations for ARA required the use of non-resident on-call staff, particularly radiographers, where a greater cost combined with logistical absences following on-call periods further disrupted normal working patterns within that DGH department. This was especially relevant in 2007 where the number of CT imaging alone increased.

An important factor for the improvement of the hospital-patient relationship is a specialist alcohol liaison nurse [26]. The Royal College of Physicians guidelines from 2001 recommend that each acute hospital should have appropriately trained staff available to assess and offer interventions to "drinkers" through a defined hospital strategy [26]. This advice is further reinforced by the latest Department of Health guidance, which advocates the appointment of alcohol health workers in the acute hospital setting [25, 27]. Current literature reports that men benefit most from such interventions and that those not directly seeking treatment actually derive the most benefit from treatment [26, 28]. The Royal Liverpool University Hospital estimated that over an 18-month period, an alcohol liaison nurse had prevented 258 admissions to the hospital, covering the cost of her salary 10-times over [26]. Similar reports from the United States showed that brief interventions such as a short discussion about the costs and benefits of drinking from the patient's point of view and providing information about the health risks, lead to a significant reduction in future health care costs [29, 30]. While previous reports have demonstrated a direct correlation between the increased price of alcohol and reduced consumption, our study did not assess patient related finances [19, 31].

While the alteration in the quantity of radiological and endoscopic investigative modalities reflect changes in clinical practice including the National Institute of Clinical Excellence (NICE) guidelines on head injuries, the resultant resource implications are significant and should be highlighted. It is unclear how other changes in clinical practice could have accounted for an increase in recurrent attenders or in the length of stay of alcohol related admissions. Consequently, this may be more likely related to the increased alcohol consumption of those that were admitted and possibly the absence of any hospital-based alcohol policy. However, an 18.9% increase in overall alcohol-related head injuries, a 15.3% increase in overall alcohol related pancreatitis, and a 22.1% increase in overall admissions with a blood alcohol level greater than 150mg/100mls of blood within a 5-year period despite local and national policy initiatives and with a significant cost burden must be emphasised. In addition, the steady increase in ARA throughout the NHS, which appear to be mirrored internationally, seem to highlight the fact that policy initiatives to date have been disjointed and only partially effective. Our aim is to highlight the significance of this problem to the general surgical ward, its burden on the surgical budget, and how simple measures such as the appointment of an alcohol liaison nurse and the institution of brief interventions by medical staff can be effective in reducing the future cost of ARA to the surgical unit.

At the time of study there were no hospital-based alcohol policies within Daisy Hill Hospital. However, throughout the time period studied, there were a number of both national and local changes that could have influenced some of our findings. The reduction in RTC secondary to alcohol could relate to road improvements in the locality that were instituted in the intervening 5-year period. The introduction of the smoking ban in April 2007 has been widely extolled as contributing to a reduction in alcohol consumption at licensed premises throughout Northern Ireland. However, there has been no alteration in local pub or nightclub closing times or a staggering of closing times as has occurred in some parts of England and Wales, and the local authority have not introduced a bus service or any other such policy initiative. It is also worth noting that extended GP opening hours had not been introduced at the time of this study and therefore could not have had any influence on the results. There have been no other local healthcare policy initiatives, such as the opening or closure of minor accident & emergency units that could have affected the study findings.

CONCLUSION

Alcohol represents a significant burden on the health service. Over the past 5-years there have been a number of policy initiatives to alter public behaviour and reduce its impact on the health service. Our study has suggested partial success with a reduction in admission rates, combined with lower rates of alcohol related road traffic collisions. However, we should not become complacent as primary alcohol-related admissions in younger patients, alcohol consumption levels and alcohol related recurrent admissions all increased at an additional cost to the health service over a 5-year period. Our findings highlight the relevance of the implementation of an

in-patient alcohol policy combined with the availability of an alcohol liaison nurse in all acute surgical units and suggest the need for further progressive public health initiatives.

The authors have no conflict of interest to declare

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Paper

Current trends in Antenatal Screening Services: Results from a regional survey

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ABSTRACT

Objective To identify variations in current antenatal screening programmes across one region and compare results with a previous survey.

Design A cross section descriptive survey.

Setting All maternity units within the region of Northern Ireland.

Sample Eleven maternity units were invited and ten agreed to participate.

Main outcome measures The number of written policies for individual screening tests; the range of screening tests offered; the frequency of training opportunities for health professionals; and the information systems in place to record data.

Results There is variation in service provision across maternity units and, in particular, inconsistency in the offer of serum screening tests for Down syndrome. A lack of training opportunities for health professionals involved in offering screening was highlighted, and no common information system employed.

Conclusion While improvements have been made since 2002, variations persist. This is leading to inequalities in the provision of antenatal screening services across Northern Ireland.

Keywords Antenatal screening, policy, survey

INTRODUCTION

Ten years ago a Health Technology Assessment[1] (HTA) review on antenatal screening warned that the screening practices employed in Britain were inequitable, fragmented and incomplete. More recent evidence has indicated this may not have significantly changed despite policy amendments regarding provision of screening[2 3]. Current guidelines by the National Institute for Clinical Excellence in Health (NICE)[4] and recommendations from the National Screening Committee (NSC) indicate that all pregnant women should be routinely offered screening for infections including asymptomatic bacteriuria, Hepatitis B, HIV, Rubella, and syphilis, anaemia, blood group and antibodies, and fetal anomaly screening. Recommended routine fetal anomaly screening consists of an ultrasound scan between 18 & 20+6 weeks gestation and serum screening for Down's syndrome, preferably the combined test but where not possible then either the triple or quadruple test[4]. This policy has been in place throughout the United Kingdom (UK), since 2003, however, these measures have not been implemented to the same degree in Northern Ireland (NI), and as a result antenatal screening practice has not been consistent[5 6]. Current NI serum screening policy covers infectious diseases in pregnancy, including Hepatitis, HIV, Rubella and syphilis[7] and it is proposed to offer Down's syndrome screening to all women by 2011[8].

In 2002 a baseline survey on screening services was commissioned by the Department of Health, Social Services and Public Safety (DHSSPS) in NI to establish the current provision of screening and inform how recommendations by the UKNSC could be developed[9]. It identified a regional service that echoed the warning made by the HTA[1] in 1999: inequitable, fragmented and incomplete. Since the baseline survey there have been a number of changes, both regionally and nationally, including the offer of HIV screening to all pregnant women, the introduction of antenatal screening coordinators and limited serum screening for Down's syndrome. This survey aimed to identify the impact of these changes on the current provision of antenatal screening.

METHODS

Study Design

A cross section descriptive survey technique was employed. The baseline survey[9] on antenatal screening provision, carried out by the DHSSPS in 2002, was adapted to take account of developments in the structure of antenatal screening services.

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These modifications were minor, for example the inclusion of items relating to antenatal screening coordinators, providing a questionnaire that enabled respondents to disclose any changes and provide a full picture of the offer, provision and management of screening programmes since the original survey.

Method of data collection

The survey was sent to the Clinical Director of Obstetrics and Gynaecology within each maternity unit. Participants were asked to complete the questionnaire with the Midwifery Manager of the unit to ensure consistency of responses and, if necessary, consult with other departments or individuals to ensure full disclosure of current practice. The units were given four weeks to complete and return the survey. Those who had not returned within the time frame were given a telephone reminder. In two cases a duplicate survey was supplied.

Population sample

There are a total of eleven maternity units across Northern Ireland, who were invited to take part. One unit declined, due to time constraints, resulting in a total sample size of ten.

Data analysis

The responses provided were analysed using a statistical database (Microsoft Excel) with descriptive statistics calculated. Results from the 2002 survey were obtained to assist in the analysis, looking specifically at changes in practice over time and highlighting current trends.

RESULTS

Service policies

The majority of maternity units (n=8) had an antenatal screening policy in place. With respect to individual screening tests, an average of 5.3 (SD = 2.4) policies per unit was reported. This compares to an average of 3.4 (SD = 3.4) in 2002. Figure 1 illustrates the expansion in the number of written policies for individual tests from 2002 to 2005.

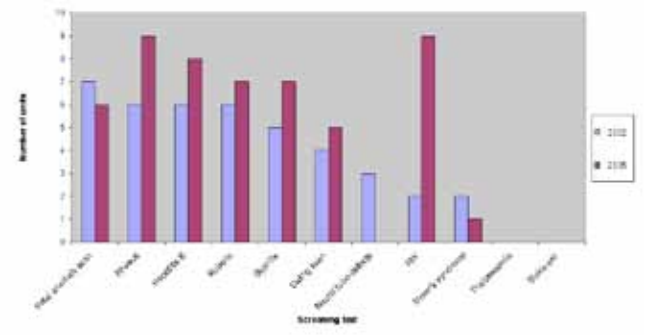

Fig 1. Number of maternity units with written policies for specific screening tests, as reported in 2002 and 2005

Current screening programmes offered

All units offered the maternal screening tests of rubella immunity, syphilis, hepatitis B, HIV and atypical red cell antibody screening (including rhesus) to all women, with every pregnancy. Of particular note is the number of units offering HIV screening to all women: from two units in 2002 to all 10 units surveyed in 2005. Screening for the conditions of B thalassaemia and sickle cell was offered to selected women in 80% (n=8) of the units. Two of these eight units indicated the selection criterion as 'ethnic origin' and 'if clinically indicated'.

For fetal screening tests, which are designed to assess the health of the baby, respondents provided details on the basis of the offer to women attending their unit. Table 1 presents results for all ten units. Those units that offered fetal screening tests to selected women were asked to report on the criteria under which this selection took place. 33% (n=3) of respondents provided details, citing 'family history', 'genetic clinic referral' and 'over 35' as the specified criterion. With the early pregnancy dating scan one unit disclosed that it was offered to selected women on the basis of, 'poor obstetric history, abdominal pain, PV staining'.

The main difference identified between 2002 and 2005 was

TABLE 1

Number of Maternity units offering fetal screening tests

Policy of offer \ Screening test	Serum AFP	Serum Down's screening	Nuchal Translucency	Dating scan	Anomaly scan	Ultrasound Markers
All women	1	1	-	9	10	3
Maternal request or private/ payment	2	6	4	-	-	-
Selected women	4	4	3	1	-	1
Test not offered	3	-	3	-	-	6

the fall in the number of units offering serum screening to selected women. In its place women are being offered the test on a private/payment basis. 50% (n=5) of the maternity units surveyed offered screening for Down's syndrome on a private/payment basis alone compared with 16.6% (n=2) in 2002. The results from both surveys also highlight a shift from using the double test to the triple test for Down's serum screening. In 2002 four units offered the double test to screen for Down's syndrome, compared with only one unit by 2005.

The multi-professional team

Six units (60%) employed an antenatal screening coordinator. One antenatal screening coordinator performed their job within two maternity units, sharing their time in relation to the size of the units. Three of the five antenatal screening coordinators reported attendance at training days within their local health board, with one coordinator also attending a one week workshop in addition to university-based study days. The subjects of these courses reported included antenatal screening and abnormalities, bereavement, ultrasound scanning, HIV and rhesus negative screening.

With regards to the remaining health professionals involved in the screening programme, there was a lack of training opportunities available to them across all the units surveyed. Ad hoc study opportunities were most frequently cited, with 40% (n=4) of units indicating that opportunities were ad hoc across all health professional groups (midwives, consultants, junior doctors and ultrasonographers). One unit provided no access to training for consultants, junior doctors or ultrasonographers. Midwives were the only group

that received training opportunities annually (n=1) or every 3 months (n=2), while junior doctors received training every 6 months within one unit.

Information systems

There was no unique information system reported by respondents that covered the whole region. Within the units a wide range of databases and information systems were employed. Seven units used NIMATS to record information for a number of antenatal services (booking, biochemistry, haematology, microbiology results, procedures, notification of birth and congenital anomalies). Laboratory test data was recorded mostly on laboratory systems (7 units). PAS was used in particular for booking and administration (5 units), but also referred to by at least one maternity unit across all the antenatal services' systems. Radiology systems (NIRADS) were mentioned by three units, and one unit referred to the NIBTS system for haematology systems. An average of 2.5 (SD = 1.4) information systems were used within the maternity units and pattern of data use and storage is similar to that reported in 2002.

DISCUSSION

The regional survey confirmed that antenatal screening services offered to pregnant women in NI remains inconsistent between and within maternity units. On a national setting, the contrast between practice in NI and recommendations by the UKNSC and NICE is most evident in the provision of serum screening for Down's syndrome. The UKNSC and NICE guidelines[4] have recommended that all pregnant women, irrespective of age, should be offered second trimester serum screening if first trimester screening is not possible, reflecting that Down's syndrome serum screening should be offered to all women with every pregnancy. Only one unit offered universal screening in the survey. The remaining eight units did not offer this test to all women and are, therefore, not meeting these national standards.

At the time of survey in 2005 the DHSSPS position reflected a lack of consensus about the provision of Down's syndrome screening in NI. Subsequent research has indicated that not all health professionals are supportive of the current test (triple test) offered[6] and midwives report feelings of both personal and professional conflict when discussing it with women partly because of the current legal status in NI, where The Abortion Act 1967, which legalised termination of pregnancy in Britain, does not apply. This creates a tension when offering screening in a context where very limited termination of pregnancy is available. Since data collection, guide lines for health professionals regarding termination of pregnancy have been released[10]. Other factors reported to impact on the discussion with women include the actual time available to give women information about the test on offer, the lack of education and training provided for midwives in relation to offering screening tests, the structure and organisation of antenatal care and the underlying social, moral or religious context in which the test is offered [5, 6 & 11]. As a result, the offer and discussion of screening is a complex interaction of several factors, some of which are not easily addressed. It is planned to introduce Down's syndrome screening for all women in NI by 2011 as noted earlier[8] and this survey would suggest there is significant discussion and work needed to achieve this target. However, developments in screening techniques for Down's syndrome, particularly in relation to tricuspid regurgitation, ductus venosus waveform and nasal bone evaluation, may shift benchmarks for screening practice even further by this time[12].

None of the maternity units surveyed offered the 'combined test', which NICE guidance, both in 2003 and the updated version of 2008[4], have highlighted as the most effective before 14 weeks' gestation. The introduction of a nuchal translucency scan would require a substantial shift in the pattern of antenatal care offered and in the training needs of those offering the screening service, which would lead to both financial and human resource implications. As a result, an initiative, led by the DHSSPS, would be required if recommendations by the UKNSC concerning testing for Down's syndrome were to be introduced across all maternity units in the region.

A lack of training opportunities available to health professionals involved in the provision of screening tests was identified by both the survey of 2005 and 2002. Training was offered largely on a need-to-know basis only. For example, HIV study days were brought in to facilitate the introduction of HIV testing on a routine basis. This survey shows the antenatal screening co-ordinators have been successfully incorporated into current practice and could play a fundamental role in identifying areas where there are training needs among all health professional groups involved in antenatal screening. A report carried out by the Regional Antenatal Screening Teams for the UKNSC[13] recommended that antenatal screening co-ordinators should assume responsibility for the education and training of the multidisciplinary team. While the introduction of screening coordinators within six units does not appear to have positively affected the amount of training opportunities reported, they are potentially an invaluable resource for future training of the multi-professional team.

Both survey reports have informed us of the limited auditing of antenatal screening, with the uptake and outcomes of screening tests relatively unknown. The inability of eight maternity units to report on the uptake of individual screening tests reflects the weaknesses of the current systems. The systems in place provide limited and fragmented information on the offer of prenatal screening, uptake rates and results. The need for a common universal maternity information system needs to be addressed in order to help with the recording of all screening tests taken and their results, as antenatal screening is now a significant component of antenatal care. Dedicated systems for collecting screening and fetal medicine data do exist, but are not being used in NI. The UK government initiative, NHS Connecting for Health, has a primary aim of supplying the NHS with new, integrated IT systems and services to enable information to be shared effectively. An integrated IT system would provide benefits for both staff and patients involved in the antenatal screening programme.

CONCLUSIONS

The survey identified a number of areas where improvements could be made to enhance the provision and management of antenatal screening services across Northern Ireland:

- Consistency in the serum screening programme for Down's syndrome.
- Improvement in the training opportunities for all professional groups involved in the provision of antenatal screening tests.
- Development of a common information system to operate across all sections of the antenatal screening services.

The authors have no conflict of interest to declare

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Paper

Laparoscopic Cardiomyotomy for Achalasia: A Single Unit study

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ABSTRACT

Aims Achalasia is a rare incurable neuromuscular disorder of the oesophagus. A number of treatment options are available. We reviewed our results of laparoscopic cardiomyotomy over a 30 month period.

Methods 18 patients with manometric features of achalasia underwent surgery between 2004 and 2006. Pre and postoperative weight and dysphagia scores were recorded (maximum score 45=normal, 0=complete dysphagia). Change in the Body Mass Index (BMI) was measured. Other symptoms (heartburn, epigastric pain, regurgitation, odynophagia and sleep disturbance) were scored on a 0-4 scale of increasing severity.

Results At mean follow up of 16.2 months the mean dysphagia score was significantly improved from 7.5 to 33.9 ($p<0.005$). BMI was significantly increased from 22.3 to 25.8 kg/m^2 ($p<0.05$). Scores for heartburn, epigastric pain, regurgitation, odynophagia and sleep disturbance were also significantly improved. The average inpatient stay was 3.1 days and average operating time 111 minutes. One mucosal perforation occurred which was repaired intraoperatively. No patients required secondary operative intervention.

Conclusions Laparoscopic cardiomyotomy is a safe, highly effective, minimally invasive treatment for achalasia.

INTRODUCTION

Achalasia is an incurable neuromuscular disorder of the oesophagus resulting from destruction of the oesophageal myenteric plexus.[1] This results in aperistalsis and failure of the lower oesophageal sphincter to relax following swallowing. Symptoms are gradual in onset and include dysphagia, odynophagia, regurgitation, sleep disturbance and weight loss. The annual incidence is about 1 in 100,000 people with an equal sex incidence. It tends to present in adult life between about 25 and 40 years old with less than 5% occurring in children.[2, 3]

Manometry provides the definitive diagnosis. The classic features are an adynamic oesophagus, hypertensive lower oesophageal sphincter (LOS) and failure of the LOS to relax on swallowing. An oesophagogastoduodenoscopy (OGD) should also be performed to investigate for malignant disease.[4] Untreated, it leads to an extremely poor quality of life because of progressive dysphagia, oesophageal dilatation, stasis and aspiration. All current treatments are palliative and aim to reduce the pressure at the LOS.[5]

Fig 1. Patient position The patient is positioned supine with legs spread apart.

Medical therapies include the use of calcium antagonists or sildenafil to relax the smooth muscle of the LOS, however results are poor.[6] Endoscopic procedures include pneumatic dilatation and injection of Botulinum Toxin. These produce acceptable short term results but long term success is limited and the majority of patients will require several interventions.[7] Surgical treatment aims to divide the muscle of the LOS longtitudinally. This can be achieved via the transabdominal, transthoracic or thoracoscopic routes. It has been suggested that the laparoscopic transabdominal route is associated with a low rate of failure and complication and a high chance of success.[8] We review here our results and experience with laparoscopic cardiomyotomy for achalasia.

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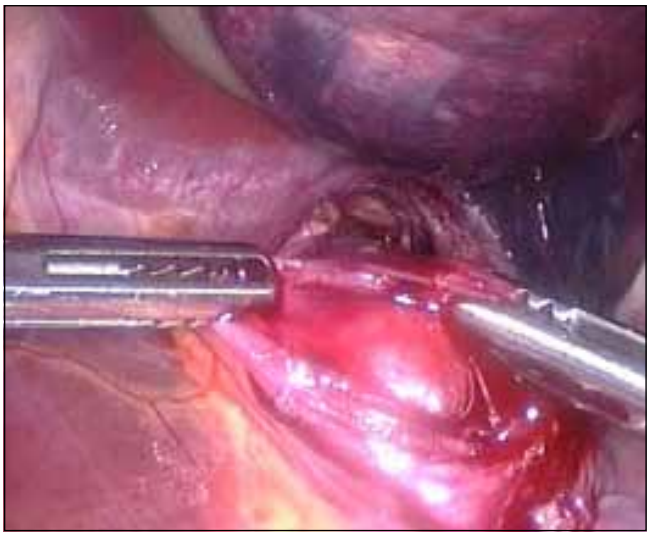

Fig 2. Extension of the myotomy. The split edges of oesophageal sphincter muscle are shown grasped by forceps. The oesophageal mucosa lies between. A plane of cleavage is developed between these two layers.

LAPAROSCOPIC CARDIOMYOTOMY: TECHNIQUE

The procedure begins with the patient in a supine position. [figure 1] The surgeon stands between the patients' legs and the assistant to the patient's left. Pneumoperitoneum is achieved by optical 10mm port insertion just below the left costal margin in the midclavicular line. An adjustable self-supporting liver retractor is inserted together with two 5mm ports and another 10mm port. The first step of the procedure is to display the oesophago-gastric junction to confirm the relevant anatomy. Then the phreno oesophageal ligament is divided with a harmonic scalpel, and the anterior oesophagus exposed. [figure 2] There is no need to mobililse

TABLE 1.

The Royal Adelaide Dysphagia score.

Each food is given an increasing score based on its difficulty to swallow. The maximum score therefore indicates that the patient never has difficulty with any of the foods and therefore scores 45.

Swallowing difficulty in:-	Always (x0)	Occasionally (x0.5)	Never (x1)
1-water			
2-milk/soup			
3-Custard/yoghurt			
4-Jelly			
5-scrambled egg/ mash			
6-fish/boiled potatoes			
7-bread			
8-apple			
9-steak			

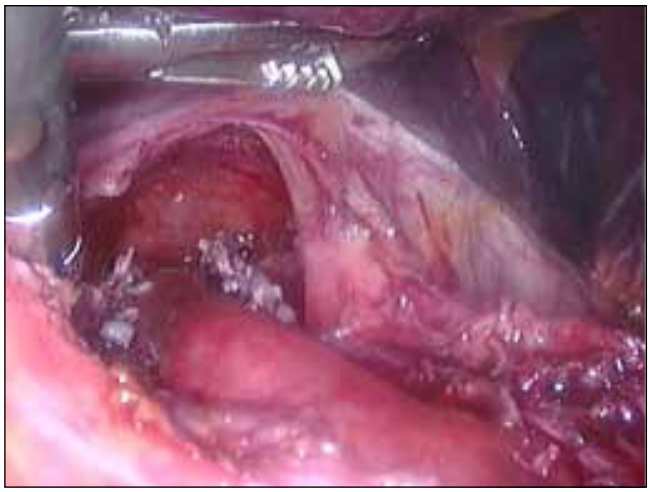

Fig 3. The competed myotomy. This extends into the mediastinum

the oesophagus circumferentially. The myotomy is then commenced and extended approximately 6cm proximal and 2 cm distal to the junction. The extent of the myotomy [figure3] is confirmed with intraoperative gastroscopy. A 180 degree anterior fundoplication (Dor patch) is then performed to prevent pathological reflux. [figure 4]. Port sites are infiltrated with local anaesthetic for post operative pain control in addition to oral analgesia. Oral fluids are commenced at 4 hours and soft diet at 24 hours.

METHODS

18 patients with manometric features of achalasia underwent surgery between 2004 and 2006. Pre and postoperative weight and dysphagia scores were recorded. Patients were contacted post-operatively by telephone by one of the authors working in the unit (RK) and a structured questionnaire carried out. The Royal Adelaide Dysphagia Score[9] was chosen as the investigative instrument. It provides an explicit functional measure of swallowing. The maximum score is 45 indicating normal swallowing. The minimum score is 0 indicating complete dysphagia. [table 1] Change in the Body Mass Index (BMI) was measured along with other common symptoms (heartburn, epigastric pain, regurgitation, odynophagia and sleep disturbance) which were scored on a 5 point 0-4 Likert scale of increasing severity.

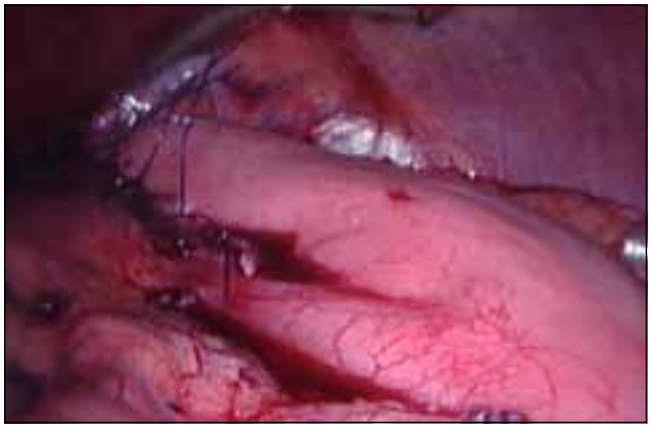

Fig 4. Anterior fundoplication (Dor patch).The fundus of the stomach is secured to the right crus of the diaphragm with non absorbable stitches.

STATISTICAL ANALYSIS

The means of all continuous variables were compared by appropriate parametric or non parametric tests. Categorical variables and proportions were compared the Chi Squared test or the Fischer exact test. Results are expressed as medians and as means +/- SD. Differences were considered significant at $p<0.05$

RESULTS

The mean age of the patients was 40 years (range 21-63) and the mean follow up period was 16.2 months. Laparoscopic cardiomyotomy took on average 111 minutes (range 75-120). Mean inpatient stay was 3.1 days (range 2-6 days) and the majority of patients were admitted the day prior to surgery. More recently patients have been admitted on the morning of surgery with further reduction in hospital stay.

One mucosal perforation occurred as a result of the procedure. This was noted intraoperatively and sutured laparoscopically with 2/0 Vicryl (Polyglactin, Ethicon, New Jersey USA) suture. Postoperatively a non ionic contrast swallow revealed that the perforation was sealed and the patient discharge on the 4th postoperative day. There was no other morbidity, no mortality and no patient required conversion from laparoscopic to open procedure. At follow up 2 patients (11%) were taking proton pump inhibitors for symptoms of acid reflux and 1 patient had had an gastroscopy revealing reflux oesophagitis. BMI was significantly increased from preoperative mean of 22.3 to 25.8 kg/m^2. ($P<0.05$) No patient had required further intervention (e.g. pneumatic dilatation or injection of botulinum toxin) for recurrent dysphagia.

DYSPHAGIA SCORES

The mean dysphagia score was significantly improved. 7.5 (range 2.5-15) to 33.9 (range 18.5-45) at review ($p<0.005$) [figure 5] 1 patient from the 18 (5.5%) had an unsatisfactory response with a dysphagia score rising only from 8.5 to 18.5 and recurrent symptoms. A gastroscopy revealed reflux oesophagitis and he is currently being managed with acid suppression.

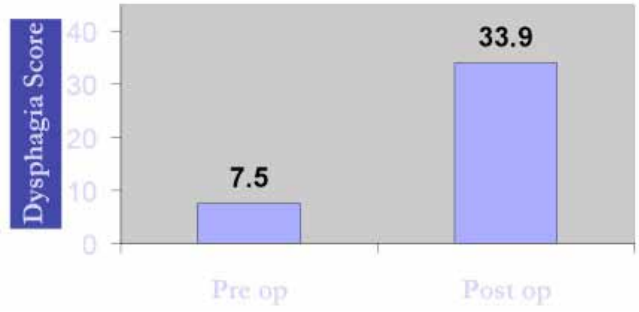

Fig 5. Dysphagia Score pre and post operatively ($p<0.005$)

OTHER SYMPTOMS

There was a significant improvement in regurgitation, sleep disturbance, epigastric pain and odynophagia. (Table 2) There was no significant difference in the severity of heartburn. The effect on regurgitation appeared to be most marked, with pre operative scores improving from a mean of 3.8 to 0.8 post operatively.

TABLE 2

Pre and Postoperative Symptom scoring

Symptom	Pre op score (0-4)	Post op score (0-4)	
Regurgitation	3.8	0.8	P<0.005
Odynophagia	2.5	0.7	P<0.05
Sleep Disturbance	2.7	0.6	P<0.05
Epigastric pain	1.5	0.5	P<0.05
Heartburn	1.6	0.8	P>0.05

DISCUSSION

The most important outcome for the patient with achalasia is relief of dysphagia. Our results indicate that laparoscopic cardiomyotomy is an effective treatment for achalasia and are in keeping with the large series in the published literature.[8, 10] Our study is limited by its small size, the use of telephone to administer the questionnaire and the fact that a single investigator collected and collated the data. Previous studies have suggested that those patients with a high (>35mmHg) LOS pressure benefit much more from myotomy than those with pressures lower than this. Indeed, preoperative LOS pressure has been shown clearly to be the single strongest predictor for successful outcome.[8] This was not specifically examined for in our study. Age, sex and a history of previous pneumatic dilatation or Botulinum Toxin injection are not correlated with success or failure.[8]

Evidence is accumulating that laparoscopic cardiomyotomy produces better results in the long term than pneumatic dilatation (PD). One recently reported randomized controlled trial (RCT) has addressed the issue[11]. Kostic et al found that at 12 months PD produced more treatment failures and that this trend increased with time. In addition, Vela and colleagues compared the long term efficacy of PD with that of laparoscopic cardiomyotomy.[7] They defined success in the long term as freedom from further interventions. At 6 years freedom from intervention was 28% in the single pneumatic dilatation group versus 57% in the laparoscopic cardiomyotomy patients. Indeed many patients from the PD group with more severe disease crossed over to cardiomyotomy, otherwise the difference may have been even greater. Cardiomyotomy has also previously been shown to be superior to PD in the long term.[12] There are no RCTs comparing the traditional transabdominal or transthoracic approaches with the laparoscopic procedure. There is good evidence from a well designed RCT that the addition of a Dor fundoplication reduces the risk of pathological gastro-oesophageal reflux without compromising relief of dysphagia. Richards and colleagues[13] found that without a fundoplication, the incidence of pathological reflux (pH<4 for more than 4.2% of a 24 hour period) was 47%. The addition of an anterior 180 degree Dor fundoplication reduced this to 9% without any effect on post operative dysphagia or LOS pressure reduction.

Treatment failures following laparoscopic cardiomyotomy are most commonly related to inadequate myotomy, and occur more frequently on the "learning curve" phase of a surgeons training. After this, rates of failure and complication are remarkably similar between surgeons and hospitals.[14] Rates

of recurrent dysphagia within one year are commonly 8-10%. Those patients with an already markedly dilated or "sigmoid" oesophagus often have recurrent symptoms following surgery. This group may be identified preoperatively via OGD and a (usually) lower LOS pressure. These patients may eventually require oesophagectomy.

CONCLUSIONS

Accumulating evidence supports early aggressive therapy of achalasia.

Laparoscopic cardiomyotomy is a safe, highly effective and minimally invasive treatment and many authorities consider it the first line treatment.[8]

The authors have no conflict of interest to declare.

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Case Report

Baffling perforation of the colon

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Idiopathic perforation of the colon is extremely unusual and unexpected, with a very limited number of published reports. The condition's definition depends on the absence of any detectable pathology in the bowel wall that could be responsible for the perforation.

A 62-year-old male patient presented with acute thrombosis of the brachial artery. This was successfully treated with an open thrombectomy and systemic anticoagulation, with rapid resolution of the symptoms. During the hospital stay the patient had regular bowel movements and no abdominal complaints. Suddenly he complained of acute abdominal pain. Physical examination and emergency CT scan of the abdomen were consistent with generalized peritonitis. Emergency laparotomy revealed two perforations of the mid-sigmoid colon, each measuring 1.5 x 1.5 cm, and located one in the antimesenteric aspect and one very close to the nutrient vessels. The edges of the perforations showed no inflammatory or necrotic changes. A 2.5 cm streak of macroscopically normal bowel wall was observed between the perforations. The rest of the bowel showed inflamed peritoneum with fibrin as a result of the peritonitis, but was otherwise normal. Sigmoid resection with a Hartmann's pouch was performed and the proximal colon was brought out in the form of an end-colostomy. The abdomen was thoroughly lavaged with warm saline and temporarily closed with plastic sheeting for second-look exploration. Bacteriology from the intra-abdominal fluid showed mixed abdominal flora and no unusual pathogens. The patient was returned to the operating room on five occasions 24-48 h apart for planned re-explorations and peritoneal irrigations. The abdominal wall was restored on postoperative day 12 once a macroscopically clean peritoneum was noted. The patient was transferred to an acute rehabilitation facility. He is known to be alive and recuperating more than eight months after the surgery.

Pathology from the colon revealed an inflamed visceral peritoneum with fibrin and otherwise normal-looking mucosa. There were no diverticula. The edges of each perforation showed no alteration of the muscle or mucosa. Histology from both perforations demonstrated normal intestinal wall architecture, normal mesenteric structures including nutrient vessels and lymphatic tissue, and no specific condition responsible for the perforations. No changes suggestive for ischemia or any other pathology were noted (Figure 1).

Idiopathic perforation of the colon is rare. The diagnosis depends on excluding other conditions that can potentially contribute to the condition's occurrence. No pathology that might have caused colonic perforation could be identified in our patient. It could be argued that, based on the preceding vascular emergency, the perforations resulted from a second thrombotic event involving the colonic nutrient vessels.

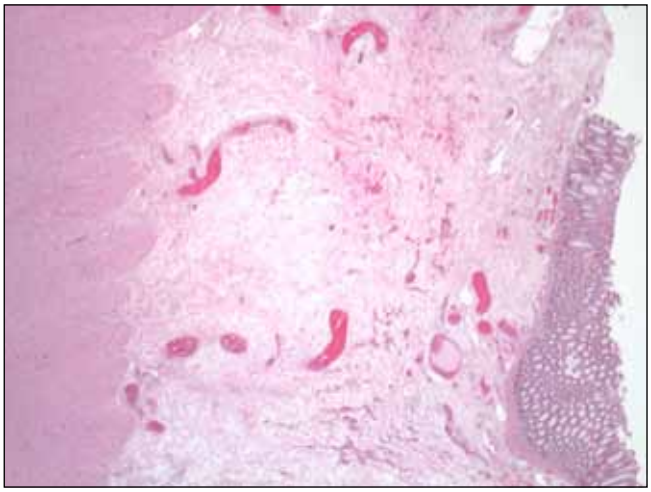

Fig 1. Microscopy of the perforation's edge showing normal mucosa with hemorrhage in submucosa, and normal muscular layer. There is no necrosis and the vessels are patent. The inflammatory changes in the serosal layer are consistent with peritonitis. Hematoxylin & Eosin, x 44.

Histologically, acute ischemia of the colon shows necrosis of the superficial portion of the mucosa, pseudomembranes, cryptitis, and crypt abscess[1]. A detailed histology review of the specimen did not reveal any of the changes, ruling out ischemic perforation of the colon.

Idiopathic perforation of the colon has infrequently been discussed in the literature, with less than 100 reported cases.[2-5] Numerous theories have been put forward to explain the condition's etiology including occult hernias, high intra-abdominal or intra-luminal pressure, colonic implosion, attenuation of the bowel wall, or laceration of the latter from hard feces, however, none of these factors has been supported

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by existing evidence.[2,4] The majority of patients affected by idiopathic perforation have been older than 40 years and presented with acute abdomen. The perforations measured from 0.5 cm to 15 cm and were typically single and located in the antimesenteric aspect of the sigmoid colon in more than 50% of the cases.[3,5] The mechanism of the two simultaneous perforations observed in our patient remains unclear. Idiopathic perforation of the colon has been observed with an increasing incidence in newborn infants. The hypotheses about its etiology in this particular group include, in analogy to the adult group, mechanical injury, muscular defects in the colonic wall, infection, perforation by meconium plugs, and necrotizing enterocolitis, with no definite supporting evidence.[2,5] The invariably normal pathological findings do not support either the above factors, or a recently proposed theory entertaining ischemic necrosis secondary to a much localized vascular accident in the wall of the affected bowel.[5]

The treatment of all idiopathic perforations is surgical and encompasses one of three treatment methods. These are: 1) Simple closure of the lesion or limited resection with anastomosis; 2) Exteriorization resection, or 3) Hartmann's pouch and proximal colostomy, depending on the topographic location of the perforation and the severity of peritonitis. Because of the small number of published cases exact guidelines as to the extent of surgery and its impact on morbidity and mortality cannot be formulated.

The etiology of idiopathic perforation of the colon remains unclear. The published literature provides no reliable information whether the mysterious entity is the same in the pediatric and adult groups. The limited number of studies so far support that early recognition and treatment contribute to a successful outcome in the majority of patients. Further studies exploring the intestinal ultrastructure are expected to yield more information about idiopathic perforation of the colon, provided that judicious criteria for its determination are applied.

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The authors have no conflict of interest to declare.

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Case Report

Paraneoplastic limbic encephalitis in an elderly patient with small cell lung carcinoma

David White, Timothy Beringer

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ABSTRACT

We report a case of paraneoplastic limbic encephalitis (PLE) in an elderly lady with small-cell lung carcinoma (SCLC) and positive anti-RI neuronal auto-antibody. PLE is a relatively rare clinical entity associated with cancer patients, but is probably under-diagnosed. PLE typically presents clinically with affective changes in personality, cognitive dysfunction and seizures in a patient with malignancy, particularly SCLC. Although diagnosis does not rely upon definitive investigation results, serum paraneoplastic antibodies, abnormal CSF, and characteristic MRI and EEG findings may support the diagnosis. As PLE often presents prior to the discovery of a primary tumour, knowledge of the disease may assist in identifying underlying malignancy.

INTRODUCTION

Paraneoplastic syndromes are a common complication of many malignancies, occurring in up to 50% of cancer patients. They involve a wide spectrum of disease processes, causing symptoms not due to direct invasion of the primary tumour or metastases. Neurological paraneoplastic syndromes cause remote effects by an immune-mediated response against normal neuronal tissue. Paraneoplastic limbic encephalitis (PLE) affects a small, but probably underestimated, proportion of all cancer patients. PLE most commonly affects patients with squamous cell carcinoma of lung (SCLC), though it has also been reported in breast, testicular, and thymus cancers, transitional cell carcinoma of the bladder, and Hodgkin's lymphoma. There has been no age, race, or sex preference reported in the literature.

The limbic system incorporates the hippocampus, hypothalamus, thalamus, amygdala, fornix, and other structures surrounding the brainstem and plays a central role in memory, learning, and higher emotion. Antigens expressed by the tumour produce antibodies, which cause an immune-mediated response against the healthy nervous system ,and thus the term paraneoplastic limbic encephalitis implies inflammation within the limbic system as a result of a paraneoplastic process.

We report a case of PLE associated with SCLC. Our primary aim is to heighten awareness of the disease entity to assist prompt initiation of appropriate investigations and improved levels of diagnosis.

CASE REPORT

An 85-year-old ex-smoker (50 pack years) presented with increasing shortness of breath and was diagnosed histologically with small-cell lung cancer. PET/CT scans at time of diagnosis confirmed a very large left hilar tumour, with extensive mediastinal involvement, but no distant metastases were identified. Prior to this she had been in good health, with no significant past medical or family history. The patient underwent 4 cycles of chemotherapy with carboplatin and etoposide the following month. She subsequently received adjuvant radiotherapy, with 15 treatments to the chest and 12 treatments to the brain. The cranial irradiation she received was a prophylactic measure, as SCLC has a predilection for CNS spread. Subsequent CT scanning confirmed a positive response to treatment, with a significant reduction in the size of the tumour and nodes.

The patient remained at home during her treatment, maintaining a reasonably good functional status. Her usual positive and outgoing personality prevailed throughout this period, although family members noticed a gradual impairment of her memory within two months of completion of her treatment. A more acute deterioration occurred six months post-diagnosis, when the patient collapsed at home. There was incontinence of faeces and urine, succeeded by marked confusion. A diagnosis of seizure was considered likely, but could not be confirmed as the episode was unwitnessed. The patient was admitted to an acute medical unit and a mini-mental score examination was recorded as 2/10. There was no focal neurology elicited. A full septic screen was negative. Routine serological tests were normal. A CT of her brain again demonstrated no evidence of cerebral metastatic disease, and a further CT of her chest showed the tumour and mediastinal nodes to be smaller than two months previously.

There followed a state of fluctuating confusion, which persisted with impairment of both short and long term memory. The most notable feature reported by the patient's family was a marked change in personality. She had previously had a positive and outgoing personality, which had remained

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even throughout her cancer treatment. However, following her collapse and subsequent admission the patient was found to be apathetic, uninterested in her family, and unsettled, with episodic agitation. This caused great distress to those close to the patient. The patient fell in hospital and unfortunately sustained a fractured left neck of femur. MMSE at this time was 4/10, and a further CT brain showed generalised atrophic change, again with no evidence of metastatic spread. The patient successfully underwent surgical fixation of her hip fracture, but progress with rehabilitation was poor primarily due to her poor cognitive state.

A diagnosis of paraneoplastic limbic encephalitis was considered on admission, and appropriate investigations were initiated. Serum paraneoplastic antibodies subsequently returned as positive for anti-RI antibodies, a highly specific paraneoplastic neuronal antibody. CSF was not obtained, as lumbar puncture was not felt appropriate given the patient's condition. Electroencephalogram showed background activity within normal limits, but with frequent generalised slowed activity throughout the recording. Some sharp wave activity was seen in the left mid-temporal region, representing a mild encephalopathy. Cranial MRI was performed but unfortunately the study was of poor quality due to patient movement, enabling only generalised cortical atrophy to be identified .

The clinical presentation with confusion, memory loss, change in personality and probable seizure in a patient with SCLC were consistent with a diagnosis of PLE. Both the EEG findings and anti-RI antibodies supported the diagnosis. Symptomatic management was deemed the most appropriate approach, and the patient died three months after her presentation of collapse. A post mortem was not performed.

DISCUSSION

The first report of a mental disorder associated with primary lung carcinoma was described in 1956[1]. Corsellis subsequently coined the term ' Limbic Encephalitis' in 1968, detailing the association with carcinoma[2]. Sporadic case reports followed, with only 16 cases verified clinically by 1990. The past decade has witnessed increasing interest in the condition. Improved recognition has allowed for structured data collection and small studies to take place. An inherent difficulty surrounds enrolment to these studies in that patients are frequently very unwell when the disease process is recognised. The condition is characterised by cognitive impairment, confusion, memory loss (usually short term), personality change, and seizures (usually complex-partial, but may be generalised). Olfactory and gustatory hallucinations are less commonly reported. There is usually a sub-acute presentation of symptoms over weeks or months. Symptoms may precede the diagnosis of underlying malignancy in up to 60% of cases[3]. It is therefore important to consider the diagnosis in any patient with unexplained cognitive changes, and not only those with a known diagnosis of cancer.

In this case report the presence of SCLC, coupled with a classical history of cognitive dysfunction, personality change, and possible seizure activity was strongly suggestive of PLE. The subsequent detection of a highly specific paraneoplastic antibody in the patient's blood supported the diagnosis. Autoimmune antibodies may serve as a helpful diagnostic tool, but their exact role in causing neuronal injury and clinical manifestations remains unclear. Neuronal autoantibodies tested for routinely are anti-HU (ANNA-1), anti-RI (ANNA-2), and anti-YO (PCA-1). Of these, anti-HU is the most commonly found, occurring in approximately 50% of cases of PLE [4]. The anti-RI antibodies discovered in our patient are less commonly found, but are the most specific for supporting a diagnosis of PLE. Voltage-gated calcium channel antibodies are also tested for as part of the paraneoplastic antibody assay. These were negative in this particular case. The prevalence of these markers in patients who definitely do not have a neuronal paraneoplastic syndrome is not reported. CSF may show mild elevation of proteins, paraneoplastic antibodies, pleocytosis, and positive oligoclonal bands, or intrathecal IgG. Unfortunately a CSF sample was not obtained in the patient discussed. EEG may be normal, but as in this case often displays non-specific generalised or focal slowed activity, which may depend on the stage of the disease. Characteristic MRI findings in patients with PLE include unilateral or bilateral medial temporal signal abnormalities, which are best identified on T2-weighted images. These are not found in every patient with PLE, but are reported in between 57% [3] and 83% [5] of cases.

This latter retrospective review [5] studied twenty-four patients attending the Mayo Clinic with suspected PLE on the basis of classical symptoms and the presence of cancer. Thirteen of these patients had a diagnosis of SCLC. The common clinical findings were cognitive dysfunction (92%), seizures (58%), and psychiatric symptoms (50%). The authors reviewed data from paraneoplastic serological studies, CSF analysis, MRI and EEG reports. Serum paraneoplastic neuronal antibodies were found in 64% of the patients. Abnormal CSF was found in 78% of patients. The only universal positive finding was that of focal or generalised slowing on EEG, with all 24 patients displaying this.

Two treatment approaches are currently available. Treatment of the underlying cancer with surgery, chemotherapy, radiotherapy, or hormonal treatment may remove the antigen source, and thus antibody production. Although this approach often causes the remission of other neurological paraneoplastic syndromes (e.g. Eaton-Lambert syndrome), the effect on PLE is less successful [6]. The other management approach involves suppression of the immune response with steroids, immunoglobulins, cyclophosphamides, or plasma exchange. Although data is limited, response to this mode of therapy has also been disappointing [3].

CONCLUSION

Paraneoplastic limbic encephalitis describes inflammation within the brain's limbic system, resulting from an autoimmune-mediated paraneoplastic process. It is characterised by a sub-acute and severe neurological disorder. The diagnosis is reached primarily from the clinical picture, coupled with supportive investigation and imaging. Negative results do not exclude the disease process. Although PLE is rare, it's prevalence is almost certainly more widespread than appreciated. Heightened awareness of this clinical entity will assist earlier diagnosis. Further work is required to improve our understanding of the exact pathophysiology of PLE, and to classify immunological subsets. This may allow more specific targeting of treatments as now occurs in many

other cancer-related disease processes. As this syndrome often precedes overt symptoms of a tumour, awareness of the disease may enable earlier detection of cancers in those patients presenting with sub-acute confusional states caused by a paraneoplastic process.

The authors have no conflict of interest to declare. We acknowledge the clinical care provided by Dr JI Logan.

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Medical History

Sir Hans Sloane (1660-1735): his life and legacy.

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SUMMARY

Sir Hans Sloane was born in Killyleagh, Co Down, the seventh and last son of Alexander Sloane. His father, who was of Scottish ancestry, had a long association with James Hamilton, Earl of Clanbrassil who had acquired the castle in Killyleagh and extensive estates in east Down. The Hamilton family took an interest in the education of the Sloane children, and much of the early tuition of Hans was conducted within the library of Killyleagh Castle.

In 1679 he moved to London to study medicine and botany. In 1683, he continued his studies in Paris and Montpellier, and graduated from the University of Orange. On his return to London, he became a protégé of Thomas Sydenham. In 1687 he was appointed physician to the Duke of Albemarle and surgeon to the West Indies fleet. While in Jamaica he added countless specimens to his collections, continuing a lifetime passion. He also invented milk chocolate there. Following the untimely death of the duke, he returned to London and built up a fashionable medical practice.

He married Elizabeth Langley, heiress of a wealthy city alderman, and widow of a sugar planter in Jamaica. They set up house in Great Russell Street. The family home accommodated his burgeoning collections of books, specimens and curiosities. In 1685 he was elected a Fellow of the Royal Society, later becoming the honorary secretary and president. Following his death, his collections were bought for the nation and formed the foundation of the British Museum.

THE LIFE OF SIR HANS SLOANE

The year 2010 is the 350th anniversary of the restoration of King Charles II to the crown in London; the inauguration on 28th November in Oxford of what was to be later known as the Royal Society; and, on 16th April, the birth of Hans Sloane in Killyleagh, Co Down. Sir Hans Sloane Bt was, in the last millennium, one of the British Isles' most influential figures in medicine and the natural sciences. He was the man after whom London streets were named - Sloane Street, Sloane Square and Hans Street. The name "Hans" was fashionable at the time in Scotland, and occurred in Scots Irish settlers. It is probably short for Johannes, as in Germany. He was destined in later years to be closely associated with royalty and with the Royal Society, acting as both secretary and president.

In Killyleagh today stands an ancient castle, owned by the Rowan Hamilton family, and still maintained as a private home. It has been altered extensively by succeeding generations of the family. At first, it was a defensive tower fort, called White Castle. A second tower was added when it was rebuilt following the severe damage inflicted during Cromwell's Irish campaigns. The castle, commanding a strategic position overlooking Strangford Lough, was acquired, with extensive estates in East Down, by James Hamilton as a result of his devotion to King James I's cause.

Fig: Statue of Sir Hans Sloane by John Michael Rysbach in the Chelsea Physic Garden

James Hamilton was the son of the Rev Hans Hamilton, minister of Dunlop, Ayrshire. During the last 20 years of the reign of Elizabeth I, he was a secret agent in Ireland for the future King James. *"His mission was to watch and steer opinion in Ireland against the day when King James might have to exert himself to gain the throne of England"*[1]. He and another Scotsman, James Fullerton set up a Latin school

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in Dublin. On the establishment of Trinity College Dublin in 1592, they were made fellows. On the accession of James VI of Scotland to the throne of England in 1603, they went to London and were knighted by the new King James I of England.

Extensive tracts of land in Ulster that had been previously granted to Viscount Montgomery of the Ards were divided into three. Montgomery kept one third, a third was surrendered to Con O'Neill and Hamilton was granted the remaining third. Relationships between the Montgomerys and the Hamiltons were strained for generations, resulting in skirmishes and worse. Much of the O'Neill land gradually fell into the hands of the Scots settlers. Hamilton, created Viscount Clandeboye, died in 1644, leaving a son and heir, also James, who became the second Viscount Clandeboye and who was also created the first Earl of Clanbrassil. He married Anne Carey, eldest daughter of the Duke of Monmouth, at Rickmansworth in 1641. He died in 1659 and was succeeded by his only son, Henry, the second Earl, who married Alice, a daughter of Henry Moore, the first Earl of Drogheda.

Hans Sloane was born in 1660, in a small house, in Frederick Street, Killyleagh, County Down. The original house stood for several centuries but was demolished in the 1960's to make way for modern homes. A photograph of it is preserved in the collections of the Ulster Museum. The keystone from above the front door seen in the photograph has been preserved in a memorial wall across the road, opposite the site of the Sloane family home.

Alexander Sloane, Hans' father, was the receiver general of taxes for County Down and agent for James Hamilton. Alexander married Sarah Hicks, who came to Killyleagh as Anne Carey's companion, after she had married James Hamilton. Hans was Alexander's seventh and last child. He was probably baptized in the parish church that was built in 1640. The early records are lost. Baptismal and Marriage registers exist only from 1836. Only three of Alexander's sons, James, William and Hans survived to adulthood. In the Killyleagh parish churchyard can be found the gravestones of John and Henry Sloane, two brothers who died in childhood. James, the eldest brother, was elected Member of Parliament for Killyleagh and for Roscommon in 1692. He was later MP for Thetford and as a barrister of the Inner Temple, spent most of his time in London.

Alexander Sloane died when Hans was aged 6. He left his property in trust for his widow and family. In 1671, his widow married John Bailie of Inishargy, which is in the Ards peninsula, near Greyabbey. Sarah had several further children by her second husband. In his childhood, young Hans Sloane showed a keen interest in natural history. He joined the school founded and supported by the Hamiltons in Killyleagh. By his own account, he explored the countryside and shores of County Down. At the age of sixteen, his studies were interrupted by episodes of haemoptysis that persisted for three years. He was largely confined indoors during this illness, receiving his tuition in Killyleagh Castle's extensive library. As a result, he adopted life-long habits of sobriety, temperance and moderation, which, no doubt, helped him survive to the age of 92. When Alexander's widow remarried and moved from Killyleagh to Inishargy, Hans remained with the Hamilton's for his schooling.

There is some suggestion that previous generations of the Sloanes and the Hamiltons were related. The evidence for this is not complete. However there is evidence that after his father's death, the education of the talented youth was encouraged and sponsored by the Hamilton family. William Sloane, born in 1658, did marry Jane Hamilton of Killyleagh, who inherited the Earl of Clanbrassil's estate. William died in Chelsea in 1728. His son William was a trustee to his uncle Hans, and played an important part in the transfer of his collections to the British Museum after the death of Sir Hans Sloane.

At the age of 19, Sloane moved to London to study medicine. He lodged in a house adjoining the Apothecaries' Hall in Water Lane, Blackfriars with Nicholas Staphorst. Sloane was in contact with the botanist John Ray (1627-1705). Ray was elected FRS in 1667 and was a former Fellow of Trinity College Cambridge. His first major work, *Methodus Plantarum Nova*[2], which proposed a new method for classifying plants, was published in 1682. Though there was an age difference of thirty years, the two struck up a lifelong friendship. The pioneering chemist, Robert Boyle (1627-1691) also assisted Sloane. Boyle, who was the seventh son of the Earl of Cork, was friendly with the Hamiltons.

According to a contemporary account by Dr Thomas Birch, secretary of the Royal Society, Sloane *"acquired a perfect knowledge of the preparations and uses of most chemical medicines"*.[3] In those days, botany, Sloane's favourite subject, was considered to be fundamental to the medical curriculum. Sloane frequented the new Physic Garden, recently established in 1673 at Chelsea by the Company of Apothecaries. There was active collaboration with the Physic Garden in Leyden to build up collections of medicinal plants. In the Physic Garden were glass houses and hot houses, heated by hot water pipes to enable the germination of seeds of exotic plants and the propagation of cuttings. Paul Herman, Professor of Botany in Leyden visited Chelsea in 1682 and arranged exchanges of plant material.

In 1683, Sloane went with a friend, Tancred Robinson, and a companion called Wakely to Paris where he continued his studies in medicine and botany, particularly with Tournefort and Magnol (after whom magnolias were named). They later encouraged him to continue his studies at Montpellier, where they had been educated, as had Ray and Boyle. As a protestant, Sloane was debarred by statute from taking degrees at Paris and Montpellier. He took his degree as Doctor of Physic at the University of Orange, near Avignon in Provence, on July 28th 1683. A contemporary account in the Archives of Vaucluse, translated by de Beer, states that Sloane was awarded the highest honours and gives a description of the young man as follows: *"of medium height, hair very short, light chestnut, face rather long and grave, marked with the smallpox"*.[4] This reference to smallpox is pertinent to later experiments carried out by Sloane. He continued his studies in Montpellier until 1684, returning to London via Toulouse, Bordeaux and Paris.

On his return to London, he lodged in Fleet Street. On January 21st 1685, he was elected FRS when Samuel Pepys was President. The two were friends and associates for the rest of Pepys' life. Years later, Sloane attended Pepys during his final illness in 1703, and subsequently performed an

autopsy on him. He continued to be associated with the Royal Society all his active life.

Sloane became a protégé of Thomas Sydenham, the most influential physician of the day in London. In fact, he lodged with him in his home as an assistant. When the older man was indisposed owing to the effects of gout and other infirmities, Sloane would represent Sydenham. From his master, whom some contemporaries called "the English Hippocrates",[5] he learned the value of meticulous clinical observation. On April 12th 1687 he was admitted a Fellow of the Royal College of Physicians.

Later that year, Christopher Monck, the second Duke of Albemarle, was appointed Governor of Jamaica. He charged his London physician to find, for him, a doctor who would accompany him and his family to Jamaica. After careful consideration and consultation with his mentors and friends, Sloane was appointed physician to the Duke, and surgeon to the West Indies fleet. Sydenham was not encouraging. It is recorded that he suggested that Sloane had better drown himself in a pond in St James's Park, rather than embark on the hazardous journey to the West Indies.[6] Ray was more encouraging, suggesting that it was a wonderful opportunity for a young botanist. Perhaps mindful that Thomas Sydenham had introduced Peruvian bark (a rich source of quinine) to London recently, Sloane contemplated adding other new discoveries to the list of medicinal plants commercially available.

In the West Indies he threw himself with enthusiasm into the study of the flora and fauna, and added countless specimens to his rapidly expanding collections of plant and animal material and indeed artifacts of all categories. The appointment as surgeon to the West Indies fleet was prematurely terminated by the death of the Duke. His last medical duty for the dead Duke was to embalm the body for transport to England for burial. While in Jamaica as he searched for new plants that might be introduced as food, his attention was drawn to a drink used by the natives, made from cocoa beans. The Spaniards were already using it. He found it was *"in great quantities, nauseous, and hard of digestion"*.[7] He derived a recipe of mixing the product of the beans with milk and sugar, and so introduced milk chocolate to England. His recipe was later sold to the Cadbury brothers. Milk chocolate would become a highly profitable sideline. Initially it was promoted for its postulated benefits to health.

During his stay in the islands he invested almost all his salary in the purchase of Peruvian bark, which he sold in London at a substantial profit. Peruvian bark first appeared in the London Pharmacopoeia third edition published in 1677. It was highly valued in London as a fever treatment. On Sloane's return to England, his plant collection alone amounted to 800 specimens. His collection of live animals did not survive the passage.

When Sloane returned to London on May 29th 1689, William of Orange was on the throne. For nearly four years he continued in the service of the widowed Duchess of Albemarle. Letters for him were addressed to her house at Clerkenwell and her country house at New Hall in Essex. Through her patronage he built up a fashionable practice. The Duchess was married a second time to the Earl (later Duke) of Montagu. In 1693 letters were addressed to Sloane *"At the Lord Montague's House"*,[8] in Bloomsbury.

In 1694, he became physician to Christ's Hospital and the Foundling Hospital. In 1695, he married Elizabeth Langley, heiress of wealthy city alderman, John Langley and widow of a sugar planter from Jamaica, Fulk Rose. Sloane not only inherited John Langley's entire estate, but also a third of the income from the Jamaican sugar plantations. With his bride he took a house in Great Russell Street, now No 3 Bloomsbury Place - a very fashionable address. They had three daughters and one son. Only two daughters survived childhood

Until ten every morning, Sloane gave the poor of the neighbourhood free advice in his own home and sent them to the dispensary of the College of Physicians in Warwick Lane for their medicines and remedies. This brought him into conflict with the Society of Apothecaries, eventually climaxing in a court case, which the physicians lost.[9]

In 1696, Sloane published a catalogue of the plants of Jamaica.[10] However his major publication, the *Natural History of Jamaica* took many years in preparation. It was published privately at his own expense in two volumes, the first in 1707 and the second in 1725.[11] His own personal copies can be found in the library of the Royal College of Physicians in Regents Park.

By the beginning of the eighteenth century, Sloane's reputation as a physician was such that in 1701, the University of Oxford conferred on him the degree of Doctor of Medicine. In 1705, he was elected to the Royal college of Physicians of Edinburgh. In 1716, Sloane was appointed Physician General to the Army and was created a Baronet by King George I, the first physician ever to receive the hereditary title. Three years later he was elected President of the Royal College of Physicians, a position that he held for sixteen years from 1719 to 1735.

Sloane gained a great reputation for the treatment of eye affections and his only academic medical paper is on this subject. He jealously guarded the formulation until it was published in 1745, when he was 85, and had retired from active practice. It contained *"tutty (zinc oxide), Lapis Haematitis (ferric oxide) prepared pearl and aloes ground in a pestle and mortar with viper's grease or fat to make a liniment"*.[12] Zinc oxide is probably beneficial. There are no modern studies on the medicinal properties of viper's grease.[13]

During his Presidency of the College of Physicians, the fourth London Pharmacopoeia appeared. It had been first published over 100 years previously, and during that time little change had been made to its contents. Many of the remedies contained within it were throw-backs to witchcraft and superstition; for example, the wormian bone from an executed criminal's skull was a constituent of some remedies. Sloane and his contemporaries encouraged a more rational approach to prescribing based upon his knowledge of the therapeutic use of plant material.[13]

As secretary to the Royal Society, many learned gentlemen corresponded with him. This correspondence numbering over 500 items can be accessed in the journal of the Royal Society of London, Philosophical Transactions. The records are

varied. Here are two noteworthy examples. It is recorded that he was offered pieces of the Giant's Causeway, but the writer found he already had some examples in his possession.[14] There is also an interesting reference to beans from the Caribbean having been found on the shores of Scottish islands. Sloane recognized the beans were identical to fruits that he had seen on trees in Jamaica, and concluded that they must have been carried across the Atlantic by ocean currents.[15]

While secretary to the Royal Society, Sloane had his detractors, in particular John Woodward, professor of Physic at Gresham College, who tried to remove Sloane from the secretary's post at the Royal Society, preferring his friend Dr John Harris. Woodward was himself ejected from the Council, as a result of overplaying his hand.[16]

Throughout his adult life, Sloane added to his collections. He was very particular about classifying plant material, and labeling specimens. In addition to collecting individual items on his own behalf, when the collections of others became available for sale, he would snap them up, being able to outbid competitors. In 1702, he acquired Charlton's Collection, in 1710, Plunket's, in 1711 Hermann's, in 1717 Kaempfer's and in 1718 Petiver's Collection. When Sloane had acquired collections that filled many rooms in his house, he purchased the house next door, Number 4 Bloomsbury Place, to help accommodate them.

He set aside a day in the week for the entertainment of his learned friends. The parties in his house in Great Russell Street were famous. Dinner was served at about five in the afternoon. He restricted himself to one glass of wine. He was a generous host and did not impose such strict limitations on his guests. It appears that his menus drew comment in several ways. Sir Erasmus Phillips is recorded as saying that salmon, champagne and burgundy were never served.[17] After dinner the guests were encouraged to retire to Sloane's museum, accommodated in his home.

Sloane attended Queen Anne on many occasions during her illnesses and was present during her final illness. The circumstances of Queen Anne's death had bearing on the succession. With the accession of George I in 1714, he won the confidence of the Prince of Wales and his wife, later Queen Caroline. One of her daughters, Princess Anne, was attended by Sloane during a smallpox infection. Sloane is recorded as saying, *"The Princess Anne, now Princess of Orange, fell ill with smallpox in such a dangerous way that I feared for her life. The late Queen Caroline, when Princess of Wales, to secure her other children, and for the common good, begged the lives of six condemned criminals, who had not had smallpox, in order to try the experiment of inoculation on them"*.[18] The practice of engrafting with smallpox to ameliorate the naturally occurring disease was current in Turkey.[19, 20] Charles Maitland, physician to the former British Ambassador in Constantinople, introduced the practice to Britain. He inoculated the ambassador's daughter in April 1721, having inoculated his son in Constantinople in 1717. The king agreed to pardon the prisoners if they survived. Sloane attended the inoculation of the prisoners. Maitland declined to perform the operation, but a Dr Terry of Endfield, who had practised in Turkey, obliged.

Inoculations were performed on six condemned criminals in Newgate. They all recovered. One of the inoculated prisoners was then sent to Hertford *"where the disease in the natural way was very endemical and very mortal"*[18] to lie in bed with a person suffering from severe smallpox. This prisoner survived unscathed. A further trial was performed on charity children, recruited in the Parish of St James. Further trials were performed in private families including Sir Hans's own grandchild before inoculating two royal princesses, daughters of Princess Caroline, in April 1722. The contemporary reports recording that Sloane's face was scarred and pitted by the effects of the pox are quoted above. Could this have made him more receptive to the suggestions that he embark on these hazardous experiments?

Sloane succeeded Sir Isaac Newton as the President of the Royal Society, a position that he held from 1727 to 1741. He is the only person ever to have held both this office and the Presidency of the Royal College of Physicians, an accomplishment that is unlikely to be repeated.

In 1712 Sloane bought the Manor of Chelsea from William, Lord Cheyne and spent his retirement years there. The estate included the Chelsea Physic Garden where he had studied botany in his youth. In 1722, Sir Hans entered into agreement with the Company of Apothecaries. For a yearly rent of £5 he conveyed, in perpetuity, the Physic Garden on condition that fifty new plants should be distributed to the Royal Society every year until the number amounted to 2,000. In token of the gratitude the Society of Apothecaries commissioned a statue of Sloane by John Michael Rysbrack of Antwerp, which was erected in the middle of the gardens where a copy can still be found. A further copy has been erected in Killyleagh in recent times.

In 1742, at the age of 82, Sloane retired from medical practice. He moved his household and collections to Chelsea and spent his old age in the Manor House. Towards the end of his life Sir Hans resolved that his collections should be offered for sale to the nation, rather than have them split up after his death. He listed 63 trustees, with three ex officio trustees from the Royal Society. Two of his grandsons were numbered among the trustees. Sloane died on 11th January 1753, after an illness of only three days. He was buried beside the grave of his wife in the corner of the graveyard of the Chelsea Old Church, where the original memorial still exists. In 1753, his catalogue[21] listed around 100,000 objects and curiosities including 5,439 insects and around 23,000 coins and medals, over 12,000 examples of plant material and around 50,000 books. His collections were bought by the nation for the sum of £20,000 and by an Act of Parliament £100,000 (£8,000,000 in today's currency) was to be raised by lottery for the storage and display of the Sloane collection which was to form, along with several other collections, the foundation of the British Museum. Montagu House in Great Russell Street, was purchased for the purpose. This was opened to the public on the 15 January 1759, just six years after the death of Sir Hans. The present building in Great Russell Street, designed by Sir Robert Smirk was built between 1823 and 1852 on the site of Montagu House.

On the foundation of the Natural History Museum in South Kensington, his collections of dried pressed plants were relocated and are still used as reference sources. Many of his books are to be found in the special collections of the

British Library, recently moved from the centre of the British Museum to its splendid new building at St Pancras.

Sloane's influence can thus be found in the British Museum, the Natural History Museum, the British Library, the Royal College of Physicians, the Society of Apothecaries and the Chelsea Physic Garden. That a man of relatively humble origins rose to such prominence is a tribute to his hard work and diligence.

The author has no conflict of interest

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Letters

EMBOLIC STROKE AS A LATE COMPLICATION OF INFERIOR VENA CAVA THROMBOSIS

Editor,

We read with interest the article entitled "Inferior vena cava thrombosis in young adults – a review of two cases" by McAree *et al.* in the May 2009 Journal [1]. In addition to the complications they describe, we recently encountered an unusual and late complication of the condition.

A 73 year old male in sinus rhythm with history of 2 embolic strokes underwent trans-oesophageal echocardiography (TOE) after trans-thoracic echocardiography demonstrated an aneurysm of the inter-atrial septum, a finding often associated with patent foramen ovale (PFO). Of note, the patient had suffered two episodes of extensive deep venous thrombosis of the legs some 44 years previously and had stopped taking aspirin prescribed for cardiovascular risk just before the first stroke.

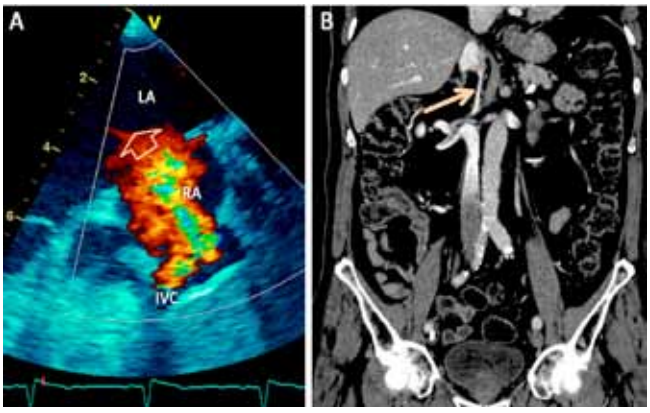

Fig 1.Panel A: IVC: inferior vena cava, LA: left atrium, RA: right atrium, Arrow: Jet crosses patent foramen ovale.
Panel B: Arrow: Inferior vena cava stenosis.

Initial TOE saline contrast study demonstrated a PFO with right to left flow. Colour Doppler interrogation revealed a high velocity jet ($1.75ms^{-1}$) entering the right atrium from the inferior vena cava (IVC). It impacted on the inter-atrial septum and crossed into the left atrium continuously via the PFO (Figure 1, panel A, arrow). The jet could be traced back for a few centimetres into the IVC before it seemed to disappear.

A computed tomography scan of abdomen showed a long stenosis of the IVC just above the right renal artery (Figure 1, panel B, arrow). There was accumulation of contrast in the IVC consistent with a severe stenosis. The remainder of the examination was normal.

The aetiology of the IVC stenosis was unclear; a congenital stenosis would usually be associated with prominent collateral veins that were not present in this case. A spontaneous thrombosis of the IVC is very rare as discussed by McAree et al[1]. It seems most likely that the stenosis represented organised thrombus related to his previous extensive DVTs.

No other potential cause of embolic stroke was found. He was commenced on Warfarin after the TOE and remains well

PFO is a well recognised cause of cryptogenic stroke [2] with paradoxical embolus being facilitated by an increase in right atrial pressure, in this case, the jet effect of the IVC stenosis. A MEDLINE search failed to find any other examples of this association in the literature.

We note that in their discussion, McAree et al. have listed pulmonary embolus as a recognised complication of the condition but PFO (present in up to 25% of the population) could potentially allow systemic embolisation of recent IVC thrombus or in our patient's case, potentially facilitate embolic stroke many years later in association with a jet effect from an IVC stenosis.

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The authors have no conflict of interest.

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SIR WILLIAM WHITLA'S FAMILY NAME

Editor

Information has recently been uncovered which merits a short foot-note to the biographical details of Sir William Whitla (1851-1933), a towering medical presence, twice President of this Society (1886 and 1901) and its greatest benefactor.

Sir William's first recorded ancestor was John **Whitly** (1680-1721) who lived in the townland of Drumnahuncheon, between Richhill and Kilmore, County Armagh. Sir William's father, Robert was born in 1817 by which time his family name was spelt **Whitley**. Due, reportedly, to a family feud, Robert and his father changed their name to **Whitlaw.** Robert **Whitlaw** went to live in Monaghan where in 1841 he married Anne Williams of a family long resident in the town. Shortly afterwards Robert changed his name to **Whitla**, and it was as **Whitla** that all twelve of the offspring were born. Such name changes were frequent at the time but those among Sir William's forebears have not previously been described.

(I am indebted to Mr Patrick Corkey, now deceased, a grandnephew of Sir William, for recently giving me this information which had been brought to light by Sir William's nephew, Commander James Whitla Gracey [1884-1969], but not reported.)

Peter Froggatt, *Former Vice-Chancellor, QUB*

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COMPARISON OF PUBLIC PERCEPTIONS ASSOCIATED WITH HEALTHCARE-ASSOCIATED INFECTIONS (HCAIS) IN NORTHERN IRELAND FOLLOWING THE 2007/2008 OUTBREAK OF *CLOSTRIDIUM DIFFICILE* IN THE NORTHERN TRUST

Editor,

Between June 2007 and August 2008, an outbreak of the spore-forming anaerobic bacterium, *Clostridium difficile*, occurred within the Northern Health Trust, particularly associated with Antrim Area Hospital. During this period, there was sustained local media attention in its reporting via radio, newspaper and television. Following the outbreak, it was the aim of this study to compare public perceptions to and fear of healthcare-associated infections (HCAIs) of responders in Northern Ireland with responders elsewhere in the UK and worldwide.

An on-line e-survey was performed over the four month period, June through September 2009, hosted at the *Infection Free by Design* (IFBD) network site (http://www.infectionfreebydesign.com/), where IFBD was supported through an Invest NI facilitation grant. Twelve questions were asked to assess the public's perception of HCAIs and how these are being challenged. In total, 201 responses were analysed, originating from 53% males and 47% females, including 104 from persons with a Northern Ireland postcode, 75 with a postcode from Great Britain and 22 responders from other countries, including Australia (n=4), Germany (n=1), India (n=2), Malaysia (n=3), New Zealand (n=1), Republic of Ireland (n=3), South Africa (n=1) and the USA (n=7). Overall, the greatest fear of going into hospital in descending order was (i) fear of catching a HCAI (120/201 (59.7%) respondents ranked this their greatest fear, (ii) waiting lists (82/201 (41.0%) respondents ranked this as their second greatest fear, (iii) being away from home , (iv) hospital food and finally, getting to/from hospital . Within the Northern Ireland context, fear of catching a HCAI was also the greatest concern regarding going into hospital (62%), which was markedly higher than GB (56%) and where waiting lists ranked the second most significant anxiety/fear (49% in NI versus 33% in GB). Most responders described themselves as having a medium level fear of HCAIs (51.3%), whilst approximately one fifth of interviewees (18.1%) expressed having a high level of fear of HCAIs, whilst approximately one third of responders (30.7%) declared having a low level of HCAI anxiety. When questioned as to where this anxiety towards HCAIs originated, media reports were responsible for the majority (62.1%), followed by what one had seen when visiting a hospital (27.7%), stories from other patients (24.6%), practical/personal experience (22.1%) and finally what one had seen as a patient (8.2%). Approximately three-quarters of responders (75.5%) did not feel that hospitals were doing enough to prevent HCAI-related infection. Three patients in Northern Ireland (2.9%) failed to keep a hospital appointment due to the fear of acquiring a HCAI during their visit to hospital. For two of these patients, the failure to attend a hospital appointment was on more than one occasion. Overall, in 2008/2009, there were 1,565,497 outpatient attendances recorded within DHSSPSNI (http://www.dhsspsni.gov.uk/volume_1_programme_of_care2pdf.pdf). In 10.8% of these scheduled attendances, the patient did not attend (7.4% of new referrals and 12.3% of review attendances). Therefore, if we attempt to estimate the total number of outpatient appointments missed in NI in the 2008/2009 period, potentially attributed to a fear of acquiring a HCAI, this crudely is 3,374 missed new referral appointments, which represents a significant cost to the HSC Trusts locally.

Unfortunately, we do not have any baseline data prior to the *Clostridium difficile* outbreak to make comparisons, although local rates appear to be higher, when compared to GB rankings . What is clear from these preliminary findings is that the fear of acquiring a HCAI from interacting with a HSC Trust is the dominant factor, ranking even higher than HSC waiting lists and that such anxiety is being driven by media reports. Statistically robust data is urgently required, particularly within the in-patient and out-patient setting, to inform policy, so that clear patient communication interventions are put in place to (i) communicate such risk to the patient in an informed and balanced manner, (ii) optimize patient management and (iii) avoid "missed" appointments by patients who fear attending a HSC Trust will result in a HCAI, thus saving the Trust valuable resources.

The authors have no conflict of interest.

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A THIRD STATUS

Editor,

As sometimes happens to asthmatic and epileptic patients, every now and then, a well controlled hypertensive patient also enters, for no apparent reason, a refractory hypertensive state that would demand urgent treatment with much higher doses of his usual medications and often with different and more powerful drugs to reverse it.

In line with the nomenclature used for the first two conditions, i.e., status asthmaticus and status epilepticus, I suggest we use for this particular hypertensive state, the name 'Status Angiotensus', meaning a refractory state of tense arterioles.

The author has no conflict of interest

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Abstracts

12th Annual Scientific Meeting of the Irish Society of Human Genetics, Friday 18th September 2009.

Nursing Building, Dublin City University, Ireland.

PROGRAMME:

10.00 – 11.00	Registration / Tea and Coffee
11.00 – 11.05	Welcome
11.05 – 12.00	Plenary I: Clinical Research - 4 Spoken Presentations:
12.00 – 13.00	**Keynote address:** "Ophthalmo-acromelic syndromes in mouse and man" **Dr David Fitzpatrick,** MRC Human Genetics Unit, Western General Hospital, Edinburgh
13.00 – 14.00	Lunch and Poster viewing
13.45 – 14.00	Council Meeting
14.00 – 15.30	Plenary II: Basic Research- 6 Spoken Presentations:
15.30 – 16.00	Tea and coffee / Poster viewing
16.00 – 16.15	Business Meeting
16.15 – 17.15	**Keynote address**: "Mapping complex traits - The human and canine genetic systems" **Dr Elaine Ostrander** National Human Genome Research Institute, NIH, USA
17.15 – 18.00	Wine reception / Presentation of Prizes / Meeting Close

SPOKEN PAPERS:

S01. Cytogenetic Analysis in Donor Cell Neoplasms.

Johanna Kelly[1], Natasha Coen[1], Lynn Barton[1], Michael O'Dwyer[2], Paul Browne[3], Eibhlin Conneally[3], David R. Betts[1]

[1]National Centre of Medical Genetics, Our Lady's Children's Hospital, Dublin, Ireland, [2]Department of Haematology, University College Hospital, Galway, Ireland, [3]Department of Haematology and Oncology, St. James's Hospital, Dublin, Ireland.

Donor cell neoplasms (DCN) are a rare entity, and the vast majority reported are either AML or ALL. We report two new cases (males, aged 25 and 43) that had an allogeneic SCT from female related donors in first CR following an initial diagnosis of AML and ALL and respectively. Both patients, approximately 5 years following transplant, re-presented with neoplastic disease which was shown to be of donor cell origin by cytogenetic methods. For patient 1, the AML showed an apparently normal karyotype. Following the occurrence of new myeloid-lineage related irregularities, a bone marrow aspirate displayed features of MDS/CMML. Cytogenetic analysis revealed a 45,XX,-7 karyotype, thereby proving the donor cell origin of disease. Cytogenetic analysis was not performed on the ALL of patient 2. On re-presentation with lymphadenopathy the bone marrow morphology was consistent with a diagnosis of DLBCL. Conventional cytogenetics was not possible, however, FISH analyses showed a MYC rearrangement and all cells had an XX sex chromosome complement. Both these patients are unusual in that their diseases have been seldom reported as donor cell neoplasms. This study demonstrates that in patients with a possible disease relapse following an allogeneic SCT a DCN also needs to be considered.

S02. Determination of the contribution of H63D/H63D genotype to iron overload, and validation of a dual hybridisation probe assay for detecting HFE genes.

Kathy Nolan, Mark Dobson, Joanne Brady, Christine Brady, David Barton.

National Centre for Medical Genetics, OLCH, Crumlin.

Hereditary haemochromatosis (HH), a disorder of iron metabolism, is caused by mutations in the HFE gene. Most patients are homozygous for the C282Y mutation, or compound heterozygotes for C282Y and H63D. The contribution of the H63D/H63D genotype to iron overload is not well characterised. We determined the prevalence of this genotype in 520 query affected HH patients (presenting with transferrin saturation >45%) in order to measure the contribution of this genotype to iron overload in the Irish population. Results were compared to the prevalence in 520 blood donors, as HH patients were excluded from donating blood in Republic of Ireland at the time of collection. We found that the H63D/H63D genotype was significantly over-represented in the iron overload group. The allele frequencies for all HFE mutations were found to be higher than previous estimates, indicating that only 51% of the Irish population have a normal genotype at this locus. A novel HH assay for the detection of HFE mutations using HybProbes on the Roche LightCycler was validated as part of the study. The assay was found to be 100% sensitive, specific, robust, repeatable and reproducible.

S03. Familial Learning Disability and dysmorphism due to a cryptic insertional translocation determined by CGH array.

Patricia Foley, Rosemarie Kelly, Nicole de Leeuw*, Andrew Green.

NCMG, Our Lady's Children's Hospital, Crumlin, Dublin 12, *Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

We describe a family of six individuals with severe unexplained

learning disability and dysmorphism in two generations who had been repeatedly investigated over a 15 year period, with no abnormality found. A cryptic chromosomal rearrangement had always been highly suspected but not proven until CGH array analysis. Affected family members showed similar facies of bitemporal narrowing, prominent jaw and abnormal palmar creases.

Array CGH analysis (whole genome; 32,000 clones with an average resolution of > 300 kb; UCSC genome browser May 2004 assembly) revealed an interstitial, 2.1 Mb loss in 2q36.3q37.1 (230.1-232.2Mb; 26 BACs, 18 genes) in three affected family members. The unaffected parent of each person carried a cryptic balanced 1:2 insertional translocation of 2.1 Mb of 2q36.3q37.1 into 1p13. Carrier testing has been carried out in nine healthy family members, and in one an asymptomatic duplication of 2q36.3q37.1 was noted.

We show how CGH array has 1. re opened a diagnosis for many families previously left without a cause for their disability 2. once a diagnosis is achieved allows carrier testing for asymptomatic family members 3. gives further insight as to the phenotypic variability of chromosome duplications.

S04. Mutational analysis of *COL8A2* in keratoconus and posterior polymorphous corneal dystrophy.

DP Dash, J Church, E Héon, CE Willoughby.

Queen's University of Belfast, Royal Victoria Hospital, Belfast and The Hospital for Sick Children Toronto.

Purpose: Mutations in collagen, type VIII, alpha-2 (*COL8A2*; MIM#120252) have been reported in posterior polymorphous corneal dystrophy (PPCD) and Fuch's endothelial corneal dystrophy (FECD). The role of *COL8A2* in PPCD and FECD remains controversial. Although PPCD and keratoconus (KCTN) involve different layers of the eye, PPCD has been associated with KC in several reports. The purpose of this study was to comprehensively screen *COL8A2* in PPCD and KCTN patients.

Methods: All patients had a full ophthalmic examination and the diagnosis of keratoconus and PPCD was made on the basis of clinical examination, a history of penetrating keratoplasty for keratoconus/PPCD and corneal topography. Mutational analysis of *COL8A2* was performed by direct cycle sequencing, in a multinational PPCD and KCTN patient cohort.

Results: A novel change, Ile171Val (c.514A>G) was detected in a PPCD patient. A previous reported pathogenic mutation in FECD, Arg155Gln (c.464G>A) was detected in a patient with KTCN from Canada. A previous reported pathogenic mutation in PPCD Thr502Met (c.1505C>T) was detected in a Canadian patient of Filipino ethnicity affected with PPCD. None of these variants were detected in Caucasian controls. Ile171Val was not seen in 24 black American controls. Arg155Gln and Thr502Met are reported in unaffected Japanese patients and we also found them in Filipino controls indicating racial polymorphisms.

Conclusions: Mutations in *COL8A2* play a minor role in the pathogenesis of posterior polymorphous corneal dystrophy and keratoconus, and are racially polymorphic.

S05. The Autism Genome Project: genome-wide association studies in autism.

Richard Anney, for the Autism Genome Project.

Department of Psychiatry, Trinity College Dublin.

Autism and autism spectrum disorders (ASD) are neurodevelopmental disorders that affect approximately 1 in 150 individuals and are characterized by deficits in reciprocal social interaction, communication and patterns of repetitive behaviours and restricted interests. Evidence to date supports high heritability and a complex genetic architecture. Thus far we have results from over 1500 ASD families, roughly half of the families we will analyze during this three-year phase of the AGP. This resource is sufficiently large to implement multiple analytical strategies for localizing susceptibility loci. We present data from association analysis from the additive model across three ancestry (all, Northern European and Southern European) partitions of the data split along two diagnostic group (any ASD) and a narrow diagnostic group (autism). At this point our results implicate only one gene from our main analyses, namely MACROD2. Other genes previously described in relation to autism have also been implicated by various splits of the data. The AGP is currently expanding the dataset to a replication analysis to 3000 ASD families. Whether these loci remain intriguing and whether new loci are implicated from this additional analysis will be determined by analyses to be presented at the 2009 ISHG.

S06. Mutation detection in 46 Retinitis Pigmentosa (RP) genes using targeted sequence capture and next generation sequencing.

Graeme R Clark, Dorota Muszynska, Sharon Alexander, Giuliana Silvestri, Colin E Willoughby, David A Simpson.

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

Introduction: Retinitis Pigmentosa (RP) is a clinically and genetically heterogeneous inherited retinal degenerative disease. Although the causative genes for approximately half of cases have been identified, it is currently difficult to test all of these and provide a genetic diagnosis for new patients. We have therefore developed a new high-throughput sequencing strategy to screen all known RP genes in a single assay.

Methods: A sequence capture array (Nimblegen) was designed which targets exons and splice sites of 46 known RP genes. Following enrichment of these regions from 5 RP patient DNA samples they were sequenced using a Genome Analyzer (Illumina). The ~10 million reads from each run were aligned to a reference sequence using Genomics Workbench software (CLCBio) and sequence variants detected.

Results: Analysis of the initial sequencing results confirmed the presence of a potentially pathogenic variant in RPGR in one sample. Many additional sequence variants, were identified, primarily known SNPs. The frequencies of novel variants are being assessed in a control population.

Conclusion: Targeted sequence capture followed by next generation sequencing provides an effective approach to the parallel screening of multiple genes, enabling the detection of both known and novel mutations in disease-associated genes.

S07. The use of SNP homozygosity mapping to identify disease genes in Irish families.

Jillian Casey[1], Judith Conroy[1], Regina Regan[1], Naisha Shah[1], Tiago Magelhaes[2], Andrew Green[3], Sally Ann Lynch[3], Sean Ennis[1].

[1]School of Medicine, University College Dublin, Ireland. [2]Instituto Gulbenkian de Ciencia, Oeiras, Portugal. [3]National Centre for Medical Genetics, Ireland.

Homozygosity mapping using high density SNP platforms has accelerated disease gene discovery in recent years. Compared to microsatellites, the resolution provided by SNP homozygosity mapping (SNP HM) offers a greater ability to fine-map the disease locus. We applied SNP HM to four disorders in consanguineous Irish families, 3 of which are Irish Travellers, an endogamous nomadic group. The disorders studied are microphthalmia (arCMIC), ACTH resistance (arACTHR), immunodysplasia (arIDS) and microcephaly. In the arCMIC study HM narrowed the genome-wide search down to four homozygous regions (0.9Mb) comprising 12 potential candidate genes. Of the 12 genes two emerge as strong functional candidates as both have been implicated in eye development. In one of the extended families with arACTHR we reduced the area of interest to 7 homozygous regions (1.38Mb with 9 genes). The arIDS study identified 33 candidate regions with 72 genes. In the microcephaly family, because of the level of homozygosity amongst the first cousin parents, we have only managed to reduce the candidate search to 188 genes. Further family samples from unaffected relatives should reduce the number of candidate genes to a manageable level. The candidate regions for arCMIC, arIDS and arACTHR are currently being sequenced in attempt to identify the disease-liable mutations.

S08. Analysis of the function of spartin, a protein mutated in hereditary spastic paraplegia.

Malgorzata Dytko, Paula Byrne.

School of Medicine and Medical Science, Conway Institute, University College Dublin, Ireland.

Hereditary spastic paraplegia describes a group of neurodegenerative diseases characterized by lower limb progressive weakness and spasticity. Troyer syndrome is an autosomal recessive form of hereditary spastic paraplegia caused by a frameshift mutation (1110delA) in the *SPG20* gene encoding spartin protein, the cellular function of which remains unknown. Knowledge about spartin interactors is also very limited. In this study we apply a broad spectrum of proteomics techniques to identify novel spartin binding proteins. We used a Tandem Affinity Purification technique followed by HPLC-mass spectrometry to characterize potential spartin binding partners. Selected putative interactions were confirmed by co-immunoprecipitation experiments. We identified 94 potential spartin-binding proteins which were grouped into functional categories. We performed co-immunoprecipitation experiments to confirm that spartin interacts with GRP78, GRP75 and nucleolin proteins. Additionally our mass spectrometry results confirmed previously published information about spartin interaction with ubiquitin and the E3 ubiquitin-protein ligases, AIP4/Itch and AIP5/WWP1. Our studies suggest that spartin is a multifunctional protein and for the first time we suggest a role for spartin in protein folding and turnover both in mitochondria and endoplasmic reticulum. We also show for the first time interaction between spartin and a nucleolar protein, nucleolin.

S09. Parental Origin Bias in *de novo* CNVs Detected in Autism Probands.

N Shah[1], R Regan[2], J Conroy[2], T Magalhães[4], J Casey[2], R Anney[5], A Green[3,2], L Gallagher[5], M Gill[5], DC Shields[1], A Vicente[4], S Ennis[2,3].

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Genetic variation occurs in humans at both individual and population level. One such variation that contributes to human genetic diversity is copy number variation (CNV) of genomic segments. In addition to contributing to common variation among healthy individuals, CNVs are associated with a number of genetic disorders and the susceptibility to complex disorders. It has also been shown that there is an association between *de novo* CNVs and complex disorders including autism spectrum disorder (ASD). Such *de novo* mutations could occur in either maternal or paternal germ line or in developing embryos.

We are investigating whether there is a parental origin bias for *de novo* CNVs in 380 Irish and Portuguese ASD probands, which were genotyped on the Illumina 1M beadarray. In our preliminary analysis of *de novo* CNVs, we observed a bias towards paternal origin ($P = 0.016$) for *de novo* deletions with 2 or more SNPs informative and congruent for defining parental origin from SNP genotype and intensity data (maternal: paternal origin ratio is 2:12 deletions). We also observed that there is a bias towards maternal origin ($P = 0.041$) for *de novo* duplication CNVs (maternal: paternal origin ratio is 31:16 duplications).

Further studies on the relationship between duplication and deletion *de novo* CNVs and their parent of origin may provide further insights into the molecular mechanisms during meiosis. Replication of this study in a larger dataset and experimental validation is to be followed.

S10. The MTHFR 677TT is Less Responsive to Folate and/or Riboflavin Deficiency Compared to the 677CC genotype as assessed by global gene expression changes.

Linda Hughes[1], Nicola Carroll[1], Christian Fiedler[1], Anne Parle-McDermott[1].

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The functional consequences of the MTHFR 677C>T polymorphism are a thermolabile enzyme that releases its FAD cofactor more readily than wildtype, particularly in combination with low folate status. While the impact of this polymorphism to the enzyme has been well researched, an understanding of how low folate status increases risk of such a range of common human diseases and how the MTHFR 677TT genotype exacerbates this risk is far from complete. The aim of this project was to investigate the early genetic changes associated with the initial response of cells to folate/riboflavin deficiency *in vitro* using gene expression profiling and cell lines homozygous for each MTHFR 677C>T allele.

Coriell® lymphoblast cell lines homozygous for each allele, 17274 (TT) and 17158 (CC) were grown for 12 days in folate deficient, riboflavin deficient, folate/riboflavin deficient and control media. Cells were harvested for RNA and subsequently hybridised to Affymetrix HG U133 plus 2.0 GeneChips. Analysis of the normalised data showed that the MTHFR 677TT cells showed less gene expression changes than the 677CC cells under all nutrient deficient conditions. This indicates that the 677TT cells already harbour a 'folate/riboflavin deficient' expression profile. Novel folate/riboflavin responsive genes and pathways are being further investigated in both cell lines.

POSTER PRESENTATIONS:

P01. Familial transitional cell carcinoma of the bladder.

Deirdre E Donnelly, Robin Brown, Patrick J Morrison.

Department of Medical Genetics, Belfast City Hospital Trust, Belfast BT9 7AB, UK.

Introduction: Transitional cell bladder carcinoma is common. The only aetiological factors identified so far are cigarette smoking and certain occupational exposures. Familial cancer of the bladder is not widely documented. However, it has been reported that there is increased risk to relatives once a case has been diagnosed which does not appear to be related to familial clustering of smoking. Further research in this area may lead to identification of candidate genes, leading to better understanding of the pathogenesis of bladder carcinoma and, ultimately, improvements in treatment.

Case history: We present a family with three cases of transitional cell bladder carcinoma in the same sibship. The proband was diagnosed at the age of 73 years, his brother at 76 years and his sister at 60 years. There are two other sisters, one diagnosed with breast cancer at 66 years and one diagnosed with basal cell skin cancer at 80 years.

Discussion: We discuss the possible modes of inheritance in this family and the potential for identifying candidate genes. Screening recommendations for at risk relatives is also reviewed.

P02. Familial Gall bladder carcinoma associated with malignant melanoma.

Patrick J Morrison, Deirdre E Donnelly.

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Introduction: Gallbladder cancer is rare - two familial cases are reported in the literature and it is unclear whether a familial entity exists. We describe a family with familial cancer of the gallbladder and melanoma.
Case History: The index case had an adenocarcinoma of the gallbladder diagnosed at 64 years, and melanoma aged 43. Her brother had an adenocarcinoma of the gallbladder aged 61 and was noted to have a 'porcelain' gallbladder on resection. Another brother had gallstones aged 52. Her son had melanoma aged 34. Her mother had gallstones requiring cholecystectomy at age 50 and died of pancreatitis aged 71.
Discussion: The combination of gallstones and gallbladder cancer suggests a predisposing gene which may be autosomal dominant. The concurrent history of melanoma could suggest a link between melanoma and adenocarcinoma of the gallbladder. We review the genetics of cholangiocarcinoma and suggest screening recommendations for patients with a family history of gallstones and / or at least one cancer of the gallbladder with regular ultrasound and biochemical investigations.
Conclusion: Cancer of the gallbladder has a hereditary component and patients with a history of gallstones or cancer of the gallbladder should be questioned about family history, and if positive, screening instigated.

P03. Replication of the finding that a SNP in the Human Renin gene enhancer region increases blood pressure.

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Variants in key genes of the renin-angiotensin system have the potential to modulate blood pressure (BP). Using a tag SNP approach, we aimed to capture maximal genetic variation in the angiotensinogen, renin, angiotensin converting enzyme and angiotensin converting enzyme 2 genes. We tested for associations of these variants with BP in two Irish occupational cohorts. Twenty-four hour ambulatory as well as clinic BP was measured in population I and clinic BP in population II. Individual SNP, haplotype, step wise regression and two-way SNP interaction analysis were performed.

Of the 22 tSNPs, only the REN-5312C/T SNP showed consistently significant associations with elevated diastolic pressures. Carriage of one REN-5312T allele was associated with the following age and sex adjusted increments in diastolic pressures (mean [95% CI], mmHg); Population 1, clinic 1.5[0.3,2.8], daytime 1.4[0.4,2.4], night-time 1.3[0.4,2.3]. Population 2, clinic 1.1[0.1,2.1]. Haplotypic analyses and multivariate analyses were in concordance with individual SNP analyses. The REN-5312T allele had previously been shown to result in increased in vitro expression of the renin gene. We have now shown, in two independent populations, that carriage of a REN-5312T allele is associated with elevated diastolic BP. Hence renin has been confirmed to be an important susceptibility gene for hypertension.

P04. Not Presented

P05. Tetrasomy 9p: a recognizable syndrome.

T Dabir, S McKee, S McCullough, L Rauch, G Smith.

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Tetrasomy 9p is a rare chromosomal aberration and was first described by Ghymers *et al*. in 1972. Since then less than fifty cases of tetrasomy 9p have been reported. Non-mosaic tetrasomy 9p cases have severe phenotype and poor prognosis. Previously described cases have a fairly recognizable phenotype comprising craniofacial, limb, uro-genital and cardiac abnormalities. We report 2 new cases of de novo non-mosaic tetrasomy 9p with similar clinical features.

Case 1: was diagnosed postnatally and survived for 10 days. She had dysmorphic features, large fontanelle, wide cranial sutures, hyper extended limbs with hip dislocations, Dandy-Walker malformation and congenital heart defects.

Case 2: was diagnosed antenatally and is currently 4 weeks old. The prenatal scan showed malrotated / hyper extended lower limbs with dislocated joints, complex congenital heart disease and Dandy-Walker malformation. She has similar dysmorphic features.

The most identifiable features of non-mosaic tetrasomy 9p seem to be characteristic craniofacial abnormalities, Dandy-Walker malformation, limb defects (hyper extended lower limbs with joint dislocations) and congenital heart defects. Antenatal diagnosis of tetrasomy 9p should be considered with these scan findings. The features noted in our cases and previously reported cases suggest that tetrasomy 9p is a recognizable syndrome with a distinct clinical phenotype.

P06. Does inhibition of the Methylation cycle Impact on the same Genes as Folate and/or Riboflavin deficiency?

Nicola Carroll, Linda Hughes, Anne Parle-McDermott.

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Folate is an essential nutrient and suboptimal levels are associated with numerous common complex diseases. However, our understanding of the molecular mechanisms underlying these disease associations remains incomplete. Since one-carbon metabolism involves both the DNA and the methylation cycle, effects of folate deficiency could be exerted through disruption of either, or both, of these cycles. We sought to identify gene expression changes that occur following inhibition of the methylation cycle in an attempt to identify those genes/pathways that could play a role in folate-related disease risk.

A lymphoblast cell line was cultured in the presence of 10mM cycloleucine for 24 hours. RNA was then extracted from both control and treated cells, and microarray analysis was performed using the GeneChip® Human Genome U133 Plus 2.0 array in triplicate to identify differences in their gene expression profiles. A total of 91 genes were found to be up-regulated and 155 genes down-regulated in cycloleucine-treated cells following stringent statistical analysis ($P < 0.01$). Pathway analysis of differentially expressed genes revealed a significant association with several biochemical pathways. We have focused on one pathway that also responded to folate deficient conditions. We are currently confirming this pathway association in additional nutrient deficient experiments.

P07. PTEN - a family's story.

Alex Magee.

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PTEN hamartoma tumour syndromes (PHTS) are rare, and include Cowden syndrome, Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome and possibly Proteus syndrome. A common feature is cellular overgrowth leading to multisystem benign hamartomata.

This boy was referred at age 16m. Macrocephaly was suspected antenatally. He was born at 38wks, birth weight 4680gm. Hypotonia was immediately noted, as well as macrocephaly. Multiple investigations ensued. Development was delayed and parents had to cope with differential diagnoses of trisomy 21 and cerebral palsy. At consultation, it was noted that father was macrocephalic, and reported his own father was the same. PTEN was considered and a mutation confirmed – exon2 c.138C>A. At review, parents decided to pursue carrier testing and the mutation was confirmed in his father. They expressed concern about their older son. They felt he was macrocephalic (developmentally normal) and had been seen by ENT because of huge tonsils. On examination, it was considered likely that he too was affected and this was confirmed.

The couple hope to pursue PGD. They are aware that PTEN syndromes are underdiagnosed and feel that opportunities for clinical diagnosis were missed. They hope that their story will alert clinicians to the condition.

P08. Natural History of a Case of Fucosidosis.

Gillian Rea, Fiona Stewart.

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Fucosidosis is a rare Lysosomal Storage Disease. Inheritance is autosomal recessive. First described by Durand in 1966, there have been less than 100 reported cases. Although the ethnic origin shows a world-wide distribution, two populations with a relatively high incidence are Italians and the Mexican-Indian Population of New Mexico and Colorado in the USA. The severe deficiency of Alpha-L-Fucosidase leads to accumulation of fucose-containing glycol-lipids, glycol-proteins and oligosaccharides in various tissues. Features include (in descending order of frequency seen) progressive mental deterioration, progressive motor retardation, coarse facies, growth retardation, recurrent infections, dysostosis multiplex, angiokeratoma corporis diffusum, visceromegaly and seizures. Originally divided into type I (severe) and type II (mild), it is now recognised that there is a wide continuous clinical spectrum. There are 22 known mutations and all lead to nearly absent enzymatic activity. Suggesting clinical variability is not due to the nature of the mutation but to secondary unknown factors. Although the angiokeratoma corporis diffusum is a clinically useful hallmark of the condition, it may either be absent or not visible at the time of presentation. We present the case of a ten year old girl born to consanguineous parents who was diagnosed at two years of age.

P09. Successful Treatment of Mucopolysaccharidosis Type II (Hunter Disease) With Idursulfase in a 36 year old man.

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Our patient was diagnosed with Mucopolysaccharidosis (MPS) Type II at the age of 12 years. MPS II is caused by a deficiency of iduronate sulphatase which is one of the lysosomal enzymes. Unwanted mucopolysaccharides are stored within various tissues in the body. Developmental outcome ranges from severe learning disability to normal intelligence as is seen in our patient. Our patient had short stature, characteristic facial features, joint contractures and marked hepatosplenomegaly. He developed worsening respiratory problems and at age 28 he was started on overnight CPAP. His FEV1 dropped from 0.98 to 0.46. He started on idursulfase (Elaprase ®) in June 2007 at the age of 36. He was gradually able to reduce his CPAP and within a year this was discontinued. His saturations are now 99% in room air. His hepatosplenomegaly has reduced and his waist is four inches smaller. He has much more energy and was able to cook Christmas dinner unaided. His joint contractures are also improving slightly.

This case demonstrates that treatment of an older MPS II individual may lead to a significant improvement in their clinical condition and quality of life and that treatment should not be discounted on the grounds of age.

P10. Tissue Specific Mosaicism of a der(18) in a Developmentally Delayed Boy.

Linda McArdle[1], Sally Ann Lynch[1], Sean Ennis[2], Thomas Morris[1], David R Betts[1].

[1] National Centre of Medical Genetics, Our Lady's Children's Hospital, Dublin, Ireland [2] School of Medicine and Medical Science, University College Dublin.

Chromosomal aberrations are frequently associated with developmental delay and in most cases they can be identified by

analysis of peripheral blood. However, in rare cases tissue specific mosaicism may exist. We report a boy who on initial examination showed colobomas of the optic discs, developmental delay and epilepsy. Cytogenetic analysis on peripheral blood was performed but showed a normal 46,XY karyotype. At 1-year-old there was a development of obesity and constriction rings on arms and legs were also noted. Based on these findings, FISH analysis was performed to exclude a microdeletion of the Smith Magenis region. A follow up examination at 18 months showed microcephaly, refractory epilepsy and a MRI showed delay in myelination. As both obesity and constriction rings are seen in pigmentary mosaicism, a skin biopsy was performed and chromosome analysis of fibroblasts showed the following karyotype:

46,XY,der(18)inv dup(18)(q11.2q21.2)del(18)(q21.2)[14]/46.XY[6]

We could thereby demonstrate a mosaic partial trisomy of 18q11.2-21.2 and partial monosomy for 18q21.2-qter. A subsequent FISH analysis on buccal mucosa smears indicated that approximately 85% of these cells contained the der(18). This patient did not demonstrate the typical clinical picture associated with duplications and deletions of chromosome 18. The milder phenotype may be attributable to tissue-limited mosaicism.

P11. Not Presented

P12. Investigating promoter hypermethylation of wnt signalling antagonists in prostate cancer.

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Wnt signalling activates cell proliferation and pro-survival genes through nuclear translocation of βcatenin. Secreted Frizzled-Related Proteins (SFRPs) block Wnt signalling, resulting in phosphorylation and degradation of βcatenin, and thus loss of expression of its target genes. Aberrant activation of Wnts is well documented in human cancers, including prostate. We are investigating promoter hypermethylation and associated epigenetic silencing of *SFRP*s in CaP.

Methylation of *SFRP1*, *SFRP2*, *SFRP4* and *SFRP5* was investigated in CaP cell lines and tissue samples of CaP (n=40), benign prostatic hyperplasia (BPH) (n=37), histologically normal prostate (n=39) and preinvasive high-grade prostatic intraepithelial neoplasia (HGPIN) (n=15). *SFRP* gene expression was evaluated using the Human Wnt Signaling TaqMan Low Density Array.

Methylation frequencies in CaP were 11.11% (*SFRP1*), 72% (*SFRP2*), 0% (*SFRP4*) and 30% (*SFRP5*). *In vitro* studies revealed *SFRP2* hypermethylation in CaP cell lines (LNCaP, DU145, PC-3 and 22Rv1). Significantly lower *SFRP2* methylation frequencies and quantitative levels were found in histologically normal prostate (10.52%; relative methylation score (RMS)=0.35), BPH (11.54%; RMS=0.05), and HGPIN (15.38%. RMS=1.39) compared with CaP (72%; RMS=56.64), $P<0.0001$. Methylation of *SFRP2* was not significantly associated with tumour grade ($P=0.47$) or TNM classification ($P=0.38$), indicating that it is widespread throughout all grades and stages of CaP. Quantitative RT-PCR confirmed differential expression of *SFRPs* in CaP compared with benign prostate tissue.

We demonstrated that hypermethylation of *SFRP2* is a frequent event in the pathogenesis of CaP. Methylation of SFRP2 may be a useful marker of CaP.

P13. Testing times: when the BRCA1/2 test comes back negative in families with a strong history of breast +/- ovarian cancer.

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Approximately 70% of families with a clear-cut autosomal dominant transmission of breast +/- ovarian cancer will carry a mutation in BRCA1 or BRCA2, but the pickup rate in most high-risk families is significantly lower than this. Many small families may still have a predisposing mutation, but lack a highly suggestive pedigree, whereas large families may display ascertainment bias. Many units now triage gene testing using the "Manchester Scoring System", which allots a score to each cancer in a lineage, and only those families meeting the scoring threshold are routinely tested. However, the DNA sample typically comes from a single affected family member; if the result comes back negative, this can mean a number of things. Firstly, the cancers may represent a chance cluster. Secondly, there may be a mutation (in BRCA1, BRCA2 or another gene) that cannot be detected by the test. Thirdly, there may still be a detectable gene in the wider family, but the person tested may have a coincidental cancer unrelated to the family mutation. Identifying families for further testing is important, and can be based on statistical analysis of the pedigree, enabling rational targeting of resources and maximisation of the chances of picking up clinically relevant mutations.

P14. Monozygous Twins discordant for Landau-Kleffner Syndrome.

SA Lynch[1], M King[2], J Conroy[3] S Ennis[1,3].

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Landau-Kleffner syndrome (OMIM 245570), also known as a syndrome of acquired epileptic aphasia, was first described in 1957. The disorder is characterised by gradual or rapid loss of language in a previously normal child. All children have abnormal EEG compatible with the diagnosis of epilepsy; however, only 70% have clinical seizures. Additional features include behavioural disturbances (including on occasions features consistent with autism), cognitive regression of variable degree, and sometimes motor difficulties, highlighting the pervasive nature of the disorder. Males are more frequently affected than females (ratio 2:1). The aetiology for this syndrome remains unclear.

We report a case-study of monozygous female twins discordant for LKS. A previous MZ discordant twin pair with the same syndrome has been reported by Feekery *et al*[1]. In this case-report, one of the twins presented at 3 years of age with developmental concerns, regression of speech and epilepsy. Her unaffected twin continues to develop normally. This study examined the potential role of CNVs in the occurrence of LKS using the Illumina 1M Infinium SNP array. We also investigated the possible role of differential methylation, as a similar disease mechanism is observed in discordant MZ twins for Beckwith-Wiedemann syndrome. Results will be presented at this meeting.

[1.] Feekery CJ, Parry-Fielder B, Hopkins IJ. Landau-Kleffner syndrome: six patients including discordant monozygotic twins. *Pediatr Neurol* 1993;**9(1):**49-53.

P15. Investigation of the NOS1 Ex1f VNTR and cognitive function in schizophrenia.

Emma M Quinn, Sarah Furlong, Michael Gill, Aiden P Corvin, Gary Donohoe, Derek W Morris.

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Schizophrenia is a chronic debilitating psychiatric disorder that affects approximately 0.5-1% of the population worldwide. The neuronal isoform of nitric oxide synthase (NOS1) gene has been identified as a putative susceptibility gene for schizophrenia based on previous linkage and association results and its glutamatergic functions within the brain. We previously reported an association between NOS1 and verbal IQ and working memory, two neurocognitive endophenotypes commonly studied in schizophrenia research. This finding was replicated in an independent German sample (Donohoe et al, *in press*). The NOS1 genetic variant in this study was a SNP (rs6490121) located in intron 10 of the gene that had no obvious impact on gene function. A highly polymorphic dinucleotide repeat termed NOS1 Ex1f VNTR is located in the NOS1 promoter. The short alleles of this VNTR are associated with decreased transcriptional activity of NOS1. Data from HapMap indicates that the risk G allele of rs6490121 is in linkage disequilibrium with the short alleles of NOS1 Ex1f VNTR. We investigated this putative functional mechanism of cognitive performance dysregulation at NOS1 by analyzing this VNTR in our schizophrenia case-control samples. The results of this study indicate that VNTR is not associated with verbal IQ and working memory but is associated tests of episodic memory. While working memory tasks are more sensitive to pre-frontal brain function, episodic memory is more reliant on temporal lobe function. The discrepancies in findings for working memory (associated with the NOS1 SNP rs6490121) and episodic memory (associated with the NOS1 VNTR) may relate to differences that reflect the more ubiquitous influence of NOS in brain function that is being differently emphasised across the two studies.

P16. First patient with 16p11.2 submicroscopic deletion detected by array CGH in Northern Ireland Regional Genetics Service.

Lisa Bradley, Simon McCullough, Peter McGrattan, Susan McNerlan, Geoff Smith, Mervyn Humphreys, Vivienne McConnell.

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The 15 month old female proband is the first child of non-consanguineous parents born after a pregnancy using assisted conception. Complex congenital cardiac disease, dysmorphism, cleft palate, right strabismus, growth retardation and developmental delay, are the cardinal features observed in the proband. Echocardiogram showed complete AVSD, supracardiac TAPVD and PDA.

The following genetic investigations were normal: karyotype, 22q11and 9q34.3 FISH, subtelomere (P036D) MLPA screen, and microdeletion/duplication (P245A2) MLPA screen. Both parents showed dysmorphic features. The 41 year old mother also had learning difficulties and short stature, while the 34 year old father had two brothers with learning difficulties and epilepsy and reported a great-uncle dying at 3 days old of an unknown cardiac condition.

Array CGH analysis using the Agilent Oligo 4x44k platform detected an approximate 0.5Mb deletion within the short arm of chromosome 16, region 16p11.2, from base pair 29581456 to base pair 30106254. This ~0.5 Mb deletion was confirmed using the Illumina HumanCytoSNP-12 platform and microdeletion/duplication (P297B1) MLPA screen.

Both parental karyotypes and microdeletion/duplication (P245A2 and P297B1) MLPA screens were normal, excluding an inherited abnormality. Parental array based CGH results are pending.

The case presented is the first positive microarray analysis result from the NIRGS following the recent introduction of array CGH to our repertoire of clinical genetic investigations.

P17. The application of Multiplex ligation-dependent probe amplification (MLPA) for investigation of pregnancy loss.

Simon McCullough[1], Niall Kissick[2], Geoff Smith[1],Mervyn Humphreys[1].

[1]Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast. [2]Department of Biochemistry, Queens University, Belfast.

Approximately 15-20% of clinically recognised pregnancies end in spontaneous abortion. Around 50% of these losses will have abnormal karyotypes following chromosome analysis. The most common chromosomal abnormalities in first trimester abortuses are autosomal trisomies, monosomy X and triploidy. One in 500 individuals are carriers of balanced translocations and these individuals have a higher incidence of pregnancy loss due to unbalanced segregants at meiosis. Chromosome analysis is therefore an important test in the investigation of pregnancy loss. This not only provides a reason for the loss of the pregnancy but also identifies those couples who require follow up karyotyping or amniocentesis in future pregnancies. Culturing of tissue samples from spontaneous abortuses often has a low success rate due to the quality of sample received and their delay in transit to the laboratory. The MLPA technique is performed on DNA and therefore does not require cells to be cultured. We have used subtelomere MLPA to investigate tissue samples received from spontaneous abortions and intra-uterine deaths. We will show that this technique has a high success rate compared with karyotyping and is reliable in the detection of chromosomal aneuploidy in tissue samples.

P18. Evaluation of long range PCR methods for resequencing of schizophrenia candidate genes using next generation sequencing technology.

Amy S Gates, Elaine M Kenny, Lynne E Cochrane, Colm T O'Dushlaine, Emma M Quinn, Michael Gill, Aiden P Corvin, Derek W Morris.

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

Schizophrenia is a devastating complex neuropsychiatric disorder, affecting approximately 1% of the population, with significant health, social and economic impact in Ireland. The disorder is highly heritability and may be caused by abnormal neurodevelopment. Recent genome-wide association studies (GWAS) have identified a number of large copy number variants, which appear to be highly penetrant risk factors for schizophrenia (ISC, 2008). This consortium has also identified a number of loci where common genetic variation is contributing to schizophrenia risk (ISC, in

press). A project underway in our group is to study schizophrenia candidate gene(s) regions identified by this GWAS and identify all common genetic variation at these loci and map true schizophrenia causal variant(s).

A pilot resequencing project was designed to resequence genomic locations of interest in a control population of HapMap samples using next generation DNA sequencing technology.

We found very high concordance between SNPs called from the sequences generated on the Illumina platform and known HapMap SNPs for each individual DNA sample.

This pilot study has shown that ultra-high throughput technology is extremely useful in the rapid sequencing of genes and can generate dense maps of genetic variation for study of common variants associated with disorders such as schizophrenia.

P19. Development of methods for resequencing of genes using indexed DNA samples and the SureSelect target enrichment system on the Illumina Genome Analyzer.

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

Next-generation sequencing technology has allowed sequencing of whole genomes to be carried out in standard molecular genetics laboratories. However, an important application of this technology is sequencing of specific genomic regions, for example disease genes in patient samples. In order to sequence parts of the genome of interest, a number of methods have been developed including long range (LR) PCR and microarray capture. Agilent Technologies have developed the SureSelect Target Enrichment System which allows targeting of 3.3Mb of the genome by using cRNA baits. Indexing methods have also been developed for next generation sequencing that allow multiplexing of samples in one sequencing library. We have combined the SureSelect Target Enrichment System with an indexing protocol to develop a cost-efficient method for targeting smaller regions of the genome in multiple DNA samples. We evaluated this method by comparing the sequence data produced using DNA enriched with the SureSelect system to data generated by a LR PCR enrichment of the same target sequence.

We will present data on the performance of the SureSelect method in comparison to the LR PCR method in HapMap test samples and present a protocol that will be extremely useful in the rapid sequencing of target genomic regions.

P20. Spectrum and incidence of BRCA1 and BRCA2 mutations in the Republic of Ireland – An Audit.

Trudi McDevitt[1,2], Mary Higgins[1,2], Anne Crowley[1,2], Nuala Cody[1,2], Marie Meany, Cliona de Baroid, Maureen Adams[1,2], Carmel Nolan[3], Michael Farrell[3], Eileen Berkeley[3], Roisin Clarke[3], Peter Daly[3], Andrew Green[1,2], David Barton[1,2].

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Comprehensive mutation screening of BRCA1 and BRCA2 has been available to Irish breast cancer families since 2005 via our Centre. We present an audit of the data to date. In total, pathogenic mutations have been identified in 154/462 families (33%). The spectrum of these mutations comprises nonsense (BRCA1: 21, BRCA2: 3), frameshift (BRCA1: 30, BRCA2: 56), splice-site (BRCA1: 7, BRCA2: 2), substitution (BRCA1: 5, BRCA2: 6) and large deletions (BRCA1: 22, BRCA2: 2). Overall, the incidence of large deletions was found to be approximately 5% in the patient group screened to date, accounting for approximately 15% of the total mutation incidence, and appears to be higher than that reported by other populations to date. Eight mutations have been identified in more than 3 apparently unrelated families: BRCA1: p.E143X (19), c.1294_1333del40 (7), exon 3 deletion (4), exon 21-24 deletion (4); BRCA2: c.8525delC (9), c.983del4 (6), c.2117delC (7). We present preliminary haplotype data for one of these recurrent mutations, which supports the presence of a possible founder effect. In addition, a large deletion encompassing exons 1-23 of BRCA1 has been identified in 4 families. We present microarray data which suggests that this may be an identical rare deletion in 4 apparently unrelated families.

P21. Association between polymorphisms in the gene regulated by estrogen in breast cancer 1 and bone mineral density variation in Caucasians.

KG Hegarty[1], M Daly[1], S Chavrimootoo[1], F Shanahan[3], MG Molloy[2].

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Using informative SNPs, we performed a gene-wide association study between a positional candidate gene, the gene regulated by estrogen in breast cancer 1 (*GREB1*), located at 2p25 and variation in bone mineral density (BMD) at the lumbar spine (LS) and the femoral neck (FN). Single marker and haplotype-based association testing was performed in a family-based discovery cohort (n = 508 (n = 229 families)) and a postmenopausal population-based replication cohort (n = 477). Significant total- and within-family association was observed between GREB1_03 (A/G; MAF 0.09) and variation in FN BMD (P = 0.003 and 0.004, respectively). There was significant within-family association observed between GREB1_03 and LS BMD variation (P = 0.005). In the replication cohort, GREB1_03 was not significantly associated with variation in BMD at either skeletal site (P > 0.05). Another GREB1 polymorphism, GREB1_04 (A/C; MAF 0.38), was significantly associated with FN BMD (P = 0.005). GREB1_04 is located in the same HapMap LD block as GREB1_03. *In-silico* analysis suggests that the associated markers may affect *GREB1* enhancer binding and splicing regulation. These results suggest that variation within *GREB1* may contribute to BMD variation. Replication in larger, independent studies is required before functional analysis is undertaken.

P22. The Northern Ireland Tuberous Sclerosis Complex Database - TSC1 & TSC2 mutations in the tuberous sclerosis complex population in Northern Ireland.

Hilda Crawford, Charles Shepherd, Shane McKee, Patrick J Morrison.

Northern Ireland Genetics Centre, Belfast Trust, A Floor, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

Introduction: There is almost complete ascertainment of the TSC population in Northern Ireland with 90 living and 8 deceased patients in 72 families in a general population of 1.68 million. The Northern Ireland Tuberous Sclerosis clinic offers a clinical genetic

service to TSC families. Mutation analysis is routinely offered to affected patients.

Results: In our database, 15 individuals in 8 families have a mutation in TSC1 and 34 individuals in 23 families have a mutation in TSC2. In 1 TSC2 family, a mutation negative parent of an affected child is presumed mosaic. In 6 families, no mutation was found. In 1 family, there is a presumed non pathogenic mutation in TSC2. In 3 families, results are pending. In the remaining patients, mutation analysis has not been done.

Conclusion: Identification of mutations in TSC confirms diagnosis and offers genetic testing to family members. It offers the possibility of prenatal genetic diagnosis for families who wish to exercise this choice. For clinicians, it offers a greater understanding of the condition and the possibility of genotype phenotype correlation.

P23. The incidence of Fragile X syndrome in Northern Ireland, 2000-2006.

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Introduction: Fragile X is thought to be one of the commonest genetic causes of mental retardation. Affected individuals can also have autistic/behavioural problems, speech delay and seizures. On examination, patients have a large head with prominent forehead and large ears. Fragile X is X-linked and is much commoner, and more severe, in males. It is caused by a triplet repeat expansion on the X chromosome and carrier/pre-mutation repeats can be found in parents.

Audit: We examined our database for cases of Fragile X syndrome diagnosed between 1st Jan 2000 and 31st December 2006. We also identified patients diagnosed with Fragile X syndrome who were born in this 6 year period. Patient data was compared to find the commonest presenting features.

Discussion: In total, 23 were diagnosed and 3 were born within the study period. This gives an incidence figure of 0.0028 per 10,000 live births per year. This figure is much lower than would have been expected and we suspect that there may be a degree of under-diagnosis in our population. We would like to raise awareness of Fragile X and its common clinical features.

P24. Incidence of Fragile X syndrome in the Republic of Ireland.

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The incidence of Fragile X varies from 1 in 2300 to 1 in 6,000 and there's evidence of geographical variation, with Taiwan having a low incidence (~ 1 in 10,000) compared to an incidence of ~1:2500 in Spanish newborns. Here we report the incidence of Fragile X cases identified at the NCMG and the Northern Ireland Regional Genetics Centre. There were 423,983 live-births in the Republic of Ireland (ROI) between 2000-2006 and 16 new cases of Fragile X were identified in that period. However, only 5/16 Fragile X cases were born between these years (2 cases were identified in 2007 & 2008). This is a minimum incidence of 0.17 per 10,000 births [1 in 60,569 births]. As many hospitals on the Western seaboard send samples to genetic testing centres outside of the ROI, recalculation of the data using births for the Eastern seaboard (282,000) gives an incidence of 0.21 per 10,000 (1 in 47,619). Despite that Fragile X is a common request referral to NCMG, the overall pick-up rate (approx 0.3%) is low and the incidence of Fragile X is very low compared to other countries. It is possible that testing may not have been targeted at the right patient group or that many cases have yet to be identified (i.e. children born in 2005 and 2006 have yet to 'worked up' by the paediatricians). The absence of a founder effect in the ROI or the possibility that the incidence is much higher in Irish counties where samples have traditionally been sent elsewhere may also account for the low incidence reported here.

P25. Maternal UPD 16 and low level mosaic trisomy 16 observed in Amniotic Fluid following non-mosaic trisomy 16 in CVS.

Claire J Breen[1], Bronagh O'hIci[1], Marice Mullarkey[1], Aiveen Carey[1], Rosie O'Shea[1], Andrew Green[1], David E. Barton[1], Fergal Malone[2], and David R. Betts[1].

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Trisomy 16 is the most commonly observed trisomy in first trimester miscarriages, accounting for over 30% of autosomal trisomies. Mosaic trisomy 16 has rarely been reported at second trimester amniocentesis and it is even more exceptional for it to be seen in liveborns. We report a case of trisomy 16 observed in a CVS taken at 13 weeks gestation referred for a high triple test score. A subsequent amniocentesis taken at 17 weeks revealed a karyotype of 46,XX in all 30 cells analysed. UPD 16 studies were also carried out on cultured cells from the amniocentesis with a range of polymorphic chromosome 16 markers. This showed maternal UPD 16 and a low level, paternal in origin, trisomy 16. Retrospective interphase FISH analysis with an Abbott 16 centromere probe showed approximately 10% mosaic trisomy 16. It is most likely that the fetal UPD 16 arose as the consequence of a 'correction' or 'trisomy rescue attempt' of an initially trisomic conceptus, which in turn was due to a maternal nondisjunction event. It is recommended that amniocentesis, UPD studies, and detailed ultrasound examinations should follow detection of trisomy 16 observed at CVS.

P26. Not Presented

P27. The copy number variant *LCE3C_LCE3B-del* on chromosome 1 confers susceptibility to psoriasis in the Irish population.

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Psoriasis (OMIM#177900) is an inflammatory condition of the skin and joints, which typically manifests as areas of inflammation and abnormal skin growth. Prevalence in European populations is approximately 1-2%. Both genetic (including HLA) and non-genetic (stress, streptococcal infection) factors are believed to play a role in susceptibility. A common copy number variant (CNV) involving the deletion of the *LCE3C* and *LCE3B* genes in the late cornified envelope gene cluster (1q21.3), which encode skin barrier proteins, has recently been associated with susceptibility to psoriasis

in several European populations. We have genotyped this deletion and 3 physically associated single nucleotide polymorphisms (SNPs, rs17659389, rs10888502, rs4112788) in 441 Irish psoriasis patients and 983 Irish controls. In addition, we genotyped 3 SNPs (rs1062470, rs130079, rs130076) in the known HLA associated region. There was strong association with all HLA SNPs ($P < 10^{-6}$). As noted in previous studies, *LCE3C_LCE3B-del* was in complete linkage disequilibrium with the *rs4112788-T* allele. Haplotype analysis showed an association between the *rs4112788-T*/*LCE3C_LCE3B-del* haplotype and disease (P = 0.02). Our results, therefore, confirm observations from other European populations. Interestingly, the observed frequency of *LCE3C_LCE3B-del* in Ireland is among the highest observed, to date, with 49% of Irish people homozygous for the deletion.

P28. The European Molecular Genetics Quality Network (EMQN).

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Molecular Genetics testing forms an increasingly important part of the diagnostic process in all branches of medicine. Studies of the reliability of such testing have indicated a significant level of inaccuracy in laboratory reports, arising from errors in sample identification, genotyping or interpretation. The European Molecular Genetics Quality Network (EMQN) aims to raise and maintain the quality of Diagnostic Clinical Molecular Genetics Testing by providing external quality assessment (EQA) schemes. In 2008 EMQN provided 22 disease specific and 2 technique specific EQA schemes. The EMQN's schemes are organised by a panel of experts and DNA samples are send to participating laboratories once a year. Participating laboratories are asked to perform their routine analysis and interpret the results. The reports are marked by a group of experts. The participants receive a report on their performance.

400 laboratories from 42 countries around the world participated in the EQA schemes in 2008 and over 1400 reports were evaluated from laboratories. The standards of genotyping accuracy were high but significant error rates were found and methods of reporting and interpreting data were varied. The error rate indicates a clear need for EQA to measure current standards of proficiency and encourage laboratories to raise their technical and reporting performance. EMQN is now the world's largest provider of EQA for genetic testing.

P29. Mapping homozygosity in Irish sporadic ALS patients to identify recessive susceptibility loci.

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Studies have shown that extended runs of homozygosity (ROHs) across the genome are common in European populations. These may be evident in genome-wide single nucleotide polymorphism (SNP) datasets as an improbably high number of successive homozygous genotypes. Mapping the locations of ROHs common to a particular phenotype may reveal recessive trait loci. Using the computer programme PLINK, we have attempted to map ROHs in an Irish population and specify overlapping, allelically-matching ROHs common only to a subset of this population described phenotypically by a neurological condition called amyotrophic lateral sclerosis (ALS). Gene ontology analysis has shown an overrepresentation of neurologically important genes in the ALS group compared to controls. Using this ROH mapping technique, various biologically plausible candidate regions across a number of chromosomes have been revealed as potential recessive disease loci. Deep re-sequencing of these regions may indicate the locations of recessive mutations conferring ALS susceptibility.

P30. Genomic Analysis of Single Nucleotide Polymorphisms (SNPs) among Children and Adults Treated for Acute Lymphoblastic Leukaemia: A Single Centre Study.

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School of Nursing, Dublin City University, Glasnevin, Dublin[1], Belfast City Hospital, Dept of Haematology, Lisburn Road, Belfast BT9 7AB[2], Trinity College Dublin, School of Molecular Medicine, Dublin[3].

Aim: The objective of the study was to explore if their was a relationship between overall survival and amplifications / deletions of diagnostic genes in adults and children treated on protocols UKALL XII and UKALL 2003. Adults (n = 15) treated on the UKALL XII protocol, (males n = 8 53.3%, females n = 7 46.7%), age range 15-67 yrs. Children (n = 12) treated on the UKALL 2003 protocol (males n = 7 58.3%, females n = 5 41.7%), age range 7 months – 16 yrs.

Methods: Bone marrow / peripheral blood samples were obtained at diagnosis. DNA was applied to Affymetrix Genechip Human Mapping Genome-Wide 5.0 SNP array.

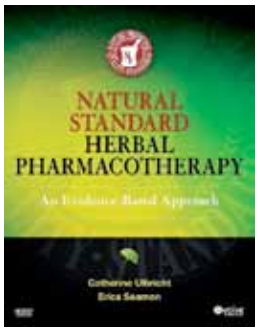
Results: There were significant differences in overall survival times between patients who expressed or did not express amplifications on chromosome 9 ($\chi 2 = 4.270$, df = 1, p = 0.039) with median survival times in those who did not express the amplification 5.7 months versus 21 months in those who did. N = 8 (89%) of children / adults who did not express amplifications on chromosome 9 died during this period. In those who did express amplifications on chromosome 9 n= 5 (31%) died.

Overall survival times for patients who expressed and did not express deletions on the CDKN2A gene approached significance ($\chi 2 = 3.779$, df = 1,p = 0.052) with median survival times in those who expressed deletions 14 months and 20 months in those who did not.

Conclusion: Further exploration of these amplifications/deletions is indicted using larger sample sizes.

Book Reviews

NATURAL STANDARD HERBAL PHARMACOTHERAPY. AN EVIDENCE BASED APPROACH



Catherine Ulbricht, Erica Seamon. Mosby Elsevier, August 2009. Hardback, 648pp. £49.99. ISBN: 978-0-323-05184-2.

This text, published in late 2009, presents an excellent guide to herbal pharmacotherapies and is well laid out. Evidence is graded from A (Strong scientific), B (good), C (unclear or conflicting), through to D (fair negative). A series of chapters on relevant organs and diseases including Parkinson's disease, insomnia, and pain, are very comprehensive.

Several diseases had some commendable and also some interesting treatment suggestions. For rheumatoid arthritis, I was interested to see Borage; and for osteoarthritis, avocado and rose hip, all listed as grade B evidence. Willow is listed as grade A (due to its aspirin effect), so some potential help for sufferers wishing to avoid mainstream treatment or as an adjunct. A helpful section on each treatment gives the mechanism of action, and lists the evidence and dose for treatment, along with potential side effects. Each chapter ends with some case studies and an integrative therapy plan. There are review questions to test the reader's knowledge.

The chapter on cancer was particularly helpful as most therapies listed have negative effects and the remainder have no real benefit and the evidence base (or lack of it) may be reassuring to show to patients who are conned into potential purchases of remedies because of desperation.

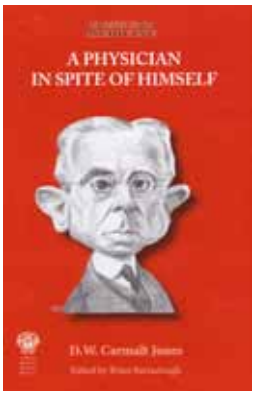
Not many listings for Grade A are in the book, but there are a few. I noticed with interest that kava has a grade A recommendation for insomnia and anxiety if used for <1-2 months, and this reminded me of when I worked in Vanuatu in the South Pacific, in the mid 1980's, of the ritual kava ceremonies which often induced relaxation if not overt sleep in the participants.

The colour plates in the centre of the book enhance it considerably with several excellent pictures, and the appendices on adverse effects, and pregnancy and lactation are very useful.

General Practitioners and general hospital physicians will be interested in having a copy of this book in the surgery or ward to check whether a remedy that a patient has taken is of any use. Obstetricians will also find this useful in determining the safety and efficacy during pregnancy and lactation. The website linked to the book has some good references and additional information. This is an excellent book which fills the large gap in evidence that existed in this area.

Prof Patrick Morrison

A PHYSICIAN IN SPITE OF HIMSELF



D.W. Carmalt Jones. The Royal Society of Medicine Press. July 2009. Hardback.268pp. £35.00 ISBN: 978-1-85515-905-3

This high quality hardback publication from the Royal Society of Medicine Press is the first volume in a new series "Lives in Medicine" and recounts the life of London-born physician and polymath Dudley William Carmalt Jones (1874-1957), based largely on his hitherto unpublished autobiography.

From a Victorian upper middle class background, he read Classics at Oxford and qualified at St. Mary's Hospital medical school. Appointed Casualty Physician at St. Mary's in 1907, he also worked under Sir Almroth Wright in the Inoculation Department where he developed an interest in vaccine therapy. There he befriended Alexander Fleming and also met Robert Koch and Paul Ehrlich who visited the department, although no anecdotes of these encounters are provided. He does recall how a discussion between Sir Almroth Wright and George Bernard Shaw provided material for Shaw's play "The Doctor's Dilemma".

In 1909 he visited Belfast to present two papers on vaccine therapy at the BMA annual meeting, which was chaired by Sir William Whitla. Having moved to the Westminster Hospital, where he was appointed Dean of the medical school, his career was interrupted by the first world war. As a member of the Territorial Force (now the Territorial Army) he was mobilised and served in the RAMC in France, Egypt and Palestine.

A chance meeting with ANZAC doctors in the Middle East was to prove pivotal and in 1919**,** following demobilisation, he was encouraged to apply for the Chair of Systematic Medicine at the University of Otago in New Zealand. He was duly appointed and continued in this academic post until his retirement in 1939.

The University of Otago at Dunedin on the South Island was founded by the Presbyterian Church and medical teaching there derived from Edinburgh (Duneideann is the Gaelic name for Edinburgh). In the 1920's, academic staff were largely drawn from the British Isles. The Dean of the Medical School was a graduate of Trinity College Dublin and a sub-Dean, Dr Murray Drennan, returned from New Zealand in 1928 to take the Chair in Pathology at Queen's University Belfast.

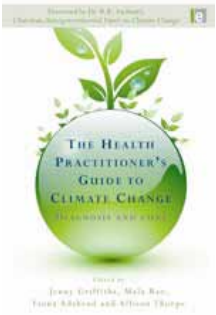
We are provided with an account of expatriate life in this remote corner of the Empire in the post-war period and during the Depression. This antipodean translocation took its toll on his personal life as his wife and children returned to England within five years and the marriage ended. He immersed himself in university life but in time became disenchanted with teaching and bemoaned the loss of clinical skills which he felt were eroded by the emergence of radiology and laboratory medicine.

A keen fisherman for many years, he tired also of this and turned to sketching and writing poetry. With his classical education he was a scholar first and doctor second and could quote Shakespeare, Milton and Tennyson at length. In retirement he wrote a history of the University of Otago medical school and also published a collection of reminiscence, verse, drawings and paintings.

The most interesting portion of this book recalls his wartime experiences and one senses here a man torn between trying to be a humane physician while discharging his duty, which was ultimately to get wounded men back to the front. His work in the RAMC was, he felt, the most useful clinical work that he had done. A man of many parts, then; and a physician in spite of himself? The book's title reflects how his career pathway was determined more by default than design, as he had gone up to Oxford with the intention of becoming a schoolmaster.

Dr Martin McGovern

THE HEALTH PRACTITIONER'S GUIDE TO CLIMATE CHANGE. DIAGNOSIS AND CURE.



J Griffiths, M Rao, F Adshead, A Thorpe (Eds). Earthscan, September 2009. Paperback, 380pp. £19.99. ISBN 978-1-84407-729-8.

Having had one of the very first solar powered water heating systems in Belfast, it was perhaps inevitable that I would be deemed by the editor to have sufficient 'green' credentials to review this book.

Climate change is a controversial topic and readers of this journal may have views somewhere between 'ardent supporter' and 'clear rejectionist'. Global temperatures naturally fluctuate over the centuries so how do you decide what is a normal time trend and what is abnormal? The authors of this book recognise that a range of views exist and very helpfully separate the book into two sections – information and action.

The four chapters on information present the evidence of how climate trends have changed significantly outside normal variation particularly since human behaviour (circa. 1950 onwards) allowed global industrialisation on a scale more significant since that seen in Western European countries in the industrial revolution. Chapters on the hard facts, and the impact and benefits to heath of taking action are extremely well written by experts in the field, and are easy to read. Some interesting facts include the aftermath of hurricane Katrina in the USA in 2006 where dangerous chemical contamination resulting from flooding, and water borne infections caused a sharp increase in morbidity and mortality. Overall $100 billion of damage ensued. Obesity resulting from lack of exercise and increased use of cars and other changes in exercise habits also add to the effect.

The eight chapters on action give plenty of advice to health professionals on how to help change behaviour at both individual and at organisational level. Individual changes in behaviour, although small, generate significant changes and as the authors point out, leading by example is always helpful as most changes have to start small to gain traction. The current economic climate has also helped organisations focus on ways of change to save money in addition to the moral reasoning behind most climate change ideas. Ideas and tips on disinvestment and potential 'big savings for big organisations' will help motivate chief executives to open a copy of this book and to read it. 11 key steps for organisations are listed and discussions on the organisations reputation are fairly interesting reading – displaying the energy efficiency certificates for the public to read may strike fear into some organisations so being proactive will help salvage some reputations.

A step by step guide is given to help calculate your individual carbon footprint so having done this, you can then either boast to your friends, or take some quiet remedial action, depending on the score.

One thing that should be fixed for the next edition is the quality of the diagrams, in black and white and possibly due to the vegetable based ink, these are not that clear, and some colour diagrams would add to the book. If cost is an issue, then a colour plate in the centre of the book would be helpful. Otherwise this is an excellent book and worthwhile reading for every health professional including managers at the top of organisations for a very reasonable price. Our local politicians should also read a copy which should be reasonably easy to claim on expenses.

And what about the solar panels – were they worth it, I hear you ask? They were put in at the start of the century thinking that within 10 years they might break even, and then make a small profit, so a long term investment was the motive as well as any potential ecological credentials. The upside is that with the price of oil rocketing two years after they were installed, they recovered their cost in under five years – half the time I expected - so a good investment, as some other forms of solar and thermal systems have extremely long payback and often are not worthwhile with current costs. The downside is that although I have excess hot water for showers and baths between March and October that we cannot use, my two teenage sons still spend as long in the shower in the morning for the other third of the year so the winter heating bills have risen even if the summer ones are tiny, but at least I have two clean sons…..

Prof Patrick J Morrison

THE ULSTER MEDICAL JOURNAL

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Cover legend: The NHS evidence 'normal' iris. See review by Morrison on page 3