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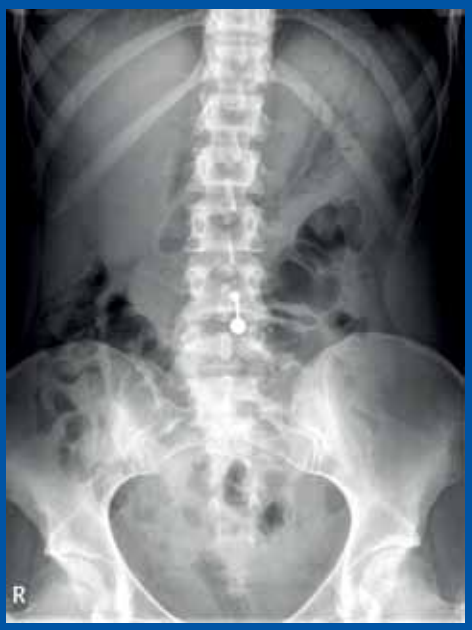

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Editorial

Hidden Depths

"For every mistake made from lack of knowledge, ten are made from lack of looking."

James Alexander Lindsay
Professor of Medicine
Queen's University of Belfast, 1899 -1921

The radiograph on this issue's front cover demonstrates a normal image of the abdomen. It is a favourite of mine and one that I use routinely in teaching undergraduate medical students. Take a good look. You may notice a curvilinear gas density projected within the pelvis. See it? This is what a tampon looks like (figure 1). It's a subtle finding, but once seen, the radiographic configuration is not forgotten. Once the tutorial group moves beyond the potentially salacious, 'Carry On Doctor' nature of the subject matter, I like to pose this question. A 24 year old lady is admitted to your hospital with a head injury. On the third day following admission, her clinical state rapidly deteriorates. Can you see anything on the radiograph that might be the cause? Clearly there might be many reasons for this deterioration, including an infection at the body piercing's skin site (also present on the radiograph) but if anyone had recognised the retained tampon then Toxic Shock Syndrome might enter the differential diagnosis. The point is: unless one looks, one never knows. Intimate examinations are, of course, problematic. Is there reluctance to perform one? Possibly. Is there an assumption that perhaps a nursing colleague has? Maybe.

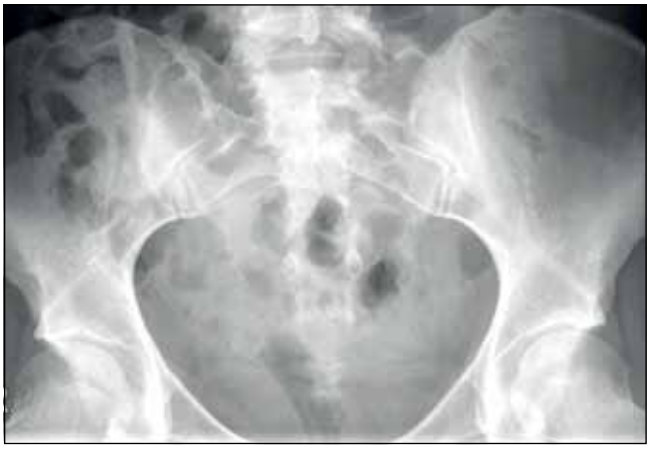


Fig 1. Vaginal tampon

And if it is so for adults, how much more charged is the atmosphere when children are concerned. Assumptions may be incorrect. For example, how distressing is it for a child or its parent if a necessarily intimate examination is required? Jarlath O'Donohoe's very interesting paper has some surprising results.

The Objective Structured Clinical Examination, OSCE, is now ubiquitous in undergraduate medicine. More mature readers will recall the major case, and the attendant fretful preparation ("Hey, there's a 'Mitral Valve' in ward 8." "Now come on, she has a personality too." "What Schizophrenic as well?'). The examiners were often considered a lottery too. Some, it seemed from a youthful perspective, were possibly exhumed specifically for the express purpose of embarrassing and harassing with a series of incoherent pet questions. This appeared as inescapable an event as the certain knowledge that your friend would get the sweetest, most reasonable consultant who might ask how many legs the patient had, and ultimately ask to be remembered to her father. I'm sure it was never really like that, but the malady lingers on for some. More importantly, was that long case a good test? Was it valid or reliable? How was the passing standard reached? Did the examiners test for the minimally passing candidate or use regression analysis? Oh dear me. Sir Lancelot would be bristling with righteous indignation.

In his excellent review article on OSCEs, Gerry Gormley explains with commendable lucidity, the rationale for such an educational paradigm shift. One thing is certain: OSCEs don't happen by themselves. The examination is constructed with military precision, and requires a commensurate number of personnel. In this regard, Dr Gormley is a Field Marshall. His capacity for organisation is exceeded only by his calming influence on the snarling hordes -and that's just the examiners.

REVIEWERS

I thought it might be timely to salute those often-forgotten individuals: reviewers.

In an increasingly fractured professional existence, taking time to review papers can assume a relatively low priority. Two things are noteworthy. Firstly I have been heartened by the very high level of support from so many colleagues both near and very far who have risen immediately to that challenge. Perhaps more astonishingly, has been the care and scrutiny with which each paper has been evaluated.

Like blood donors, such reviewers display an altrusim and a belief in the necessity of this, the longer view and a sense of thoughtful enquiry. It is a an activity written, as it were, on water. Impossible to measure and I would wager, overlooked as important or even relevant when the scales are produced to gauge the cost of something, rather than its value.

So to all of them, I, on behalf of the editorial board, say thank you. Please continue to send me your good papers.

Barry Kelly

Gaucher Disease may be underdiagnosed in the UK and Northern Ireland

Gaucher is currently underdiagnosed in the UK

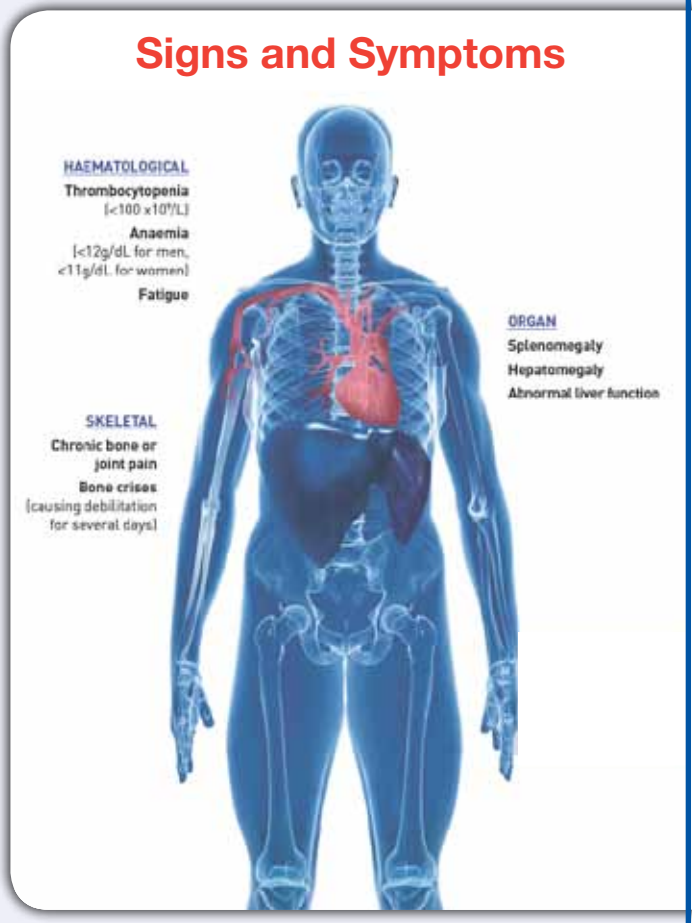
Gaucher disease is a rare inherited lysosomal storage disorder caused by the deficiency of the glucocerebrosidase enzyme, which results in the accumulation of glucocerebroside within the lysosomes of macrophages.

The prevalence of type Gaucher disease is estimated at 1 in 50,000-100,000 in the general population (and 1 in 850 in the Ashkenazi Jewish population).[1,2] However, there are only around 300 patients in the UK and only 3 cases in Northern Ireland with known Gaucher disease (approximately 1 in 200,000 of the population).[2]

This may partly be because Gaucher disease is a heterogenous multi-systemic disorder with variable symptoms and progression. The presenting symptoms can also be similar to other conditions, which may delay diagnosis and access to appropriate management.[1]

Misdiagnoses include leukaemia, immune thrombocytopenia purpura, autoimmune disease, hepatic cirrhosis, idiopathic avascular necrosis, viral disease, idiopathic splenomegaly, and anaemia of chronic disease.[1]

When haematological malignancies have been ruled out, Gaucher disease should be considered[1]



WHEN SHOULD YOU TEST FOR GAUCHER

All patients requiring splenectomy with no diagnosis

Any patient with any of the following: anaemia, thrombocytopaenia, bone pain, Splenomegaly, Hepatomegaly, Monoclonal gammopathy of undetermined significance

HOW TO TEST:

Blood should be sent for glucocerebrosidase assay in the first instance which requires 5 ml in EDTA. The biochemical marker chitotriosidase is usually markedly elevated in this condition as well. It is a good idea to speak to your local biochemistry laboratory before sending the sample in. DNA testing may be carried out to identify the mutation in a particular case but this is not the first line investigation.

For further information or advice about Gaucher disease please contact the Department of Medical Genetics at Belfast City Hospital or the Gaucher disease association www.gaucher.org.uk

[1] Mistry PK et al. Am J Hematol 2011; 86(1): 110–5.
[2] Connock M et al. The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review. Health Technology Assessment 2006; 10(24): 1–156.

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Review

Summative OSCEs in undergraduate medical education

Gerry Gormley

Accepted 3 August 2011

INTRODUCTION

Making judgements on the competency of our peers and trainees is important in patient healthcare.[1] Inaccuracies in such judgements could place patients at risk. First described in 1979[2], Objective Structured Clinical Examinations (OSCEs) have become one of the most widely used methods of assessing aspects of clinical competency in healthcare education.[3] This method of assessment was originally developed in order to address the unreliability and lack of generalisability of traditional forms of clinical assessment such as the *long case*.[4] The overarching philosophy in OSCEs is that all candidates are presented with the same clinical tasks, to be completed in the same timeframe and are scored using structured marking schemes.[2] Compared to the *long case*, OSCEs reduce bias relating to the type of clinical case selected and who performs the assessment. Ideally the only variance in an OSCE should be the candidate's performance. In *formative* forms of assessment the main purpose is to provide feedback to the student. *Summative* forms of assessment define those who have achieved a passing standard and can progress in their studies.[5] This article aims to provide a review of summative OSCEs in undergraduate medical education.

ASSESSMENT OF CLINICAL COMPETENCY: *WHERE DO OSCES FIT INTO THE BIGGER PICTURE?*

The assessment of clinical competence is of significant importance. The General Medical Council emphasises the importance of accurately assessing the competency of medical students.[6] Such decisions help to protect patients by determining whether candidates can progress to higher levels of study or medical qualification.

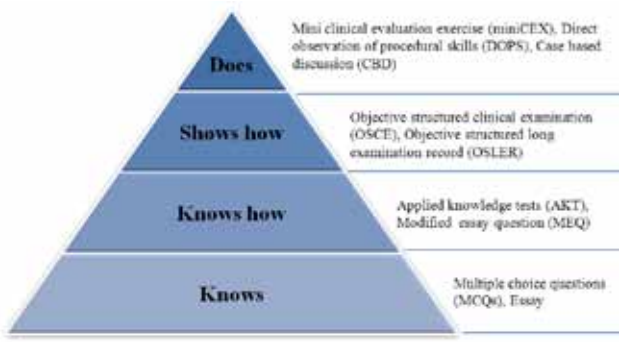

Fig 1. Adapted version of Millers' pyramid of clinical competency.

Miller provides a conceptual framework for assessing clinical competency (Figure 1).[7] This pyramidal model describes the various domains of clinical competency. In achieving clinical competency, candidates are not only required to demonstrate that they *know* the facts which underpin clinical practice but also *know how* to apply these facts. Crucially they also need to *show* that they can perform the clinical tasks and skills. This facet of clinical competence relates more to behavioural than cognitive attributes. OSCEs are a common method of assessing the *shows how* aspects of clinical competency.

Despite the popularity of OSCEs it is important to note they do not provide a complete profile of an individual's level of competency. No valid single method of assessment exists. OSCEs aim to assess certain aspects of clinical competency. Using multiple assessment tools longitudinally is considered the best approach in forming a more holistic opinion on an individual's level of clinical competency.[5] By using several methods of assessment the inadequacies of individual methods may be overcome.[8] Attaining clinical competence is not a one-off event but a career long learning routine.[5]

WHAT IS THE TYPICAL FORMAT OF AN OSCE?

In the UK there is no standard operating procedure for running OSCEs. Therefore there will always be institutional variation in how OSCEs are delivered. However the underlying principles of OSCEs are common to all medical schools. In an OSCE, candidates sequentially rotate around a series of structured clinical cases or stations. Typically in a final year OSCE there may be anywhere between 10-20 individual stations. Stations aim to sample across a wide range of clinical competencies (Figure 2). For example:

- communication and professionalism skills *(e.g. breaking bad news)*
- history taking skills *(e.g. taking a history from a patient presenting with acute chest pain)*
- physical examination skills *(e.g. performing a respiratory examination)*
- clinical-reasoning skills *(e.g. interpreting clinical data and then prescribing therapy on a drug chart)*

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- practical / technical skills *(e.g. insertion of a peripheral venous cannula)*

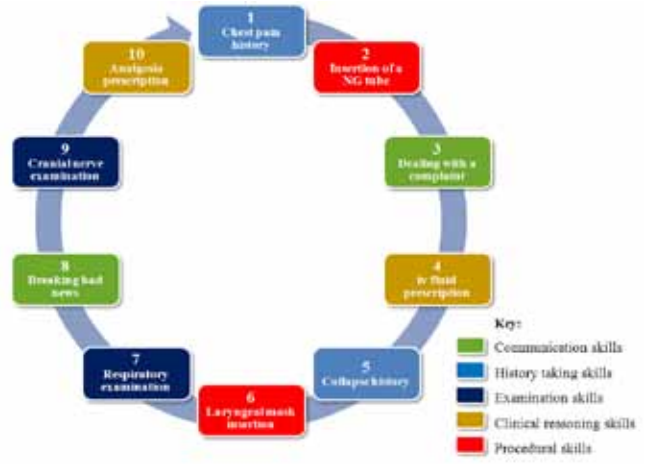

Fig 2. Graphical representation of a theoretical graduating medical OSCE.

At each station candidates are assigned a specific clinical task to perform. In these stations they may encounter a *real* or *simulated* patient, manikin, part-task manikin (i.e. a simulated patient in combination with a manikin), a computer based simulation (e.g. clinical video of a real patient with signs of Parkinson's disease) or clinical information (e.g. a fluid balance chart, blood results and an intravenous fluid prescription chart). Each station has a predefined structured marking scheme or *checklist*. There usually is an assessor in each station who observes the candidate and scores their performance according to the checklist. After a set time period, a bell will signal for candidates to move on to the next station. The circuit of stations is followed in sequence by all candidates. In circumstances where there are a large number of candidates, the OSCE may run across different examination venues and sometimes over the course of one day or more.

WHAT MAKES AN OSCE A *GOOD* FORM OF ASSESSMENT?

There are many attributes of a good and useful test. Van der Vleuten described five such criteria – namely: *reliability, validity, educational impact, cost efficiency* and *acceptability* of the test.[9] Although excelling in all criteria would be ideal, pragmatically there often has to be compromise.

Reliability of OSCEs

Reliability of a test is a measure of its reproducibility and accuracy. In other words the degree to which a test consistently measures what it is intended to measure. OSCEs are widely considered to be a reliable form of assessment. There are many features of OSCEs that contribute to their reliability. Assessor consistency is improved by the use of highly structured marking schemes. Individual assessor bias is reduced by the use of multiple assessors. Ultimately having multiple cases, and sufficient test time, are the most important features that contribute to the reliability of OSCEs.[10] Godfrey Pell and colleagues describe a number of metrics *(such as Cronbach's alpha and R^2 coefficient)* that give an indication of the reliability and quality of an OSCE.[11] The GMC emphasise the importance of using such reliability metrics to quality assure and improve the assessment process.[12]

Validity of OSCEs

The validity of an OSCE is determined by its ability to actually measure what it is intended to measure. In other words an OSCE is considered valid if it succeeds in measuring competencies that it was originally designed to test. There are different types of validity evidence. For example *content validity* of an OSCE is a measure of how well the OSCE stations match the learning outcomes of the course. Blueprinting an OSCE (i.e. stations selected to be used in an OSCE are representatively and systematically sampled from the entire range of learning outcomes for the course) enhances its *content validity*.

Educational impact of OSCEs

Assessment provides a crucial role in the educational process. Not only does it check that learning has occurred but it can provide a powerful influence on future learning.[8-10] The current emphasis in education is moving away from 'assessment *of* learning' to 'assessment *for* learning'. Strategically designing OSCE content and format can have both a positive and negative impact on students' learning behaviours.[9,13]

Students often focus their studies on what they predict will occur in an OSCE. The challenge for faculty is to encourage students not to focus on predictions but the stated learning outcomes of the course. Such as effect is known as *consequential validity*. A criticism of OSCEs is that they can promote students to learn the *checklist* rather than having a deeper understanding of the skill.[14] Given these concerns there is now a trend in more senior level OSCEs to group together single 'lower-level' *checklist* items to more 'higher-level' items – also know as "*chunking*".[11] For example instead of using separate single marks for hand washing, identification of patient, explaining purpose of encounter – these items are grouped into one rating scale (e.g. Overall introduction with patient: *good, adequate or poor?*). Use of such rating scales can improve the reliability of an OSCE.[11]

Cost efficiency of OSCEs

OSCEs are expensive and sophisticated forms of assessment. They are highly resource-dependent and require contributions from a large number of individuals. For example, a 16 station OSCE for over 250 medical students could require in excess of 128 examiner days. Of course there are also patients, faculty staff and other supporting personnel required for the assessment. Considerable effort is also required prior to the OSCE. In terms of planning the logistics of the exam also in development of the stations and training of assessors and patients. Costs regarding equipment, venue hire, catering and other sundry costs also need to be taken into account. Given the current economic imperative on academic institutions to make cost savings, there has never been a greater need to rationalise resources used in assessment. Later in this article I will discuss sequential OSCEs and their potential to reduce the number of examiners slots required - whilst maintaining the reliability of the assessment.

Acceptability of OSCEs

OSCEs need to be acceptable by all stakeholders. Therefore it is important to seek feedback from candidates, examiners and patients involved in the OSCE. Future employers of the candidates also need to have an active role. Given the perceived unfairness of the *long case*, OSCEs have become widely accepted and popular in undergraduate medical education.[4, 8]

In OSCEs, all candidates should experience the same assessment experience and conditions. Inevitably there is potential for variation in OSCEs - for example between different circuits of the same OSCE and between different examiners.[11] The GMC have highlighted this issue and emphasise the importance of institutions paying special attention to assessor recruitment, training and monitoring.[12]

SETTING THE PASSING STANDARD IN OSCES

To establish creditable standards, faculty must use a systematic approach in gathering expert judgments about acceptable levels of competency.[15-16] To ensure the integrity and fairness of such passing scores, several standard setting procedures have been developed. [16] Norm referenced (or *relative*) methods of standard setting are used when a fixed proportion of candidates are required to pass. In such methods of standard setting, competent candidates may fail to progress if the cohort are of above average ability. Therefore norm referencing methods of standard setting are generally unacceptable in undergraduate medical OSCEs. Methods that define a cut-off score, thereby identifying candidates who are competent and eligible for progression, are preferred in undergraduate OSCEs - i.e. criterion (or *absolute*) referencing. The borderline regression (BLR) method is a popular criterion-referenced method of setting a passing standard in OSCEs. The BLR method is generally considered robust and defendable.[11, 14, 17-19]

In the BLR method - assessors directly observe candidates performing the clinical task in each station. They score the various components of the clinical task on the predefined *checklist*. Assessors then provide a separate overall rating or a *global score* of the candidate's performance (for example: *Outstanding, very good, pass, borderline or fail).* The pass mark for each OSCE station is then calculated by statistically regressing candidates' *checklist scores* on *global scores* for each station (Figure 3).

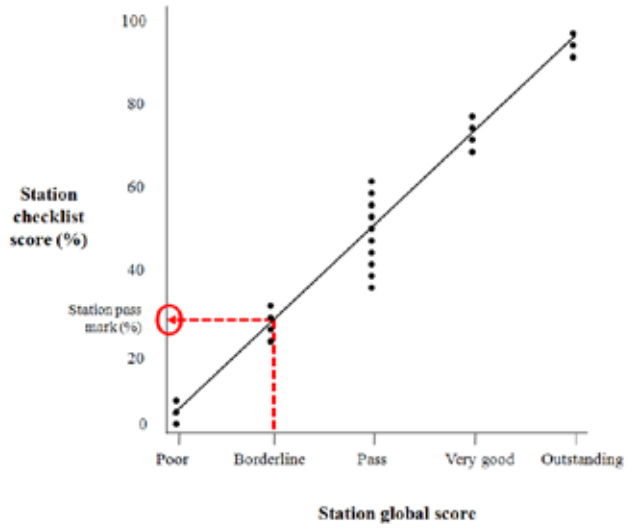

Fig 3. Graphical representation of the borderline regression method of calculating an OSCE station pass mark (i.e. linear regression of station checklist scores on to global scores)

The overall pass mark of the OSCE is calculated by aggregating the pass marks for each of the separate OSCE stations. Upward adjustments maybe made by using the Standard Error of Measurement (SEM). Making such an adjustment reduces the probability of passing an incompetent candidate.[20] However there is also a chance of failing an only-just competent candidate. Protecting patients from incompetent doctors would support the argument for making such adjustments.

ASSESSORS IN OSCES

Assessors play a vital role in delivering a robust and fair OSCE. Ultimately the decision to pass or fail a candidate in an OSCE does not fall on one assessor but on the entire panel of assessors. In the United States simulated patients often act as assessors in OSCEs.[14] However in the United Kingdom and other parts of the world, clinicians tend to examine in OSCEs.

There is an imperative that institutions ensure assessors are competent to undertake their role.[6, 12, 14] The GMC set out clear recommendations of the roles and responsibilities of assessors.[1] The Academy of Medical Educators also set out professional standards of *good educators* involved in assessment.[21] Ideally the only variation in OSCEs should be due to candidates' performance and not due to any assessor effects or bias. Therefore in order for assessors to carry out their role consistently, they require training and feedback on their judgements and behaviour.[12] Most institutions now have established training programmes for OSCE assessors. At Queen's University Belfast we also supplement assessor training with an online learning module (www.med.qub.ac.uk/OSCE).[22] This online training package outlines the roles and responsibilities of an OSCE assessor. Users are also provided the opportunity to practice scoring on an OSCE *checklist* and awarding *global scores* using online videos. In an anonymised fashion they can calibrate their decisions by comparing their awarded scores with that of their peers. However there remains a need for research in this area particularly on the effect that training has on assessor variance in OSCEs.[23]

PATIENTS IN OSCES

Most OSCE stations allow the observation of candidates interacting with patients. Patients may be either *real* or *simulated*. Real patients provide the opportunity to assess candidates' ability to examine for actual clinical features (e.g. auscultation for a cardiac murmur or examining a thyroid goitre). There are, however, significant issues regarding the use of real patients in OSCEs.[24] Firstly, OSCEs are demanding and have the potential to cause discomfort to a patient after being repeatedly examined by a large cohort of students (e.g. knee examination in a patient who has osteoarthritis). Furthermore real patients, and their clinical features, are often difficult to standardise - which can lead to candidates experiencing differences in OSCEs. Because of these challenges there ultimately has been a reduction in the use of real patients in undergraduate medical OSCEs.[25]

Such a reduction in the use of real patients in OSCEs appears to influence some medical students' learning behaviours. In a recent survey of Final MB medical students, patients with *cardiac murmurs* and *pulmonary fibrosis* were predicted as the 'most likely' types of real patient cases that would occur in a graduating OSCE.[25] These predictions were based on the notion that such clinical cases were easy to standardise across different examination venues and amenable to repeated examinations. Such strategic predictions appear to influence students in their learning and encourage them to ignore 'less likely' cases in their clinical training. Faculty need to meet the challenges of using real patients in OSCEs and widen their participation.

Simulated patients (i.e. individuals without actual clinical features) are more commonly used in OSCEs. They can be used in different formats in order to portray a clinical scenario. For example they may be given a script of the symptoms of a patient who presents with acute coronary syndrome. Candidates then have to elicit the clinical history from the simulated patient. Scripts that are based on actual patients' accounts of their condition enhance the validity and patient centeredness of the OSCE station.[26] Simulated patients can also facilitate the assessment of candidates' physical examination skills (e.g. performing an abdominal examination). Simulated patients can also mimic certain clinical signs (e.g. a visual field defect or 'tenderness' in their right iliac fossa). However the potential range of signs that can adequately be reproduced are limited. Such clinical sign simulation requires effective training of simulated patients in order for them to portray the signs consistently.

Fig 4. Example of part-task simulation. A venepuncture manikin arm is attached to a simulated patient. Candidates in this station are asked to obtain a venous blood sample from the manikin arm but also interact and explain the procedure to the simulated patient.

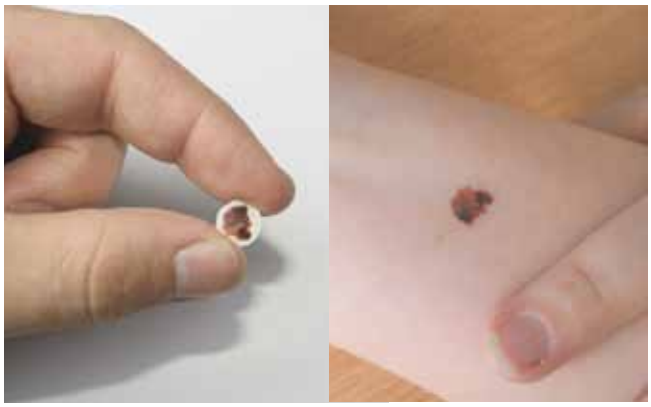

Fig 5. Example of an inexpensive method of high fidelity simulation in an OSCE station. In this station - a temporary transfer tattoo of a malignant melanoma is placed on a simulated patient. Candidates are asked to interact with the patient, assess the 'skin lesion' and explain the potential diagnosis to the patient.

Increasingly the use of manikins and other technical equipment, in combination with simulated patients, are being used in OSCEs. For example attaching a venepuncture manikin arm to a simulated patient (Figure 4).

Such *hybrid* or *part-task* simulation not only allows for the assessment of the technical aspects of the clinical skill but also the humanistic dimensions of the encounter. Another example of such enhanced simulation include the use of high fidelity transfer tattoos of skin lesions.[27] The use of temporary tattoos can allow candidates to be assessed on their ability to diagnosis a skin lesion in a more realistic and patient-centred context (for example a high fidelity transfer tattoo of a malignant melanoma).

The Ventriloscope® is an electronic stethoscope that can realistically and consistently simulate 'abnormal' auscultatory findings.[28] Such technology appears to enhance validity within an OSCE setting.[29]

CONTEMPORANEOUS ISSUES RELATING TO OSCES

Patient ratings on candidates' performance in OSCEs.

Where appropriate, patients are often asked to rate a candidate's performance in an OSCE station.[26, 30] For example at Queen's University Belfast we pose our simulated patients with the following statement *'I would be happy to come back and discuss my concerns with this student again'*. Simulated patients then provide a response using the following scale *(Strongly agree, agree, just agree, neutral or disagree)*. Such ratings tend to focus on the humanistic aspects of the clinical encounter (e.g. attentiveness, empathy and rapport). There are a number of reasons why simulated patients are asked to rate candidates' performances. Not only does it highlight the importance of patient-centred care to our students, it also promotes simulated patients engagement in the assessment process. Furthermore, including simulated patients ratings to assessors *checklist* scores can potentially enhance the psychometric reliability of an OSCE.[31] Simulated patients' ratings may also be used as a separate progression criteria for candidates in an OSCE (eg. regardless of the total OSCE

score, a candidate may fail to progress if a minimum number of simulated patients do not rate their performance as being satisfactory). Such a process requires effective training and quality control of simulated patients and their decisions.

Sequential OSCEs

As outlined previously in this paper, OSCEs are complex and expensive forms of assessment. In recent times sequential OSCEs have been developed so that reliability of the assessment is maintained but resources are targeted where they are needed the most i.e. the pass / fail divide.[32] In a sequential OSCE, candidates go through an OSCE with a reduced number of stations (for example a 10 rather than a 16 station OSCE). The BLR is used to determine the cut score in this OSCE. However an upward adjustment of 2 or more SEMS are made to this pass mark. This invariably will produce a larger cohort of candidates who don't meet the standard. Within this group of candidates there are those that are truly *incompetent* and others who are truly *competent*. This group of candidates then go through an extended OSCE (e.g. a further 6 stations). Therefore the overall reliability of correctly identifying those students who are competent, in this small cohort of candidates, is maintained. In essence the OSCE does not have to be as reliable for all candidates, but focuses on those who are on the pass / fail boundary. Such an OSCE design requires fewer examiner days - which is of course more cost effective.

Quarantining ('corralling') in OSCEs

OSCEs often span the course of a day or more. With such practice there is potential for OSCE content to be leaked between different cohorts of candidates sitting the same examination. However there is a general consensus in the literature that such conduct does not have any significant statistical bearing on candidates' performance in OSCEs.[33-34] OSCEs assess *showing* rather than *knowing* skills. Therefore the notion is that there is insufficient time to rehearse a skill in order to obtain any advantage.[34] Nonetheless such violations of OSCE content can potentially endanger the integrity and creditability of the assessment process. Therefore some institutions quarantine candidates between different sittings of the same OSCE (i.e. following an earlier sitting of an OSCE, candidates are placed in a holding area without access to their mobile phones or other electronic devices - until the next cohort of candidates have finished the OSCE).

Serious concern ('yellow card') reporting systems

A criticism of OSCEs is that a candidate can be incompetent in a particular skill, but can still pass the overall OSCE due to compensation from their performance in other stations. In response to this criticism, a number of institutions, including Queen's University Belfast, have developed a serious concern or 'yellow card' reporting system in their OSCEs. Such a system represents a qualitative mechanism of providing feedback to a candidate (and faculty) about their performance in an OSCE. Issues that would warrant a serious concern report include unprofessional practice *(e.g. being rough with a patient)* or unsafe actions that could potentially cause harm to a patient in clinical practice *(e.g. administration of an incorrect and dangerous drug)*. In such significant situations candidates are asked to meet with faculty in order to critically review the event. Before such candidates can progress on with their studies they are required to go through a remedial process until they have satisfactorily demonstrated competency in that particular skill. Future research is required to examine the predictive validity of serious concerns reports on future student performance in clinical practice.

CONCLUSION

Since their original development, OSCEs have become one of the main methods of assessing clinical competence in undergraduate medical education. Without question, OSCEs are more reliable than traditional methods of assessing clinical competence such as the *long case*. However they are not without their weaknesses. The high reliability of OSCEs is often at the expense of their validity. However with increased validity evidence, OSCEs have become more sophisticated and are portraying more realistic clinical scenarios. Used in combination with other methods of assessing clinical competency the shortcomings of OSCEs can be minimised. If correctly designed OSCEs can have a beneficial impact on medical students learning and future performance.

The author has declared no conflict of interest.

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Paper

A 22-Year Northern Irish Experience of Carotid Body Tumours

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ABSTRACT

Objectives: Carotid body tumours (CBTs) are rare vascular neoplasms originating in paraganglionic cells of the carotid bifurcation. The aim of this study was to review all patients diagnosed with CBTs in Northern Ireland.

Methods: A retrospective review was performed of all patients who had CBTs treated at our institutions between 1987 and 2009. Patient demographics, clinical symptomatology, investigative modality, therapeutic intervention, pathological analysis and long-term outcomes were assessed.

Results: Twenty-nine patients were identified with 33 CBTs and three glomus intravagale tumours (GITs). Six patients had bilateral CBTs (21%), one of whom had a synchronous GIT. Twenty-six patients underwent a total of 30 operative procedures for the resection of 28 CBTs and 3 GITs. Conventional operative treatment included subadventitial tumour excision. A vascular shunt facilitated arterial reconstruction following the removal of seven (23%) tumours and on six of these occasions (19%) continuity was restored with an interposition vein graft. For access the external carotid artery was ligated during the removal of four tumours (13%). Two tumours were considered malignant. No peri-operative mortalities were recorded. Immediate complications included peri-operative stroke secondary to an occluded vein graft (n=1), requirement of tracheostomy (n=2), emergency haematoma drainage (n=2) and transient cranial nerve damage (n=8). Late complications included pseudoaneurysm of vein graft with subsequent stoke (n=1), permanent cranial nerve damage (n=9), Horner's syndrome (n=1) and an asymptomatic vein graft occlusion (n=1). One patient had tumour recurrence two years post-operatively and died due to pulmonary metastases. Two other patients died of unrelated causes. All other patients remain well with no evidence of tumour recurrence at mean follow-up of 1801 days (range 159-9208 days).

Conclusion: Our long-term experience is comparable with other reported case series where surgical intervention conferred a long-term survival advantage despite associated cranial nerve co-morbidities.

Keywords: Carotid Body, Complications, Outcome, Surgery, Tumour.

INTRODUCTION

Carotid body tumours (CBTs) are rare vascular neoplasms originating in the paraganglionic cells of the carotid bifurcation. They have a reported incidence between 0.06 and 3.33 per 100,000 patients [1, 2]. Male and female distribution is equal except at high altitude where females appear to predominate [3, 4]. The second commonest type of cervical paraganglioma is a glomus intravagale tumour (GIT), which is derived from closely adjacent paraganglionic tissue located on the vagus nerve [2].

Clinically, CBTs typically present as a non-tender, rubbery, pulsatile mass. Classically, the mass can be displaced laterally but not vertically, due to carotid artery adherence, which is known as a positive *Fontaine* sign. Diagnosis is commonly confirmed by duplex ultrasound, computerised tomography (CT), magnetic resonance imaging (MRI) and rarely conventional angiography [5].

Although technically challenging, surgery remains the only definitive treatment [1, 2]. Mathews (1915) remarked that *'this rare tumour presents unusual difficulties to the surgeon and should one encounter it without suspecting the diagnosis, the experience will not be forgotten'* [6]. Since the initial reports of peri-adventitial dissection by Gordon-Taylor (1940), modern methodologies, including intra-luminal carotid artery shunting and carotid arterial reconstruction with autologous vein grafts or prosthetic grafts if necessary, have dramatically reduced the most significant peri-operative complications of stroke and death [1, 2, 7, 8]. Other early local complications encountered include the risk of bleeding and airway compromise, loss of baroceptor function and neurovascular damage. Longer-term CBT complications include recurrence, metastatic dissemination, graft pseudoaneurysm or occlusion and permanent cranial nerve palsies [9-12]. As a result graft surveillance is recommended [13].

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Histopathological analysis is a poor predictor of malignant potential. Malignancy is therefore defined only by the presence of distant metastases [14]. Although 95% of all CBTs are benign, they remain locally aggressive tumours with growth rates of 2cm every five years, which can lead to localised mass effects or neurological dysfunction due to pressure or infiltration [1, 6].

Ten-percent of CBT cases will have a familial trait [15]. Autosomal dominance may be associated with variable penetrance where the oncogenes *c-myc*, *bcl-2* and *c-jun* have been implicated. Succinate dehydrogenase complex subunits B, C and D (SDHB, SDHC and SDHD) gene mutations are associated with genetic susceptibility. SDHB and SDHD, the most commonly implicated, also predispose to pheochromocytoma while SDHD gene mutations have been shown to correlate with the development of multiple CBTs. Approximately 30% of these familial tumours will be bilateral. Therefore, clinical surveillance combined with radiological imaging remains important for early identification of contra-lateral tumours [17].

The aim of this study was to review all patients treated by vascular surgeons in all tertiary referral centres for CBTs in Northern Ireland over a 22-year period and to compare our experience with published evidence.

TABLE 1:

Clinical presentations for the 29 patients in our series.

	Number	%
Clinical Presentation		
Painless neck mass	19	65.5
Painful neck mass	5	17.2
Collapse	1	3.4
Pre-auricular pain	1	3.4
Familial surveillance	1	3.4
Identified on follow up	1	3.4
Unavailable	1	3.4

METHODS

A retrospective case note review of all patients who had CBTs managed in our institutions between 1987 and 2009 was completed. To identify patients, pathology archival databases in laboratories related to each referral centre were searched for all diagnoses of CBT and theatre log books were explored for operative procedures on CBTs. Data collated into a predefined database included age, sex, presenting symptoms, pre-operative investigations, use of pre-operative embolisation, operative details including tumour size, Shamblin classification, need for arterial sacrifice or reconstruction, post-operative morbidity, pathological assessment, use of radiotherapy and long-term follow-up specifically with regards subsequent recurrence and development of disseminated malignancy.

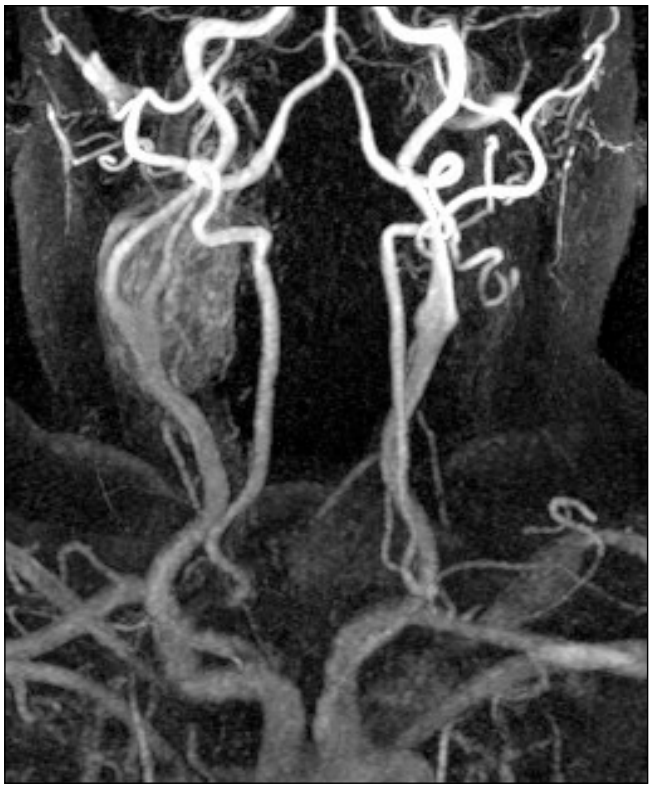

Fig 1. Magnetic resonance angiogram (MRA) with intravenous gadolinium showing an avidly enhancing 4 x 3.5 x 2.5cm right CBT with multiple small blood vessels within (Note the characteristic splaying of the carotid bifurcation with the external carotid artery bowing over the tumour and the internal carotid artery slightly narrowed in calibre as it passes through).

RESULTS

Clinical Presentation

Twenty-nine patients were identified with a total of 33 CBTs and three GITs. There were 14 male and 15 female patients with a mean age of 49-years (range 16-85 years). Twenty tumours were located on the right side and 16 on the left. Six patients had bilateral CBTs (21%). One of these patients had a synchronous GIT. There were four cases of confirmed familial disease (14%) (Table 1).

Investigations

Investigative modalities for the 29 patients included routine ultrasound (n=14), duplex ultrasound (n=5), computed tomography (n=18), magnetic resonance imaging (n=9) (Figure 1), radionuclide perfusion scan (n=6) and percutaneous angiography (n=11). Although percutaneous angiography and radio-isotope scans were commonly performed at the beginning of our series, ultrasound is now advocated as a first-line diagnostic or screening modality. Computed tomography and more recently magnetic resonance imaging are now used during pre-operative planning.

Other investigations included a PET scan which was performed to investigate tumour dissemination in a patient with previously diagnosed bilateral CBTs. Five non-diagnostic (C1) and one normal (C2) fine needle aspirations were recorded during the investigation of neck masses prior to referral to our units. Two patients also had incidental CBTs

diagnosed during attempts at open biopsy of neck masses in other surgical units.

Pre-operative Treatment

Pre-operative embolisation was performed in two patients with successful occlusion of the main feeding branch of the right parapharyngeal artery four days pre-operatively in the first patient (F, 61). Despite two attempts in the other patient (M, 45), pre-operative embolisation served to increase collateral vasculature and was therefore deemed unsuccessful. No complications were caused by embolisation in either patient.

TABLE 2:

Shamblin classification - Definitions and corresponding patient data from our series.

Shamblin Classification	**Definition**	**Number**	**%**
I	Small with minimal arterial attachment	6	19.4%
II	Moderate arterial attachment partially surrounding carotids	5	16.1%
III	Encasement of carotid bifurcation	9	29.0%
Unclassified	Surgeon didn't specify grade	11	35.5%

Surgical Intervention

Surgical intervention was not considered appropriate in three patients because of medical co-morbidities. One patient with bilateral CBTs was not considered for contra-lateral CBT surgery. A total of 26 patients underwent surgical excision of 28 CBTs and three GITs.

Shamblin classification demonstrated six grade I, five grade II, nine grade III and eleven unclassified tumours (Table 2). Surgery was performed by three experienced vascular surgeons using an oblique lateral neck incision along the anterior border of the sternocleidomastoid muscle followed by careful dissection to expose the carotid vessels characteristically splayed by the associated CBT (Figure 2). Control of the external, internal and common carotid arteries along with any major branches was completed using vascular sloops. The blood supply to CBTs generally arises initially from the external carotid artery and this has important implications in terms of obtaining exposure and control of this vessel. The glossopharyngeal, vagus, hypoglossal, ansa cervicalis, recurrent laryngeal, accessory and superior laryngeal nerves were protected when identified. A peri-adventitional caudal-cranial dissection was performed along the relatively avascular "white line" plane using bipolar diathermy for haemaostasis. Where possible, the tumour was subsequently enucleated without disturbing either the carotid vessels or cranial nerves (Figure 3). The external carotid artery was preserved where possible. Conventional subadventitial tumour excision was successful for the excision of 20 tumours (65%).

Intraluminal shunting and carotid artery reconstruction were performed for the removal of seven (23%) tumours where the tumour could not be enucleated without excision of a segment of carotid artery. Six of these tumours (19%) required *en-bloc* resection of the carotid bifurcation with continuity restored with an interposition long saphenous vein graft. For either access reasons or haemostasis, the external carotid artery was ligated in three more cases and during the removal of a total four tumours (13%). The internal carotid artery was preserved in all cases.

Fig 2. Intra-operative exposure of a right-sided CBT which has splayed the carotid bifurcation.

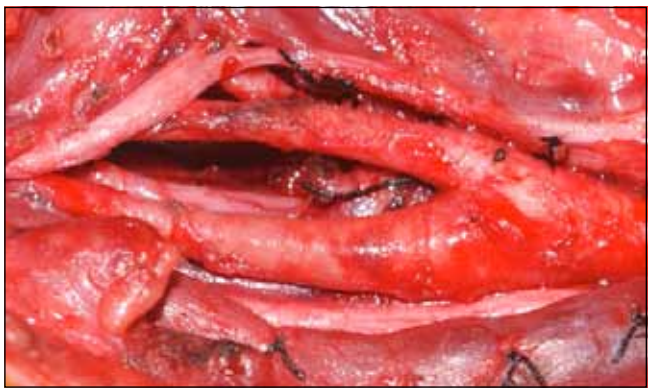

Fig 3. Undisturbed carotid arteries following excision of the right-sided CBT from figure 2 using the standard peri-adventitional dissection.

Complications

Early local complications included cranial nerve injuries in 17 patients where nine patients had multiple cranial nerve injuries. These included nine isolated hypoglossal, five facial and three accessory nerve injuries. Transient dysphagia was observed in seven patients with two patients requiring temporary nasogastric and percutaneous endoscopic gastrostomy (PEG) feeding respectively. Early systemic complications included one peri-operative stroke presenting with hemiparesis secondary to an occluded vein graft, which was treated with graft thrombectomy followed by partial resolution of symptoms. There were no peri-operative deaths (<30 days) (Table 3).

Long term local complications included nine patients with permanent cranial nerve damage comprising five patients who

sustained injuries to multiple nerves including one superior laryngeal, one facial, two hypoglossal and two accessory nerve injuries. Only three patients required secondary procedures to address neurological symptoms which included thyroplasty (n=2) and teflon injection (n=1) for vocal cord paralysis while one also underwent pharyngoplasty for palatal paralysis. Long-term systemic complications included an asymptomatic vein graft occlusion diagnosed on follow-up surveillance treated conservatively. A further patient suffered a late stroke, seven years post-operatively, secondary to pseudoaneurysm of the vein graft which was treated with an endovascular stent (Table 3).

Table 3:

Early and late post-operative complications (CNI – Cranial nerve injury).

	Number	%
Early Complications		
Immediate		
Airway obstruction	2	6.7
Local		
Haematoma	2	6.7
Wound infection	1	3.3
Transient CNI	8	26.7
Vein graft occlusion	1	3.3
Systemic		
Stroke	1	3.3
Late Complications		
Stroke	1	3.3
Vein graft occlusion	1	3.3
Vein graft pseudoaneurysm	1	3.3
Permanent CNI	9	30.0
Horner's syndrome	1	3.3

Pathological Analysis

Full pathological reports were available for 28 CBTs and three GITs. Mean tumour size was 3.72cm (range 1.8cm–8.0cm) (Figure 4). The majority of tumours (n=28, 90%) were well encapsulated and locally confined although three had an infiltrative growth pattern including perineural infiltration (n=1), vascular and capsular invasion (n=1) and regional lymph node spread (n=1). Histology demonstrated a typical nested growth pattern of monomorphic cells in most tumours with only focal pleomorphism and no significant mitotic activity. Tumour cells typically stained strongly with the neuroendocrine marker chromogranin A while sustentacular cells surrounding tumour cell nests stained with S100 (Figure 5).

Adjuvant Therapy

Three patients received post-operative radiotherapy for lymph node spread (F, 36), large tumour size with capsular invasion (M, 45) and local recurrence (F, 52). The remaining 23 surgical patients required no further post-operative treatment.

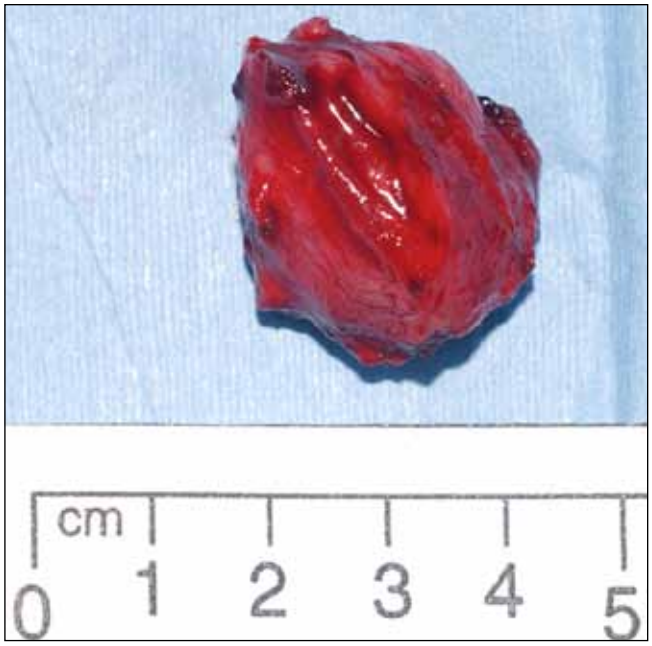

Fig 4. Gross specimen of the previously excised right-sided CBT (3 x 2.8 x 1.8cm, 6.5g).

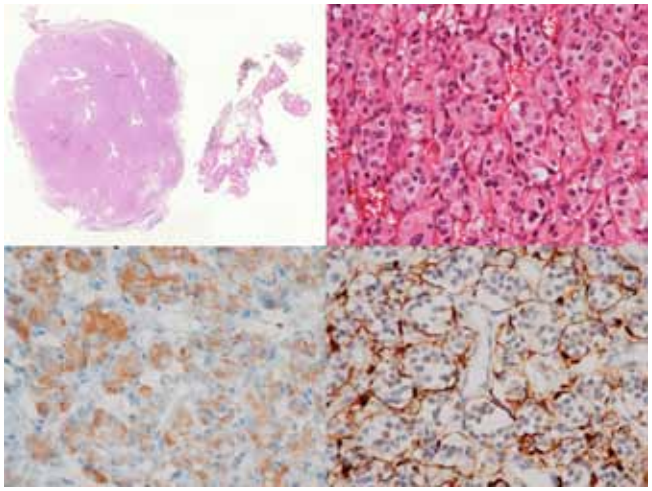

Fig 5. Low power view of a typical CBT, showing a thinly encapsulated, well-circumscribed mass, with some adherent wisps of connective tissue (H&E x 1) (Top left). High-power magnification displays a nested growth pattern of monomorphic cells with granular eosinophilic cytoplasm (H&E x 400) (Top right). Immunopositivity within tumour cell cytoplasm for the neuroendocrine marker chromogranin A (immunoperoxidase x 400). (Bottom left). Immunopositivity within surrounding sustentacular cells for S100 (immunoperoxidase x 400) (Bottom right).

Clinical Outcome

Twenty-six patients remain well with no evidence of recurrence or disease dissemination at mean follow-up of 1801 days (range 159-9208 days). Two patients had metastatic disease and the first (F, 36) who had pathological evidence of nodal spread at the time of initial operation remains well without evidence of tumour recurrence at 9208 days follow-up. The second patient (F, 52), with perineural invasion in

TABLE 4:

*Literature review of all previous CBT studies (Pts=patients with CBTs, Surg=patients managed surgically, M=Male / F=Female {*sex distribution figures for all paragangliomas highlighted}, Age=mean patient age, No.Tu=total numbers of tumours, Bilat=% bilateral tumours, Malig=% malignant tumours, Famil=% familial tumours, ECA Lig=% times ECA ligated, ICA lig=% times ICA ligated, ICAR=% times ICA reconstructed, CNI=% total cranial nerve injuries, TCNI=% temporary cranial nerve injuries, PCNI=% permanent cranial nerve injuries, CVA=% cerebrovascular accidents, Death=peri-operative mortality).*

Studies	Pts	Surg	M	F	Age	No. Tu	Bilat	Malig	Embol	Famil	ECA lig	ICA lig	ICAR	CNI	TCNI	PCNI	CVA	Death
Koskas et al 2009	36	36	14	22	44.4	39	3%	0%	3%	5%	56%		23%	72%	46%	26%	3%	0%
Papaspyrou et al 2008 *	38	36	39	81	42	46	18%	3%	5%	10%		3%	25%	23%			4%	0%
Makeieff et al 2008	52	52	17	35	43	57	6%	2%	0%	12%	26%	2%	9%	42%	35%	7%	2%	0%
Van der Bogt et al 2008	94	94	44	50	41	111	61%	2%	0%	64%		1%	3%	38%	15%	23%	0%	0%
Sajid et al 2007	95	95	32	63	55	95	18%	4%		18%				19%	18%	1%	1%	1%
Antonitsis et al 2006	13	12	5	8	41	14	8%	0%	79%	0%	25%	0%	8%	54%	54%	0%	0%	0%
Bakoyiannis et al 2006	11	11	8	3	35	12	9%	0%	0%				8%	25%	25%	0%	0%	0%
Kasper et al 2006 *	20	20	13	12	51	25	25%		52%	12%	32%		4%	52%	40%	12%	0%	0%
Knight et al 2006	16	15	4	12	68	16			7%	7%				0%	0%	0%	0%	0%
Smith et al 2006	62	62	26	36		71	55%		77%	19%			23%	35%			0%	0%
Davidovic et al 2005	12	12	3	9	52	12	0%	0%		0%	42%	0%	42%	25%	25%	0%	0%	0%
Luna-Ortiz et al 2005	66	46	2	64	50.2	69	5%	0%	0%	0%	11%	7%	6%	49%	12%	38%	4%	0%
Heis et al 2003	9	8	4	5	48	9	0%	0%	0%	0%			13%	25%	25%	0%	0%	0%
Patetsios et al 2002	29	28	10	19	43	34	17%	10%	0%		25%		29%	46%	29%	17%	0%	4%
Dardik et al 2002	25	25	9	16	48.2	27	24%		96%	4%	33%	4%	15%	33%	7%	26%	4%	0%
Persky et al 2002 *	26	24	22	25	47	28	8%	12%	100%			12%	4%	46%	34%	12%	0%	0%
Por et al 2002	7	7	2	5	43	8	14%	0%	38%		50%			75%	25%	50%	13%	0%
Huang et al 2001	30	30						0%	17%		27%						0%	0%
Plukker et al 2001	39	35	14	25	43	45	15%	5%		26%	34%	2%	10%	24%			5%	0%
Thabet et al 2001	16	16	11	5	42	18	13%			6%		6%	6%	44%			6%	6%
Liapis et al 2000	18	16	7	11	45	18	0%	11%	19%					25%	25%	0%	0%	0%
Wang et al 2000	29	28	16	13	39.5	36	3%	0%	61%	10%				41%	17%	24%	0%	0%
Bastounis et al 1999	17	17	6	11	45	20	18%		10%	0%	35%	5%	10%	15%	15%	0%	6%	6%
Rodriguez et al 1998	120	80	11	107	49		5%	3%		1%		3%		20%			4%	3%
Westerband et al 1998	31	31	15	16	48	32	3%	3%	19%		29%		26%	13%			6%	0%
Leonetti et al 1997	19	16	7	9	42.5	16	0		0%		19%	0%	0%	69%	44%	25%	0%	0%
Muhm et al 1997	24	19	10	14	51	28	17%	4%	42%	13%	36%		9%	26%			5%	0%
Litle et al 1996	21	21	8	13	46	22	24%		50%		23%	5%	18%	45%	27%	18%	5%	0%
Mitchell et al 1996 *	14	14	9	8	54.4	17	18%	6%	0%	14%	29%		6%	41%	29%	12%	6%	6%
Matticari et al 1995	20	19	9	11	51.3	22	10%	0%	0%		0%	0%	5%				0%	0%
Netterville et al 1995	30	29	13	17	42	46	53%	7%		53%		3%	24%	34%	10%	24%	0%	3%
Sanghvi et al 1993	20	20	13	7		21	5%		0%	0%			15%	45%			5%	0%
Rabl et al 1993	11	11	4	7	58.7	12	9%	16%	8%				16%	16%	8%	8%	0%	5%
La Muraglia et al 1992	17	17	5	12	44	19	12%	0%	58%		37%	0%	11%	16%	11%	5%	6%	0%
Wax et al 1992	16	16	7	9	40	19	19%		56%				16%	44%			6%	0%
Williams et al 1992	30	30	10	20	54	33	10%	9%			40%	0%	3%	20%	13%	7%	3%	0%
Torres et al 1991	96	32	11	85	52.3			2%		1%							0	3%
Yang et al 1991	27	27									44%	30%	15%				2%	7%
Hallett et al 1988	139	139			52	153		2%	1%		33%		25%	40%	21%	19%	14%	3%
McPherson et al 1988	25	25	9	16	47	26	10%	4%	8%		0%	0%	8%	15%			0%	0%
Gaylis et al 1987	50	46	33	17	49	52	4%	14%					13%	17%			4%	5%
Pachedo-ojeda 1988	19	19	5	14	52.5	20	5%	0%	0%	11%	10%	0%	10%	26%	11%	15%	5%	0%
Dickinson et al 1985	32	25	10	22	41	37	14%	0%			27%	0%	15%	40%	20%	20%	4%	0%
Lees et al 1981	39	37	18	21	49	43	10%	15%		5%		10%	15%	17%			5%	2%
Rosen et al 1981	27	24	14	13		30	11%	8%		7%		8%	33%	33%	17%	16%	0%	4%
Farr 1980	43	43	31	31	46	44	2%	7%	0%		18%	18%		16%			9%	14%
Shamblin 1971	90	70	62	28		96	7%	2%			33%	21%		55%			22%	6%

the initial resection specimen, developed local recurrence on computed tomography two years post-operatively. The recurrent tumour was successfully removed from the medial aspect of the distal end of a long saphenous vein anastomosis that had been fashioned at the time of the initial surgery following excision of a Shamblin class III tumour. This patient subsequently developed pulmonary metastases and despite a pulmonary wedge resection, died from progressive pulmonary metastases 4 years following her initial CBT surgery. The last of the three patients who received post-operative radiotherapy

(M, 45) for capsular invasion remained well at 326 days until lost to follow-up. Two other patients died of unrelated causes. The overall CBT related mortality in our series was 3%.

DISCUSSION

All CBTs in Northern Ireland are managed by vascular surgeons, within the two main tertiary referral centres included in the study. Our study reports an incidence of CBTs in Northern Ireland of 0.08 per 100,000 people each year with a population prevalence equating to 1.5 per 100,000 people, which is comparable to the reported literature (Northern Ireland Statistics and Research Office). However, our 15% rate for familial tumours is relatively high compared to other regions with familial CBT rates around 10% [3, 5, 10, 12, 15, 16, 17, (Table 4).

CBTs are often asymptomatic with most patients presenting with neck asymmetry or a distinct lump. If symptomatic, as shown in our study, neck pain is the most common complaint (17%). Although patients can present with the effects of functional tumours secreting histamine, serotonin, adrenaline and noradrenaline, this did not occur in our study [1, 5].

Non-invasive investigative modalities utilised in the work-up of patients with suspected CBT include duplex ultrasound, computerised tomography angiography and magnetic resonance angiography (MRA) [5, 17]. Fine needle aspiration is rarely employed because of the risk of carotid injury or haemorrhage in these highly vascular tumours and open biopsy is clearly contraindicated due to the risk of catastrophic haemorrhage [5]. We advocate duplex ultrasound as first line diagnostic or screening modality particular in patients with a positive family history [18]. However, similar to other units, we now use MRA to follow-up CBT patients. MRA is safe, non-invasive, highly specific and sensitive for lesions involving the skull base or with a multicentric morphology [19, (Figure 1). Although invasive, routine angiography permits an accurate assessment of vascular anatomy, particularly carotid arterial neo-vascularisation, combined with intra-cerebral flow on the contralateral side, which is important to consider prior to intra-operative occlusion of the ipsilateral carotid circulation when excising the CBT [15].

Schick *et al* (1980) first described the use of pre-operative arterial embolisation which has been reported to decrease blood loss and subsequent transfusion rates whilst leading to potential reductions in tumour size by up to 25% if performed within 48-hours of surgery in medium to large CBTs with well-defined feeding vessels [13, 15, 17, 20]. However, if surgery is delayed, revascularisation oedema combined with a localised inflammatory response can create difficulty with the periadventitial dissection [19, 21]. Embolisation is also a time consuming process associated with the inherent risks of distal migration of the embolisation medium and a stroke incidence as high as 10% [17, 19-20]. Other authors have described no effect on blood loss, transfusion requirements or duration of surgery following embolisation [22]. Consistent with these conflicting results, use of pre-operative embolisation varies widely across the literature with rates between 0% and 100% (Table 4). Although we report a 7% use of pre-operative embolisation, which is low in comparison to the majority of studies, we experienced no complications secondary to the procedure such as transient ischaemic attacks and strokes [21-23].

Advances in endovascular surgery suggest the possibility of vascular exclusion of external carotid artery feeding branches to the tumour through deployment of covered stents. These limited case reports postulate that the use of endovascular stents, without the use of coils or intra-arterial gel foams, may potentially lower the risk of peri-procedural stroke [10]. However, these techniques are rarely used and indeed were not performed in any of the 47 case series reviewed in Table 4. We advocate preservation of the carotid circulation and also report no endovascular external carotid artery occlusions throughout our study period.

Despite a low risk of malignant behaviour, surgical resection remains the treatment of choice for CBT. In our series, we reserved conservative management only for elderly patients with extensive co-morbidities or in those patients with multiple tumours where operative intervention had a high risk of severe debility due to the potential for injury to multiple cranial nerves. Gordon-Taylor (1940) described a meticulous subadventitial "whiteline" dissection which aimed to enucleate the tumour without disturbance of the carotid vessels [2]. Early case series reported the necessity of internal carotid artery patency, particularly in patients with CBTs encasing the internal carotid artery and where internal carotid artery occlusion was associated with unacceptably high peri-operative stroke rates of 30% [10, 24]. We advocate the insertion of an intraluminal shunt to maintain cerebral perfusion in such patients which may then facilitate the subsequent reconstruction of the resected section of carotid artery using saphenous vein grafts. This was required in 19% of cases in our series where the median tumour size was 5cm in diameter. Netterville *et al* (1995) reported that vascular repair was performed in only 10% of patients when the tumour was less than 5cm compared to 55.5% in patients with tumours larger than 5cm [25]. Therefore the authors feel that a pre-operative diagnosis of tumour size of 5cm or more suggests that a carotid resection and reconstruction is more likely.

Other authors report the ligation of the external carotid artery to devascularise feeding vessels of the tumour[10, 15]. Temporary external carotid artery occlusion may also be used to minimise bleeding. However, we have never routinely performed elective ligation of the external carotid artery except in four (13%) patients where it was necessary for either haemostasis or to facilitate access to the CBT. External carotid artery ligation varies from 0% to 56% in the reported literature (Table 4).

Cranial nerve damage is the most common early local complication following excision of CBTs due to the close proximity of facial, glossopharyngeal, vagus, accessory and hypoglossal nerves to the CBT itself or secondary to invasion of these nerves by tumour expansion and distortion of normal anatomy by the tumour leading to inadvertent damage during dissection. We report a 27% transient and 30% permanent nerve injury rate for this series. This is comparable to other case series where reports of transient and permanent cranial nerve damage vary from 0% to 54% and

0% to 38% respectively (Table 4). However, it is important to acknowledge that due to the retrospective nature of our study, pre-operative cranial nerve involvement or impairment was rarely recorded in the early patients from our series. Also the inclusion of three GITs correlated with obligatory damage of the vagus nerve in each case.

Cranial nerve injuries identified post-operatively by the operating vascular surgeon were referred on to the appropriate specialty, usually Otolaryngology, for a more detailed assessment and treatment where necessary. The majority of cranial nerve injuries occurred early in the series with a subsequent reduction identified over time with increasing experience.

Post–operative cranial nerve injury is known to correlate with the Shamblin classification of the tumour [7]. A higher risk of cranial nerve injury may also be attributed to vascular reconstructive procedures during resection. However, this may just reflect tumour morphology of invasion and higher Shamblin classification [8]. Due to the higher number of tumours unclassified at the time of operation we are unable to perform an accurate subgroup analysis on this factor. However it was found in this series that cranial nerve injury was more likely following the removal of larger tumours. The average tumour size in patients who suffered no cranial nerve injury being 3cm while those that suffered cranial nerve injuries was 3.95cm (transient injury = 3.7cm and permanent = 4.3cm).

Specific nerves such as the vagus are more often affected during CBT surgery because of occasional nerve retraction or sacrifice to facilitate tumour excision. In addition, excision of GITs almost always requires vagal nerve sacrifice followed by vocal cord paralysis which was observed in all three patients in our series who had GITs removed. Although not identified in our series, other early local complications may also include bilateral loss of carotid body or sinus function, which can lead to adverse blood pressure control, and bilateral loss of chemoreceptor function which may cause severe hypoventilation necessitating ventilatory support post-operatively [3].

Post-operatively, radiotherapy is indicated where histological analysis demonstrates an infiltrative growth pattern. Local control rates for CBTs between 96% and 100% have been reported with radiotherapy alone. However, this practice should be balanced against the potential risks of subsequent radiation-induced malignant degeneration particularly in younger patients [19-24]. Other side effects from radiotherapy may include ageusia, xerostomia and a skin rash. Adjuvant radiotherapy was administered to three patients (10%) in our study because of capsular infiltration, regional lymph node spread and local recurrence respectively. Only the latter patient developed further recurrence and died of metastatic disease. Seven out of the forty case series reviewed documented the use of adjuvant radiotherapy post-CBT excision at rates between 2% and 15% (Table 4).

Clinical follow-up is paramount to identify any evidence of tumour recurrence or development of a contra-lateral CBT especially in patients with a family history or with confirmed underlying gene mutations. Sequential clinical examination is unreliable so we advocate an annual duplex ultrasound with two yearly MRA, which has an increased sensitivity for multicentric tumours in patients with a history of multiple paragangliomas or gene mutations [19]. Screening of family members for occult disease should also be considered as an asymptomatic CBT in our series was identified in the father of a patient with bilateral CBTs who was known to be a SDHD gene mutation carrier [5].

CONCLUSION

Management of CBTs remains complex and technically challenging. Despite a dramatic reduction in stroke and mortality, significant morbidity is still associated with surgical treatment particularly to the adjacent cranial nerves. Our long-term experience is comparable with other modern case series reports where surgical intervention carried a low risk of stroke or death and conferred a long-term survival advantage.

KEY LEARNING POINTS

Over 22 years the incidence of CBTs in Northern Ireland was 0.08/100,000 people/year.

Our experience is comparable with other modern case series reports where surgical intervention carried a low risk of stroke or death.

The management of CBTs requires the ability to safely reconstruct carotid vasculature. This was required in 19% of cases in our series where the median tumour size was 5cm in diameter.

Morbidity from surgery mainly results from the persisting risk of cranial nerve injury.

Conservative management may be considered for those unfit for surgery as the majority of tumours are benign.

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Paper

Views of Foundation Doctors (Year 2) on Distress Likely with Genital Examination in Children

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Abstract: Little is known about the attitude of newly qualified doctors towards intimate examination of children. During the 2 course of a training day in child protection, an exercise was undertaken to ask Foundation doctors (FY2) what impact they thought genitalia examination had on children. These responses have been compared with the only systematic examination of the response of children and their parents to such examinations that has been published.

The doctors in question believe such examinations to be more distressing than children or their parents appear to perceive. It is likely that such perceptions may inhibit newly qualified in efforts to acquire such skills that may not have been acquired as medical students. This may be an area of continuing difficulty for the future because of the changes in access to relevant learning experiences for medical students.

Key Words: intimate examination; children; training; perception

INTRODUCTION:

The ethics of learning intimate examination by medical students and junior doctors has been a topic of discussion in recent years. Both ethical [1]and legal [2] considerations have reduced some of the traditional opportunities to learn such examinations. There have been various efforts made to replace traditional approaches, ranging from simulators [3] to patient or volunteers acting as teachers [1].

Little attention has been paid to the impact of this change on doctors' attitudes to examination of the genitalia of pre-pubertal children and there is relatively little information about children's views on genitalia examination nor on that of junior doctors.

METHODS:

In the United Kingdom (including Northern Ireland) newly qualified doctors are enrolled for two years in a generic skills training rotation referred to as Foundation Training. Various arrangements have been made for formal training activities in different regions of the UK. In Northern Ireland all such Foundation Trainee Doctors have to attend eight mandatory training days and one of these is devoted to child protection.

During one such session the Foundation Doctors were asked about their opinions on what young children would feel about examination of the external genitalia. 41doctors attended this session, one of seven sessions on the topic of child protection for the cohort of 235 doctors in their 2nd year of foundation training in 2010/2011.

The information about children's' views were taken from a study involving Norwegian children and their parents in 2007 [4]. For this study the authors devised two scales, which were published in English translation in the original article. - Children's were asked to indicate on a 'smiley faces' scale (Fig 1) what they felt about the experience of examination. Parents were asked for their observations as to the degree of anxiety / restlessness on a scale ranging from 'none' to 'a whole lot'.

During the course of the session on Child Sexual Abuse the Foundation Doctors were asked to indicate on the same scales how they believed children would describe their experiences and how parents felt their children reacted during the examination.

Fig 1. Faces Rating Scale

Statistical Analysis was undertaken using WINPEPI. [5] Effect size was also calculated using WINPEPI.

RESULTS:

The data are presented in three ways: as scores and 95% confidence intervals; differences between groups were analysed by chi-squared analysis and effect sizes were calculated to summarise the size of the differences between groups

SCORES AND 95% CONFIDENCE INTERVALS

The results are summarised in Tables 1 and 2. For ease of comparison the 95% confidence intervals for the comparisons are presented graphically in Figs 2 and 3.

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Table 1:

Perception of Examination of Genitalia - Comparison of perceptions of Children examined with opinions of Foundation Doctor's (FY2)

	FY2 Doctors			Children		
Category- Perception of Examination of Genitalia	Number	Proportion	95% Confidence Interval for Proportion		Proportion	95% Confidence Interval for Proportion
Positive	0/37	0*	0.000 to 0.078	77	0.49*	0.410 to 0.565
Somewhat Positive	0/37	0*	0.000 to 0.078	35	0.219*	0.162 to 0.291
Neutral	14/37	0.3784*	0.234 to 0.541	34	0.213*	0.156 to 0.284
Somewhat negative	15/37	0.4054*	0.257 to 0.568	7	0.045*	0.020 to 0.086
Somewhat negative	15/37	0.4054*	0.257 to 0.568	5	0.032*	0.012 to 0.069

** chi squared = 103.8, d.f. = 4 p = 0.000*

CHI SQUARED ANALYSIS

As indicated in Tables 1 and 2, the difference between children's' views and doctors opinions was statistically significant as was the differences between parents opinions and doctors opinions.

EFFECT SIZE

The effect sizes for the difference between Children and FY2 doctors perceptions was calculated as Cohen's w = 0.68 (corrected for table size = 1.316). By Cohen's criteria [6] this is a large effect size. The effect size for the difference between FY2 doctors and parents was calculated as Cohen's w = 0.604 (corrected for table size = 1.073). By Cohen's criteria this also is a large effect size.

DISCUSSION:

These findings suggest a significant gap between the views of children about intimate examination and the views of junior doctors, with junior doctors anticipating it will be experienced as producing more anxiety than it does produce. This discrepancy may result from a natural reluctance about intrusion into a private domain, a reluctance that may only be overcome with experience.

However it may also represent one of the consequences of the apparently restricted access to learning such examinations that may be the case in recent years. The study guide provided by the medical school which the vast majority of the doctors had attended defined intimate examinations as involving 'breast, external and internal female genitalia, penis, scrotum and rectum' and also says that such examination is 'Not appropriate' in Minor(s) (aged <18years) who are conscious and Gillick incompetent' and that "Students are always at liberty to refuse to examine a patient for educational purposes". [7] These findings parallel the findings about limited knowledge of anatomy of the genital area described for colleagues of this group in preceding years.[8]

The existence of such an area about which doctors are not knowledgeable and are reluctant may be one of the factors producing a reluctance about engaging with child protection matters in general, for example by inducing a fear of stumbling across an area of which the individual doctor has little knowledge or experience. At the same time the limitations of the evidence needs to be recognised – the sample of children from whom the above values are taken were a small percentage of those approached, although the study in question has been described as "good science" [9]

It may also be that attitudes to such examinations are different in the Norwegian population from which the original data comes. There is good evidence for different response styles (i.e. tendency to use the extremes or the middle values of a

Table 2:

Perception of Stress produced - Comparison of perceptions of Parents examined with opinions of Foundation Doctor's (FY2)

	FY2 Doctors			Parents		
Category Perception of Stress of Examination	Number	Proportion	95% Confidence Interval for Proportion	Parents (No)	Parents (% of 158)	95% Confidence Interval for Proportion
None	2	0.0571*	0.010 to 0.176	105	0.664*	0.588 to 0.735
Little	17	0.4857*	0.325 to 0.649	48	0.303*	0.235 to 0.379
Some	12	0.3429*	0.201 to 0.510	4	0.026*	0.008 to 0.060
Alot	2	0.0571*	0.010 to 0.176	1	0.007*	0.000 to 0.031
A Whole Lot	2	0.0571*	0.010 to 0.176	0	0*	0.000 to 0.019

** chi squared = 66.3, d.f. = 4 p = 0.000*

scale) in different cultures. [10] Children and adults may also have different response styles with young children tending to use the extremes more than older people. [11] However the distribution of results does not suggest that differing response styles are responsible for the differences described. For example there is no evidence of such clustering of the distributions of answers in Figs 2 & 3.

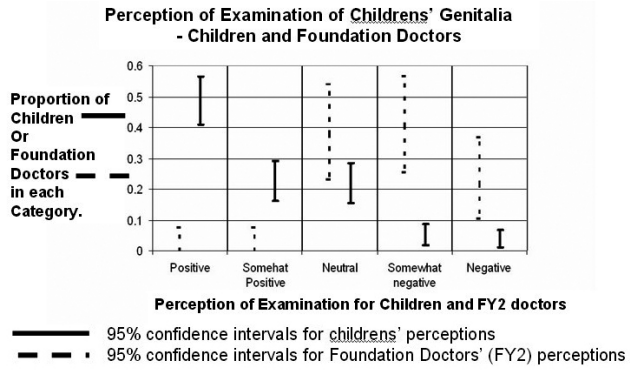

Fig 2. Comparison between FY2 doctors perception and children's perception of examination of genitalia.

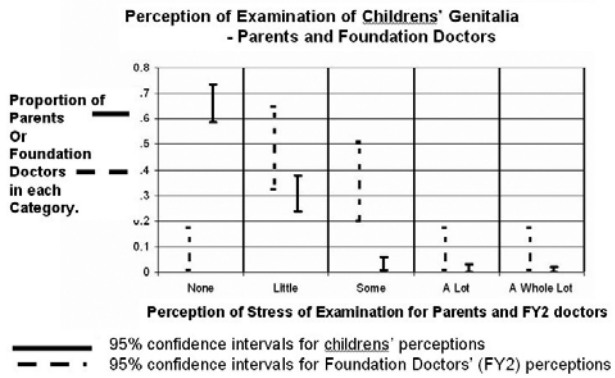

Fig 3. Comparison between FY2 doctors perception and parents perception of examination of genitalia.

The determinants of a patient's anxiety about a particular type of examination is likely to be related to characteristics of the examiner as well as that of the examinee [12]. It is possible that an unwarranted anticipation of anxiety may produce reluctance on the part of the examiner that will in turn make the examinee more anxious. Since the attitude of the parent is also likely to be one of the determinants of the child's response to such examination there is likely to be a group of interacting factors relevant. A review of the presence of parents during painful procedures suggests that their presence does not have any clear-cut advantage but there is no evidence to suggest it causes extra difficulties.[13] The factor that is most amenable to change is probably that of the doctor and the need to help doctors acquire attitudes which minimise patients discomfort with examination is likely to be a valuable contribution to doctors training, helping them overcome their fear that they "might break one". [14]

The author has no conflict of interest.

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Mucopolysaccharidosis Type I

Mucopolysaccharidosis type I is a lysosomal storage disorder that is caused by a deficiency of the lysosomal enzyme α-L-iduronidase and it is inherited in an autosomal recessive manner. In affected individuals decreased activity of the α-L-iduronidase leads to the accumulation of glycosaminoglycans (GAG) dermatan and heparan sulphate. This abnormal storage affects cellular functioning and ultimately causes multi organ involvement.

MPS I is a markedly heterogeneous disorder with a wide spectrum of disease. Historically it tended to be referred to as Hurler, Hurler Scheie and Scheie depending on the severity. These days we recognise that there is a lot of overlap and tend to view it as a spectrum. At the more attenuated end of the spectrum, intelligence is usually normal. Many paediatricians in Northern Ireland will be familiar with the severe end of the spectrum, commonly known as Hurler disease, as this is common in, though not confined to, the Irish Traveller community.

The more attenuated forms of the disorder may not be so familiar particularly as the facial appearance is very normal and so the possibility of an MPS disorder may not be apparent.

So what features should alert the clinicians to the possibility of MPS I? A very common presentation is clawing of the hands. This can come on at any time from childhood into adulthood. (figure 1)

There can be stiffness of other joints so the possibility of juvenile arthritis may be considered. However x-ray changes should show the presence of dysotosis multiplex which is the hallmark of MPS disorders. There may be hip dysplasia which can be put down to Perthe's Disease though a full skeletal survey should show that the bone changes are more widespread.

There is also a very high incidence of carpal tunnel syndrome. The possibility of MPS I should be considered in any young person presenting with carpal tunnel syndrome.

Patients may be found to have corneal clouding on a routine eye examination. They may also present with hearing loss. This can be conductive secondary to glue ear, sensorineural or a mixture of both.

A careful review of the medical history of MPS patients will often reveal a history of recurrent ENT infections. There may be a history of hernias which have required repair.

INVESTIGATION

If a diagnosis of MPS I is suspected then a sample of urine should be sent for GAG testing. It is very likely to show GAG's. If this is positive then a blood sample can be tested to look for α-L-iduronidase deficiency.

MANAGEMENT

Patients with MPS I require multidisciplinary follow up co-ordinated by a specialist clinic. They should be sent o cardiology because of the risk of valvular involvement, ENT, ophthalmology and orthopaedics. Anaesthetics are more problematic in MPS I so anaesthetists need to be aware of the diagnosis before any surgery is undertaken. For patients with the sever Hurler form of the disease the treatment of choice is a bone marrow transplant with enzyme replacement therapy (ERT) prior to the transplant and for a limited time afterwards. ERT on its own is not a suitable treatment for severe MPS I as it does not cross the blood brain barrier and cannot prevent the neurocognitive decline seen in these patients. ERT is a suitable treatment for the more attenuated forms in which neurocognitive decline is not a feature.

As MPS I is inherited in an autosomal recessive manner it is important that families are offered genetic counselling.

For further information on MPS I (and other MPS and related disorders) please contact the MPS Society at 0845 3899901 www.mpssociety.co.uk

Features which should alert the clinician to the possibility of MPS I

- Clawing of the hands
- Carpal tunnel syndrome especially in a young person
- Joint stiffness
- Hip dysplasia
- Corneal clouding.

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Paper

Pyloric Stenosis – Do Males and Females Present Differently?

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ABSTRACT

Aims: In infants with pyloric stenosis we explored (a) if males develop symptoms and present to hospital earlier than females and (b) does any delay in presentation influence the severity of metabolic derangement.

Method: A retrospective casenote review of 99 infants who underwent pyloromyotomy (with confirmation of pyloric stenosis) over a two year period (Jan 2006-Dec 2007) in our hospital. The data collected included: sex, age at onset of symptoms, age at presentation to hospital and initial blood results.

Results: The group comprised 84 males and 15 females. Symptoms developed at 26 (0-70) days in males and 35 (0-77) in females. (Mann-Whitney U=428, p=0.04 two tailed). Males presented to hospital at 34 (13-91) days, females at 45 (13-98) days (Mann-Whitney U=391, p=0.01 two tailed). The differences between males and females for (1) age at onset of symptoms and (2) age at presentation to hospital became more significant when weighted averages were calculated using SPSS (Statistical Package for Social Sciences). The lower weighted averages for male infants can be seen in the final table. Increasing duration of symptoms showed a positive correlation with fall in Chloride level. (Spearman's rho: r_s = -0.2, p=0.049 two tailed). There was a positive correlation between duration of symptoms and bicarbonate level but this was not significant. (r_s=0.06, p>0.05 two tailed). There was a positive correlation between duration of symptoms and pH, but this was not significant (r_s=0.12, p>0.05 two tailed).

Conclusion: In our hospital, females with pyloric stenosis develop symptoms and present significantly later than males. This should be considered when assessing a female with vomiting outside the usual 20-40 day range.

Keywords: pyloric stenosis; gender difference; time to presentation

INTRODUCTION

Infantile hypertrophic pyloric stenosis is the most common cause of gastrointestinal obstruction in the first few months of life. The incidence is 1-8 per 1000 live births in the Caucasian population. Salient features of the descriptive epidemiology of pyloric stenosis are well documented in the literature. Pre-eminent among these is the male predominance of the condition over females [1]. A genetic predisposition to pyloric stenosis is well established and it has been associated with several genetic syndromes [2,3]. The literature is also thronged with examples of the various ways in which to perform pyloromyotomy [4, 5]. However following a remark that 'girls with pyloric stenosis always present later'; a literature search for similar populations drew a blank. One of the authors was therefore challenged to provide the science behind this statement. Our study had three main objectives: firstly to determine whether females develop the symptoms of pyloric stenosis later than males. We also wanted to establish whether they present to hospital later than males. Lastly we wanted to ascertain whether increasing duration of symptoms is associated with a greater severity in metabolic derangement.

METHODS

A retrospective case-note review was conducted of all infants who underwent pyloromyotomy (with confirmation of pyloric stenosis) over a two year period in the Royal Belfast Hospital for Sick Children. Data collected included: sex, gestation, age at onset of symptoms (A) and age at presentation to hospital (B). From these data we calculated the gap (A-B) i.e. the mean duration of symptoms. The venous blood gas results upon admission to hospital were also identified and the biochemical values for pH, bicarbonate and chloride were recorded. The data were analysed using the SPSS 17.0 package. Statistically, all factors were assessed by the Mann-Whitney method. Some data were also analysed using Spearman's rho test of correlation, Chi-squared testing and risk ratios calculation. The threshold p value for statistical significance was <0.05. Selection criteria for this descriptive study included: all infants in Northern Ireland who had a diagnosis of pyloric stenosis with the International Classification of diseases and a hospital admission for pyloromyotomy between January 2006 and December 2007 in the Royal Hospital Belfast for Sick Children. There were no exclusion criteria in this study.

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RESULTS

General Results

A total of 99 infants underwent pyloromyotomy in the two year period. The group comprised 84 males and 15 females and therefore approximately 85% of this patient population was male with a 6:1 male-female ratio. The mean age when symptoms developed (A) in the study population was 27 days (range 0-77) and the mean age when children presented (B) was 35 days (range 13-98). The mean duration of symptoms (A-B) was 8 days (range 1-35). 17% of patients began symptoms before the fourteenth day of life and 75% began their symptoms between the fourteenth and forty-ninth day of life.

Male v Female

Males developed symptoms at 26 (0-70) days and females at 35 (0-77) days (Mann-Whitney U=428, p=0.04 two tailed). Males presented to hospital at 34 (13-91) days and females at 45 (13-98) days (Mann-Whitney U=391, p=0.01 two tailed). These results, analysed by the non-parametric Wilcoxon-Mann-Whitney test are shown in figure 1.

Ranks

	Sex	N	Mean Rank	Sum of Ranks
A	Male	84	47.60	3998.00
	Female	15	63.47	952.00
	Total	99		
B	Male	84	47.15	3961.00
	Female	15	65.93	989.00
	Total	99		
Gap	Male	84	49.52	4160.00
	Female	15	52.67	790.00
	Total	99		

Fig 1. Non parametric Wilcoxon-Mann-Whitney test sum of ranks

Figure 2 shows A (age in days when symptoms began), B (age in days when infant was brought to hospital) and the gap (A-B) with their corresponding relationship statistically to the sex of the patient. There was statistical significance with respect to A(0.048) and B(0.019).

Test Statistics[a]

	A	B	Gap
Mann-Whitney U	428.000	391.000	590.000
Wilcoxon W	3998.000	3961.000	4160.000
Z	-1.973	-2.336	-.394
Asymp. Sig. (2-tailed)	.048	.019	.694
Exact Sig. (2-tailed)	.048	.019	.698

a. Grouping Variable: Sex

Fig 2. Non parametric Wilcoxon-Mann-Whitney test showing statistical significance

This significance is alternatively seen by the percentiles table featured in figure 3, where in both cases A and B the males have a very definite lower weighted average. This deduction made from these results is that males tend to develop symptoms earlier, and present to hospital earlier than females. The gap between males and females increases as one moves from the 25th to the 75th percentile and therefore the table clearly demonstrates that at the upper percentile the gap between males and females is even wider.

Percentiles

		Sex	Percentiles 25	50	75
Weighted Average(Definition 1)	A	Male	18	26	31
		Female	22	34	52
	B	Male	25	30	42
		Female	34	40	59
	Gap	Male	3	7	10
		Female	4	6	13

Fig 3. Percentiles Table

Biochemical Results

From figure 4 it can be seen that increasing duration of symptoms showed a positive correlation with fall in Chloride level. (Spearman's rho: rs= -0.2, p=0.049 two tailed). There was a positive correlation between duration of symptoms and (a) bicarbonate level and (b) pH but this was not significant. (Bicarbonate: rs=0.06, p>0.05; pH: rs=0.12, p>0.05 two tailed).

Correlations

			Cl	HCO3	pH	Gap
Spearman's rho	Cl	Correlation Coefficient	1.000	-.669**	-.494**	-.200*
		Sig. (2-tailed)	.	.000	.000	.049
		N	97	94	96	97
	HCO3	Correlation Coefficient	-.669**	1.000	.342**	.062
		Sig. (2-tailed)	.000	.	.001	.555
		N	94	94	94	94
	pH	Correlation Coefficient	-.494**	.342**	1.000	.122
		Sig. (2-tailed)	.000	.001	.	.237
		N	96	94	96	96
	Gap	Correlation Coefficient	-.200*	.062	.122	1.000
		Sig. (2-tailed)	.049	.555	.237	.
		N	97	94	96	99

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 4: Table showing biochemical analysis by Spearman's rho

A categorical analysis of the 99 infants was undertaken with Chi-square testing and risk estimate statistical analyses. The two categories were: pH <=7.5 and >7.5 tabulated against infants whose delay in presentation to hospital was <=5days and >5days respectively. 75% of infants on presentation to hospital had a pH of <=7.5, and of this 75% subgroup, 71% were delayed for more than 5 days in presenting to hospital. The odds ratio was calculated as 1.55 and is not statistically significant as the 95% confidence intervals include 1(0.588-4.087). However we can deduce from the risk estimate result that infants are 55% more likely to have a metabolic alkalosis if the presentation to hospital is delayed for > 5 days.

DISCUSSION

An observational remark was shown to be supported in our data population. Females not only developed the symptoms of pyloric stenosis later than males but they also presented to hospital later in addition. These results were statistically significant in both categories. Males displayed lower weighted averages in both categories in the percentiles tables, again confirming that they develop symptoms and present earlier than females. On moving from the 25th to the 75th

percentile, the gap between the sexes widened. Indeed at the 75th, the gap is widest, again showing that females develop symptoms and present to hospital later than males. Increasing duration of symptoms showed a positive correlation with fall in chloride level. This was statistically significant. Although the results also showed a positive correlation between duration of symptoms and both bicarbonate and pH levels, unfortunately these results were not statistically significant.

The main limitation of this study is the small sample size, however the Royal Belfast Hospital for Sick Children is the Paediatric surgical unit in Northern Ireland and therefore our 2 year period is a good representation of the population. Given this the study does show with statistical significance, that females develop the symptoms of pyloric stenosis and present to hospital significantly later than males. This should be taken into account when assessing females with vomiting outside the usual 20-40 day range.

The authors have no conflict of interest

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Case Report

Locked-in, walked out

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Abstract: Locked in syndrome is typically associated with significant morbidity and mortality. We report a patient who had an unusually good recovery from locked in syndrome due to pontine infarction. The good recovery exhibited by our patient may have resulted from resolution of oedema at the site of infarction and brainstem plasticity being augmented by initial supportive measures in the intensive care unit and early, intensive rehabilitation.

INTRO

The term 'locked in' refers to the syndrome of tetraplegia and anarthria with preserved awareness. It was first coined by Plum and Posner in 1966, and is usually due to a lesion of the ventral pons[1]. It was initially believed to have a grim prognosis, but prolonged survival has been demonstrated in some cases in the last three decades[2-4]. The condition continues to have significant associated mortality and morbidity, and considerable functional impairment persists in the vast majority of survivors[2-4]. We report a patient who was 'locked-in' due to bilateral pontine infarction, who exhibited an unusually good functional recovery.

CASE REPORT

A 37 year-old previously well female, with a history of migraine with aura, with no other known vascular risk factors experienced a transient episode of diplopia, vertigo and vomiting with subsequent complete recovery. She felt that this was an unusual for her typical aura. The following day she was found unresponsive in her car, with no evidence to suggest a road traffic accident had occurred. Leg twitching was observed by paramedics, and the patient was intubated, ventilated, and admitted to the intensive care unit (ICU) at a district general hospital where a computed tomography (CT) brain scan demonstrated no abnormality. She was subsequently transferred to the regional ICU on the following day, and on sedation withdrawal she was breathing spontaneously, but tetraplegic and anarthric. Full range of eye movements was observed and upper eyelid movements were preserved, which facilitated appropriate 'yes/no' responses. A clinical diagnosis of locked-in syndrome was made and magnetic resonance imaging (MRI) brain demonstrated bilateral pontine and right cerebellar infarction (Figure 1). These areas exhibited restricted diffusion, consistent with acute infarction. A magnetic resonance angiogram (MRA) of her intra-cranial vessels was normal, indicating presumed spontaneous recanalisation of the basilar artery. Full blood count, inflammatory markers, fasting glucose, renal and liver function tests were all normal. Fasting lipid profile revealed and elevated cholesterol (6.16 mmol/L) and triglycerides (4.63 mmol/L) levels, and a raised cholesterol/high-density lipoprotein (HDL) ratio. A thrombophilia screen was negative, and no abnormality was detected in an electrocardiograph or transoesophageal echocardiogram.

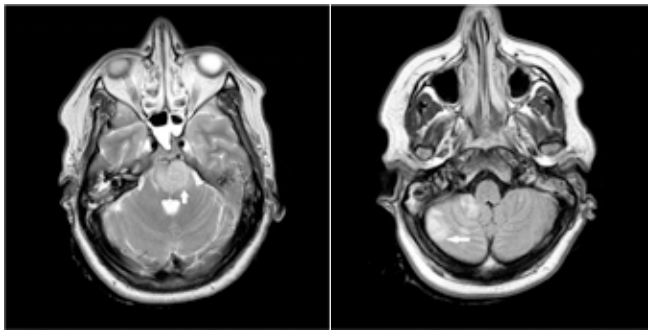

Fig 1a & b. T2-weighted axial MRI brain demonstrating bilateral pontine and right cerebellar infarction (August 2008).

A method of communication was established using her preserved eye and upper eyelid movements, similar to that described in a previous review of LIS[5]. Aspirin and atorvastatin were commenced for vascular disease secondary prevention. Two weeks after her initial presentation, she was transferred to a neurology ward at which stage she remained anarthric and tetraplegic. There was early and intensive involvement from physiotherapists (PT), occupational therapists (OT) and speech and language therapists (SALT). A gastrostomy feeding tube was inserted and she also had early and regular review by the neurorehabilitation team. She remained completely quadriplegic for three weeks and completely anarthric for six weeks. At three weeks, a flicker of voluntary left leg movement was observed. Subsequently, she exhibited a slow but surprisingly continual recovery in limb power initially and bulbar function later (Table 1).

Eight weeks after her ictus, she was transferred to the Regional Acquired Brain Injury Unit (RABIU). At that point, she had significant dysarthria and could only safely swallow soft foods. She required a hoist for all transfers and could walk using a rollator with the maximum assistance of two physiotherapists. Her 10 metre walking time was 1 minute and 39 seconds. Functionally she required assistance with all

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activities of daily living (ADLs). During a ten week in-patient stay at RABIU, with ongoing multi-disciplinary rehabilitation team input, her recovery continued. On discharge from RABIU 18 weeks after her initial presentation, her speech was easily intelligible and she was managing a soft to normal diet safely. She was independent with all ADLs, transfers and could walk independently, but preferred the additional security of a rollator, her 10 metre walking time being 18 seconds. An MRI brain was repeated 9 months after her symptom onset, which demonstrated an extensive gliotic scar incorporating nearly all of the left pons (Figure 2). She has continued to improve since discharge from inpatient rehabilitation and is considering a return to employment.

TABLE 1

Summary of recovery

	Initial assessment	Transfer to RABIU (8 weeks)	Discharge from RABIU (18 weeks)
Speech	Anarthric	Significant dysarthria	Easily intelligible
Swallow	Nil by mouth	Soft diet	Soft-normal diet
Transfers	Hoist	Hoist	Independent
Walking	Not applicable	Rollator, maximum assistance of 2	Independent
10m walk time	Not applicable	1 min 39 secs	18 secs (with rollator) 42 secs (independently)
Activities of daily living (ADLs)	Assistance with all ADLs	Assistance with all ADLS	Independent with all ADLs

DISCUSSION

Despite the improvements in outcomes from LIS reported in recent decades, the degree of recovery experienced by our patient is notable. A sub-classification of LIS exists in which Plum and Posner's original description, where vertical eye movements are the only preserved motor activity, is termed the classical form[6]. Incomplete LIS is similar to the classical variety but also has remnants of other voluntary movements in addition to vertical eye movements. Using this sub-classification, our patient initially had incomplete LIS as there was preservation of horizontal eye movements. However, she was undoubtedly at the most extreme limit of the incomplete

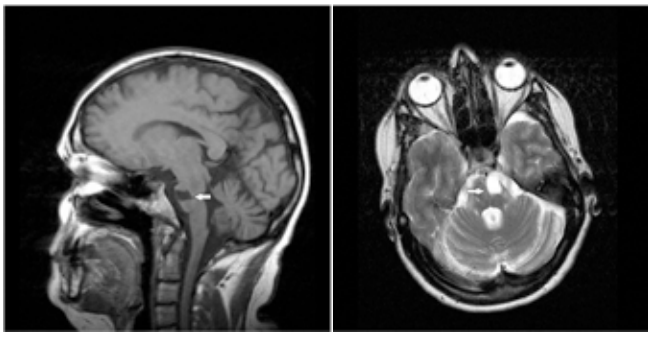

Fig 2a & b. T1-weighted sagittal and T2-weighted axial MRI brain demonstrating an extensive left pontine gliotic scar (May 2009).

TABLE 2

Comparable cases

Authors	Year	Journal	Total Cases (n)	Comparable Recovery (n)
Bauer et al	1979	J Neurol	12	2
Khurana et al	1980	Ann Neurol	3	3
McCusker et al	1982	Arch Neurol	4	1
Ebinger et al	1985	Int Care Med	2	1
Yang et al	1989	Arch Phys Med Rehab	1	1
Richard et al	1995	Paraplegia	11	2
Casanova et al	2003	Arch Phys Med Rehab	14	1
Doble et al	2003	Arch Phys Med Rehab	29	0
New et al	2005	Arch Phys Med Rehab	1	1
Høyer et al	2010	Brain Injury	9	2
Leeman & Schnider	2010	Rev Med Suisse	1	1
Total				**15**

LIS sub-category. The only classification scale of recovery from LIS is for motor recovery (Figure 3), and has been used in the majority of the literature relating to LIS recovery and outcomes[2]. In accordance with this scale, our patient exhibited a 'full recovery' of motor function. Table 2 summarises the 15 previous cases of LIS that we considered to be comparable to our case, in terms of aetiology (vascular), initial severity and duration of locked-in state and extent of recovery[3, 6-14]. Very few prognostic indicators pertaining to LIS exist, but non-vascular aetiologies and early preservation of horizontal eye movements have been associated with better outcomes[2, 10]. Horizontal eye movements are initiated in the brainstem in the paramedian pontine reticular formation beside the sixth nerve nucleus in the pons. Vertical eye movements are initiated higher in the brainstem in the midbrain and diencephalon[15]. The favourable outcome sometimes associated with preserved horizontal eye movements in LIS is believed to be reflective of a more limited pontine lesion.

No recovery	No return of motor function, total dependence for all ADLs
Minimal recovery	Minimal motor return, total dependence for all ADLs
Moderate recovery	Moderate motor return, independence in some but not all ADLs
Full recovery	Independence in all ADLs, but some minimal neurological deficit
No neurological deficit	No reported residual deficits

Fig 3. Classification of recovery from LIS[2]

The impressive recovery observed in our patient may partly be explained by an eventual resolution of oedema surrounding the site of infarction. In addition, the development of a large gliotic scar encompassing the left pons on her repeat MRI scan (Figure 2) in a patient with marked and symmetrical motor recovery is suggestive of a degree of brainstem plasticity. These intrinsic mechanisms of recovery are also likely to be

supplemented by the initial supportive care she received in ICU and her subsequent rehabilitation. Improved long-term survival rates and functional outcomes have been observed in patients who had early and intensive rehabilitation[2, 4, 14]. Furthermore, in the cases comparable to ours, all had access to critical care environments if necessary and initiated intensive rehabilitation early at dedicated rehabilitation units.

In summary, this case demonstrates an unusually good functional outcome following LIS from pontine infarction. Similarly good outcomes from LIS have rarely been reported. In concordance with previous reports, there was good recovery after early intensive rehabilitation. Such cases also strengthen the claim that the full range of supportive therapies, including management in critical care units, should be considered in patients presenting with LIS.

The authors have no conflict of interest.

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Case Report

Complications of gastric bypass surgery, a Northern Ireland experience.

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ABSTRACT

Amongst western nations there are increasing levels of adult obesity. In Northern Ireland the majority of patients who undergo bariatric surgery travel to centres in the UK mainland. Thus, local experience of this type of surgery and the complications which can arise is limited.

We report the case of a young woman who had previous bariatric surgery and a significant complication. In the future, greater numbers of patients will undergo this type of surgery. Therefore all emergency doctors need to be familiar with these procedures and the common complications.

Keywords: Hernia, Gastric bypass surgery

Obesity is now a World Wide epidemic and is associated with both physical and psychological morbidity. Over the last decade, increasing numbers of patients have undergone bariatric procedures as these interventions have consistently been shown to be the only way to achieve sustainable weight loss with improvements in co-morbidities such as type II diabetes and hypertension[1].

Currently in Northern Ireland, no funding exists for a designated centre for bariatric surgery and local patients travel to centres in the UK mainland. Last year (2009), 150 patients were referred from this Provence for consideration for surgery, 80 patients subsequently underwent bariatric procedures. This year, 44 patients have had surgery (number correct to May 2010) and the total number for the year is expected to exceed 80[2]. In addition, a significant number of patients are thought to self-refer to bariatric centres in both the Republic of Ireland and mainland Europe. Therefore, significant numbers of these patients do exist locally and, since they travel for surgery, local experience of the complications which may arise is limited.

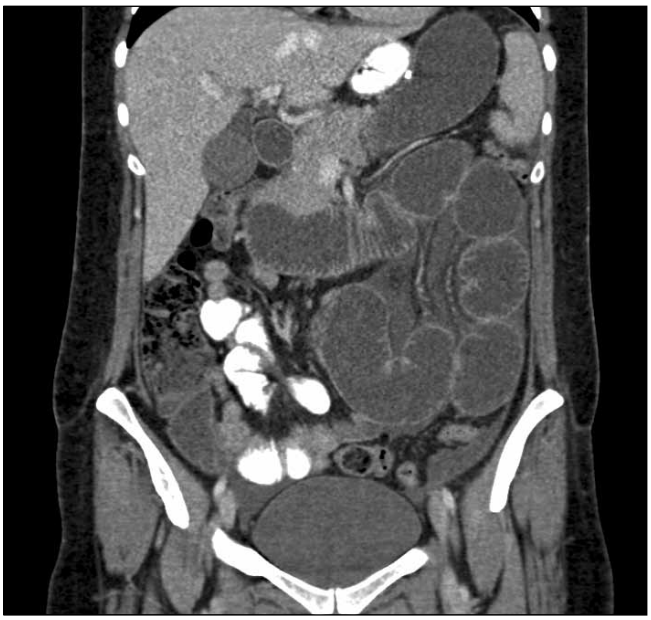

Fig 1. CT scan showing dilated small bowel, (note contrast in the gastric pouch and collapsed small bowel).

REPORT

A thirty four year old woman was admitted under the care of the gynaecologists with a six day history of left iliac fossa pain. She had no history of vomiting and her bowels were moving satisfactorily. She had a past history of gastric bypass surgery in 2003, which had been so successful that subsequently she had an abdominoplasty in 2007. Following senior review, the pain was not felt to be gynaecological in origin and surgical opinion was requested.

At surgical assessment the patient was found to be apyrexic and haemodynamically normal. Abdominal examination found tenderness in the left iliac fossa with localised peritonism. White cell count was 4g/dL and C reactive protein was 65ug/L. Plain film of the abdomen did not demonstrate any significant abnormality, but in view of the clinical findings, a CT scan was arranged.

The CT scan found that the oral contrast passed from the gastric pouch into collapsed small bowel (Figure 1). This was an unusual finding. The gastric remnant was dilated and there were multiple dilated loops of small bowel in the

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left abdomen. The Radiologist reported a suspicion of an internal hernia.

The patient proceeded to laparotomy where it was established that a retro-colic Roux en Y gastric bypass had been fashioned at the bariatric operation. In addition, two causes of obstruction were identified. A closed loop bowel obstruction involving the pancreatico-biliary limb was caused by a band adhesion to the proximal jejunum. This was simply divided. An internal hernia was also found involving the common jejunal channel, which was herniating through a defect between the transverse mesocolon and the free edge of the mesentery of the alimentary (Roux) limb as it ascended to the supra-colic compartment. This site is known as Petersen's space by bariatric surgeons and the hernia is labelled Petersen's hernia. Fortunately, it was possible to relieve both causes of obstruction without the need for small bowel resection or disruption to the neo-anatomy. The mesenteric defect which caused the internal hernia was closed and post-operatively the patient did well.

DISCUSSION

In the UK, the predominant bariatric surgical procedure is laparoscopic gastric banding. This involves the placing of a silicone ring-like inflatable device around the stomach just below the gastro-oesophageal junction[1]. In North America, laparoscopic gastric bypass is the most common procedure[3]. This involves partitioning the stomach to create a 15-30ml gastric pouch just distal to the oesophagus. An area of jejunum about 50-100 cm distal to the ligament of Treitz is then selected for division. The distal jejunum (alimentary/ Roux limb) is then brought to the supra-colic compartment, either through the transverse mesocolon or anterior to the transverse colon and anastomosed to the gastric pouch. The bypassed segment, which includes the gastric remnant, duodenum and proximal jejunum, is anastomosed at a variable location down the alimentary (Roux) limb (generally 100-150cm length). This form of bariatric surgery has been shown to result in greater and more consistent weight loss than other bariatric procedures and induces weight loss by decreasing the absorption of nutrients and calories[4].

Abdominal pain following gastric bypass has a broad list of differentials. Although common diagnoses cannot be discounted, complications specific to gastric bypass such as: biliary disease; anastomotic strictures; marginal ulceration at the gastro-jejunal anastomosis and internal hernia must be considered first.

Internal hernias, although quite rare in the general population, are well described following laparoscopic gastric bypass. Clinical presentation can be vague. Patients often present with ambiguous symptoms such as nausea or intermittent abdominal pain. Vomiting is frequently absent due to the reconfigured anatomy and other findings, such as abdominal distention may be masked by the patient's body habitus[1,3]. Hence, the diagnosis of obstruction is frequently overlooked. Laboratory investigations add little. Upper GI contrast studies and CT scanning have proved more useful[3]. However, surgeons should bear in mind a 2003 report by Higa et al. Higa et al reported a series of 63 patients who had previously underwent laparoscopic gastric bypass. Nine of these patients had reported "normal" contrast enhanced radiological studies,

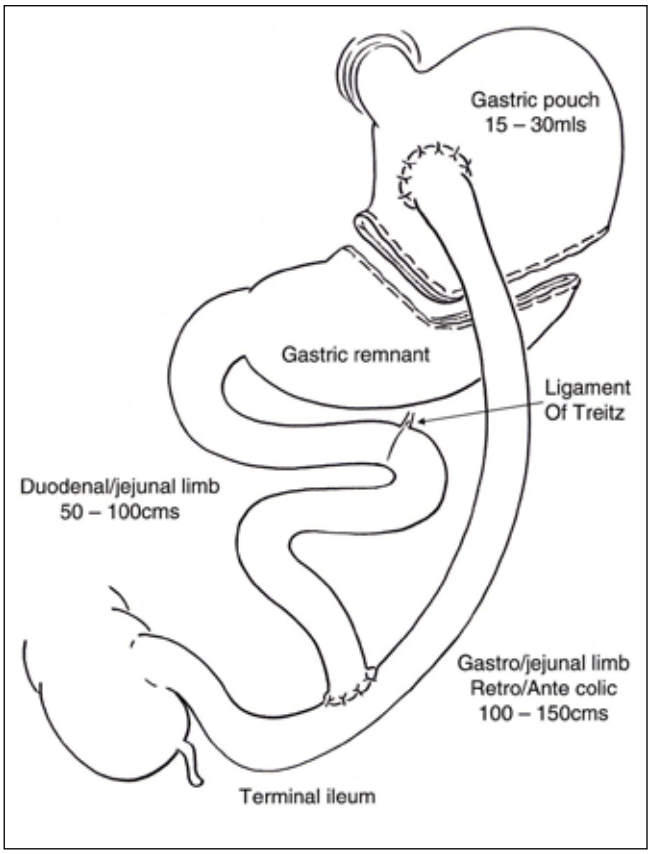

Fig 2. Simplified drawing of the neo anatomy following gastric bypass surgery.

yet proceeded to laparotomy due to ongoing abdominal pain. At operation, all were found to have internal hernias[5].

The mechanism of hernia formation following bariatric surgery is thought to be due to the expansion of potential internal hernia sites that follow loss of intra-abdominal fat. In addition, although not a factor in this case, is the reduced tendency to form post-operative adhesions following laparoscopic procedures[4,5]. This increased mobility allows the bowel to enter the potential sites of hernia more frequently. Three locations are well described where internal hernia are likely to occur following a retro-colic Roux en Y gastric bypass, the mesomesenteric defect at the jejuno-jejunostomy, Petersen's defect which is the space posterior to the alimentary (Roux) limb, and, the mesocolonic defect which can be avoided if the alimentary (Roux) limb is brought to the supra-colic compartment anterior to the transverse colon[4,5].

Surgical treatment consists of hernia reduction and ideally this should be conducted by the original bariatric team. However, if bowel ischemia is a possibility operation should not be delayed. Hernia reduction has been reported laparoscopically, but for those surgeons who have no experience of bariatric surgery, an open procedure is advised. Following any emergency management, the patient should then be referred back to a dedicated bariatric team to provide appropriate follow-up[1].

CONCLUSION

With bariatric surgery becoming more prevalent, all

emergency doctors need to be familiar with the procedures preformed and the common complications. Following gastric bypass, patients can have a small bowel obstruction without displaying the classical symptoms of abdominal distention, absolute constipation and vomiting due to the reconfigured anatomy. These patients are difficult to assess and vague symptoms maybe all that heralds the onset of serious complications. Therefore, it is advised that all post-operative bariatric patients who present with abdominal pain should be evaluated quickly and undergo early contrast enhanced CT if obstruction is suspected. If a diagnosis of an internal hernia is confirmed or still thought likely regardless of "normal" radiological studies, surgical exploration should not be delayed. This early and aggressive approach after gastric bypass will prevent bowel ischaemia and perforation.

The authors have no conflict of interest.

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Annual Oration

The Doctor's Dilemma: Clinical Governance and Medical Professionalism

Royal Victoria Hospital 2010

Roy Maxwell

I would like to thank Dr Beringer and the Medical Staff for the privilege of giving the oration. Two duties fall to me this morning. The first is to welcome the new medical students to the Royal Victoria Hospital and this I do most warmly.

My second duty is to offer some thoughts on a subject related to medicine. The topic is entirely of my choosing and I approach my task conscious of the risk that you are subjected to the ramblings of someone approaching the end of his medical career – the danger of giving a grumpy old man a platform. Some of the matters that I wish to discuss have caused considerable distress to our profession in recent years. But then, no challenging enterprise is going to be comfortable all the time.

I should begin by confessing a bias. It is that the answers to many of our questions are to be found in history and literature. Simply stated, if we want to understand our present position, we need to understand how we reached it.

And so I come to the first part of my title. George Bernard Shaw's play, *The Doctor's Dilemma,* was first produced in London in November 1906. It was published five years later with a 'Preface on Doctors' almost as long as the play itself. The subject of the play was one which remains topical – the distribution of limited resources. The dilemma confronting the doctor, Sir Colenso Ridgeon, was that he was able to treat only a limited number of patients with tuberculosis and he must decide between the talented, but feckless artist, Louis Dubedat and the worthy, but ordinary young Doctor Blenkinsop.

Shaw was friendly with Sir Almroth Wright who was Professor of Pathology in St Mary's Hospital Medical School, the department where Alexander Fleming discovered penicillin. Wright was a polymath, conversant in literature and philosophy. As a youth he had lived in Belfast where his father was vicar of St Mary's Church on Crumlin Road. He attended the Royal Belfast Academical Institution for a time, but was educated mostly by his parents and tutors. He studied languages and medicine simultaneously in Trinity College Dublin. Shaw, by all accounts, often visited the library in Wright's department where he enjoyed hearing the unguarded conversation of the medical men. When one of Wright's young assistants complained that the Inoculation Department had more work than it could manage and had to select who should receive treatment, Shaw had the idea for his play. Wright walked out on the first night of the play, not because Shaw had caricatured him, but because he disagreed with Shaw's choice of whom to treat.

Shaw addressed one medical dilemma in his play, but in the preface he discussed many others. He dealt at length with vivisection, of which he was a trenchant opponent. He was also strongly opposed to private practice and thought that paying doctors according to the complexity of the treatments they provided was as illogical as paying judges in proportion to the severity of the punishments they handed down. He concluded that "Until the medical profession becomes a body of men trained and paid by the country to keep the country in health it will remain what it is at present: a conspiracy to exploit popular credulity and human suffering"[1]. Other objects of his attention included whether medicine was a science or an art – he thought that it was an art - and the misinterpretation of statistics and evidence. Little escaped him; he even had an opinion on the psychology of surgeons. Whilst Shaw was often critical of doctors, he blamed most of the problems on the circumstances in which they had to work. In moral terms, he considered them no better or worse than the rest of the population. All the professions were, in his view, conspiracies against the laity. In 1930 he wrote of the need to bring the medical profession under responsible and effective public control, advocating lay representation on the General Medical Council.

In recent years, regulation of medical practice has achieved a prominence which Shaw could hardly have imagined. My main theme for this morning is to consider the methods used to regulate and control medical practice. The term clinical governance entered the consciousness of doctors with the publication of a white paper, *The New NHS: Modern, Dependable*[2] in December 1997. There was much uncertainty as to what exactly was meant by clinical governance and how it would affect practice. The idea of governance was not new; it was adopted from the corporate business world and its origins there yield some insight into the effects that it has had on medicine. Misdemeanours by directors and executives resulted in the collapse of business and financial organisations and, as a result, a committee chaired by Sir Adrian Cadbury was set up in May 1991. What came to be known as the Cadbury report was published in the following year. Ten further reports and codes of conduct were produced in the next thirteen years. Then came the Companies Act of 2006. The Financial Services Authority commenced a review in 2002 to include corporate governance and the Financial Reporting Council established a committee in 2004

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specifically to deal with corporate governance. With all this regulation, shareholders and investors might have thought that they were quite well protected – until the catastrophic failure of Northern Rock in 2007 and the Royal Bank of Scotland in 2008. There are three obvious lessons. First that regulation is difficult. Secondly, that regulations tend to proliferate, and thirdly that they were not effective, at least, in the corporate world.

What then of clinical governance? It was driven by a number of instances in which there was widespread media coverage after patients had been damaged. In Bristol in the late 1980s and early 1990s a high death rate following some paediatric cardiac surgical operations led to the largest inquiry the General Medical Council had ever undertaken and to a hearing lasting 74 days. Two doctors' names were erased from the Medical Register and a third had restrictions placed on his practice. Harold Shipman was arrested for murder of patients in 1998 and convicted two years later. Rodney Ledward and Richard Neale, both gynaecologists, were struck off the Medical Register, but there was criticism of the length of time taken to identify and act upon their poor practice.

The White Paper that introduced the concept defined clinical governance as "a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence of clinical care will flourish". Clinical governance was to be achieved by:

Application of evidence-based care

Use of clinical guidelines

Clinical audit

Professional education

Research

Risk management

Individual appraisal and re-validation

All of these are worthy objectives, but could deliver only if implemented effectively. None has been, at least so far. Evidence-based practice has been misinterpreted as the simplistic enforcement of rules. The requirements of good quality clinical audit have not been recognised so that it has not achieved anything approaching its potential. The importance of professional education was acknowledged in the consultant contract, but time for supporting professional activities has been a casualty of financial pressures. Clinical academic departments have been emasculated in recent years with the loss of much potentially valuable clinical research. Risk management is now a mature discipline with a significant research base, but even its most basic principles have not yet been adopted by NHS management. After the Bristol case, the GMC brought forward the idea of re-validation as a means of ensuring that practitioners continued to perform effectively throughout their working lives. That was in 1998 and no functioning system of re-validation has yet been devised. Annual appraisals continue, but their effectiveness remains to be shown. Sir Gerry Robinson had a view on appraisal in the business world. He said: "I hate appraisal systems. The best way of tackling a staff issue is to do it instantly...[3]"

So, the experience of implementation of clinical governance has not been good. If its objective was to ensure the quality of care for patients and prevent news stories of the kind which contributed to its introduction, it did not succeed. In March 2009 a report by the Healthcare Commission of poor care and excess mortality of between 400 and 1200 patients in Mid Staffordshire Hospitals made headlines. Stafford Hospitals were a foundation trust, a status achieved because their management procedures were considered of such quality that they could be allowed greater autonomy in running their affairs. Robert Francis QC, in the report of his inquiry[4], said "The story of Stafford shows graphically, and sadly, that benchmarks, comparative ratings and foundation trust status do not in themselves bring to light serious and systematic failings." At the House of Commons question time, Gordon Brown blamed hospital managers. Andy Burnham, the health secretary, spoke of a dysfunctional organisation. Stafford was said to be an isolated incident, but some months later there was a similar report of poor care and over 400 preventable deaths at Basildon and Thurrock Hospitals, also a foundation trust. There were allegations that the problems at Mid Staffordshire and Basildon should have been identified sooner and the Doctor Foster organisation claimed that other hospitals, too, had high mortality rates. Despite its laudable aims, the verdict on ten years of clinical governance must be one of failure.

What, then of medical professionalism? The rise of professional society in the first half of the 20th century was created by education and consolidated by exclusion of the unqualified. The welfare state with the expansion of medical technology and an ageing population increased the demand for the services of professionals. The oil crisis of 1973 and subsequent world recession led, as hard financial times often do, to questioning of attitudes and policies. Schools, universities, and the welfare state were seen as parasitic upon the wealth-creating private sector. Despite this rhetoric from the new political right, expenditure on health continued to rise, but the view gained ground that healthcare needed to be managed.

The new management of the NHS began after the first Thatcher-led government asked Roy Griffiths, Managing Director of Sainsbury's, to examine the problem and advise. His report[5] called for a management structure with devolution to hospital level and he thought that doctors should contribute more to management of the service. It was eight years before devolution occurred with the introduction of trusts in 1991/2. But it was never true devolution. Central control became stronger and all that was really devolved was the enforcement of that control.

The result was that, in the last quarter century, concepts of medical professionalism were sidelined in the drive for central control. But not entirely. Professional standards for modern times were defined in the late 19th and early 20th century writings of physicians such as Sir William Osler, and were part of a culture, taught mainly by example. Although the principles of professionalism were well established, the practice did not keep pace with a changing society and the replacement of paternalism by patient autonomy. Sir Donald Irvine, who was president of the GMC at the time of the Bristol case, spoke of a new professionalism[6], but all

of the core components he described were, in fact, included in the old professionalism which had just not kept pace with changing times. What then is professionalism? We could simply say that, like art or obscenity, it's difficult to define, but everyone knows it when they see it.

The literature on professionalism includes long lists of attributes, 90 in one publication[7], the commonest being altruism, accountability, respect, trustworthiness, responsibility and excellence. Whether professionalism can be taught remains unclear, but it does seem likely that it can be learned. Whilst it might be assessed subjectively, a validated means of measuring professionalism remains elusive. Perhaps we should remember with Einstein that not everything that matters can be measured and not everything that can be measured matters.

There are two aspects of professionalism which I would like to discuss further, first, trust and secondly excellence. Surveys show that the level of trust which patients place in their doctors is high. Nevertheless, society in general is much less trusting than in the past and this distrust extends to all those perceived to hold authority or expertise. Although education is more widespread, society is more complex. Everyone is a layman, except in his own specialty. Distrust is an easy response to that which we don't understand. People are more fearful of risks, not just in medicine, but with everything from nuclear power to genetically modified crops. With doctors, trust will be based mostly on the citizen's expectation that their doctor has gone through a process of selection and education, and be in possession of the skills and qualities that justify their trust.

Onora O'Neill, in her Gifford Lectures[8] of 2001 to the University of Edinburgh and the BBC Reith Lectures[9] of the following year, gave a most lucid exposition on the subject of trust. She cited four reasons for what she described as the culture of suspicion. First, the human rights movement with its emphasis on rights without reference to the corresponding responsibilities. Secondly, current concepts of accountability with paralysing burdens of managerial targets and bureaucratic process. Thirdly, she thought that demands for transparency in the information age had displaced the obligation not to deceive. Finally, she criticised the double standard of public culture, often credulous of its own standard and critical of everyone else's. It may be that wider societal factors are stronger determinants of whether our patients trust us as doctors than anything we do individually or collectively, or even that regulatory bodies might impose.

Now, to excellence. How can it be achieved? Pre-requisites would include the selection of practitioners with the appropriate attributes and providing them with the necessary knowledge and skills. But scientific knowledge and technical skills alone are not enough. The art of medicine is in the judgement that applies the available science and technology to the needs of the individual patient. Excellence is the achievement of the best possible outcome for everyone, which brings me to evidence-based medicine (EBM). Its recent history starts with Professor Archie Cochrane's Rock Carling lecture of 1971 entitled '*Effectiveness and Efficiency: Random Reflections on Health Services'*. His short book of the same title, published in the following year, had a national and international impact which continues until this day. Cochrane's early experience shaped his views. As a young doctor, he found himself in a prisoner of war camp where tuberculosis was rife. Treatments were available, but Cochrane, had no idea which to use or when, and was fearful that some of his interventions might even have been detrimental. After the war he joined the Medical Research Council and, through his attempts to answer clinical questions scientifically, became interested in the conduct of clinical trials – observer error, reproducibility and bias. In his book, he wrote that he had once asked a crematorium worker, who had a contented look on his face, why he found his work so satisfying. The employee replied that he was fascinated by the way in which so much went in and so little came out. Cochrane thought that if the man took a job in the NHS he could increase his job satisfaction even more. The central argument of Effectiveness and Efficiency was that the NHS was spending enough – it was 4% of GDP at that time – but just needed to be more rigorous in ensuring the effectiveness of the interventions offered and the efficiency with which they were delivered.

We move from Archie Cochrane to Dr David Sackett's Department of Clinical Epidemiology and Biostatistics at McMaster University. Sackett, like Cochrane, was interested in examining critically the available research evidence and applying it to clinical practice. The term evidence-based medicine first appeared in an introductory document written by his colleague Gordon Guyatt for residents at McMaster. Interestingly, evidence-based medicine was the second name Guyatt used to describe the practice philosophy. The term scientific medicine which he tried first had aroused hostility amongst his colleagues with its implication that what was practised until then was unscientific medicine.

Evidence-based medicine, as Sackett defined it, was an integration of the best available evidence with clinical expertise and patient values. He described the steps by which this was to be achieved by bringing together and appraising critically the published research. Back to Archie Cochrane who wrote, in 1979: "it is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all randomised clinical trials". This took some time, but in 1993 The Cochrane Collaboration was founded as a repository for the Cochrane Library of Systematic Reviews which now has over 4,300 systematic reviews and 625,000 randomised trials available online. It was intended that these reviews would form the basis for practical guidelines – a means of making the large volume of information manageable and therefore applicable as Sackett advocated.

EBM has had its critics, mostly along the lines that it devalues traditional clinical skills and the art of medicine. On the contrary, Sackett and his colleagues went to great lengths to explain that it should enhance clinical medicine. They emphasised that evidence alone was not enough if the clinical skills were not of a high order. Sackett wrote that, because EBM required clinical expertise and involved patient choice, "it cannot result in slavish cook-book approaches to individual patient care.[10]"

So much for recent medical history. Where are we now? Shaw's dilemma of demand exceeding the ability to provide remains a major challenge, probably the major challenge

for modern healthcare. The dilemmas highlighted by Cochrane of the need to make health services effective and efficient remain timely. The NHS has had unprecedented funding in the past ten years, but evidence of commensurate improvement is difficult to find. Take for example the National Cancer Plan of 2000, reminiscent of President Nixon's National Cancer Act signed into law in December 1971. The American plan was to find cures for the major forms of cancer by the bicentenary of the state in 1976. Nixon called for the same kind of effort that split the atom and sent a man to the moon. It might have been good short term politics, but was poor science. Strategy documents were drawn up extending to 1000 pages which Ralph Moss, in his book, *'The Cancer Industry'*[11] said would undoubtedly live on as an example of bureaucratic obscurity. Despite massive expenditure, no cure was found, indeed no significant advance was made in cancer management. Our own UK cancer plan[12] promised survival rates to match the best in Europe by 2010. Like the American plan it has absorbed huge resources and been associated with a massive bureaucracy. We can only hope that the similarities with the Nixon plan end there and that it will produce benefit. However, it must be said that the evidence of its effectiveness, never mind cost-effectiveness, is slow in coming.

Much has been spoken and written about efficiency recently; it's the obvious easy answer to the conflict between demand and supply. Unfortunately, most of the measures taken to achieve it have had little or no basis in evidence, or even in common sense, but were driven by crude arbitrary targets. It's hardly surprising that these have resulted in some poor quality care. As a result of the drive for efficiency, management imperatives have become the major force in healthcare. If we move forward 30 years from Cochrane, the Rock Carling Lecture of 2001 was given by Theodore Marmor, Professor of Public Policy and Management at Yale University. His title was 'Fads in Medical Care Policy and Politics: The Rhetoric and Reality of Managerialism[13]'. His view was that "the managerial attack on the dominance of medical professionalism had helped to deflate public confidence and to increase the probability of proposals threatening professional autonomy". He described how the fads of business management had been transferred to healthcare despite important differences. There was no managerial panacea; it was a complex business, balancing upsides and downsides. Mindless attempts at cost control may, in fact incur costs and reduce the morale of both patients and healthcare professionals. We cannot, of course, have clinical anarchy. There must be rules, but we should remember that compliance is likely to be inversely proportional to their number and complexity.

Thus we come to the nub of the problem of how to achieve effectiveness and efficiency - managerialism versus professionalism, rigid rules versus culture and values. They never should have been in conflict: properly implemented they would have been complementary. Griffiths envisaged that a balance between managers and doctors in management would produce a balance between clinical quality and cost. But increasingly, cost pressures became predominant. The clinical directorate system, despite its theoretical strengths, fails to solve even the simplest issues in service improvement and efficiency. For example, why has something so seemingly simple as making patients' appointments become so complex? And, why should our patients trust us with decisions about their lives and health if we cannot even organise their appointments reliably? Could it be that we've lost sight of the lessons of Cochrane and Sackett and become entangled in the management fads described by Marmor? Governance which was intended to assure professionalism and quality has become an instrument of enforcement, too often of measures which have undermined quality. Sackett, with foresight, wrote "Some fear that evidence-based medicine will be hijacked by purchasers and managers to cut the costs of healthcare. This would not only be a misuse of evidence-based medicine but suggests a fundamental misunderstanding of its financial consequences."

These problems of how to ensure quality and efficiency are not confined to this country. Dr Jerome Groopman, a professor of medicine at Harvard Medical School, in a paper in the New York Review[14] earlier this year, described the conflicting advice given to President Obama from his health advisers. One group advised coercive legislation, aggressively pushing doctors and patients to do what the government defined as best whilst another recommended greater clinical freedom. Groopman made his own position clear, declaring that "The care of patients is complex and choices about treatment involve difficult tradeoffs. That the uncertainties can be erased by mandates from experts is a misconceived panacea".

So, the dilemma remains, but I am not pessimistic. Good ideas come to the surface, eventually. The concepts of EBM and clinical governance are intrinsically sound and should promote the best aspects of professionalism. They have been antipathetic only because they have been misused. Medicine can learn from business, but cannot be run as a business. That clinical excellence and financial control can be reconciled is well demonstrated at the Mayo Clinic. The central tenet of the practice at Mayo is that the needs of the patient come first. It hardly needs to be said for it is evident that the concept pervades all levels of the organisation. A recent book, *Management Lessons from the Mayo Clinic*[15] describes the management structure and processes. The currency of respect is clinical excellence. Physicians have as much at stake as do managers to ensure the financial viability of the institution. Managers have at much at stake as physicians to ensure good patient care. Leaders are invited; physicians who appear conspicuously ambitious for leadership have a high chance of rejection. The committee system works to achieve consensus which is easier where there is mutual respect and shared objectives. None of this is new. Peter Drucker, the management academic wrote more than 20 years ago about the need for organisations to have values and pointed out the differences between businesses and not-for-profit organisations.

Mervyn King has described the principles of good governance in his short book, *'The Corporate Citizen'*. King is well-placed to combine the business and professional, having been a former Judge of the High Court in South Africa and chairman and director of several companies. He wrote that "Good governance will not result from a mindless quantitative compliance with a governance code or rules. Good Governance involves fairness, accountability, responsibility and transparency on a foundation of intellectual honesty.[16]"

A paper in the Harvard Business Review of April 2010 entitled 'Turning Doctors into Leaders' focused on the need to dismantle the current dysfunctional processes in healthcare. Delivery of care should be organised around patients' needs with services focused on outcome rather than activity. It was gratifying to see, in a business journal, recognition of the primacy of clinical care and outcome, and powerful advocacy of the view that leadership should be clinical.

And so I come back to the new students. I hope you're not discouraged by the problems I've described. You have chosen one of the most fascinating, challenging and rewarding occupations anyone could have. You are living in interesting times. In my working lifetime, we have seen the failure of both socialist and free market ideologies in handling public services. We now hear public discussion of the need to find new ways in which society might organise its affairs better – how much the state should intervene in people's lives, what services it should, and should not, provide, and how it should deliver them effectively and efficiently. The health service is a paradigm for these larger political issues. Many of the answers are already available in the medical and management literature. If I have encouraged at least some of you to become interested in these wider aspects of healthcare, I shall be well satisfied. I wish you every success in the future and it is my hope that your generation will be more effective in dealing with some of these doctors' dilemmas than has mine.

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Medical History

The Scarlet Thread

John Leckey

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There are references to "the scarlet thread" in both Christian and Jewish theology. "The scarlet thread" which is the title of my talk does not refer to any aspect of any theology. It does not refer to either the scarlet cord Rahab, the harlot, who lived in the city of Jericho, let down from her window to save her and those of her household from the Israelites (to find out more about her salvation and the aftermath see Joshua Chapter 2: verses 18-19 are the starting point) or the blood of Jesus. The theme of my talk is secular rather than sacred. So, you may wonder, what is "the scarlet thread" of my talk? I have taken it from the novel "A Study in Scarlet" by Sir Arthur Conan Doyle. It was published in 1887 and was the first of his novels to feature Sherlock Holmes. In a speech to his companion, Dr Watson, Holmes states:

> "There's the scarlet thread of murder running through the colourless skein of life, and our duty is to unravel it, and isolate it, and expose every inch of it."

In many ways that has been a job description for a coroner since 1194 when the office of coroner was founded to the present day. When an unnatural death is reported to the coroner, he has a duty to investigate and establish certain facts and that investigative role is part of his inquisitorial function. To a greater or lesser extent the investigation of each death reported becomes a study in scarlet. Many deaths investigated by a coroner are not the result of murder, but each has a thread that needs to be unravelled to elicit the true facts behind the death. The colour of that thread is not always scarlet – that colour is reserved for murder - but when it is it may not always be apparent to the coroner that the same single scarlet thread links a series of deaths.

In her crime novel "Sister" Rosamund Lupton said this of the colour red:

> "…the colour of cardinals and harlots; of passion and pomp; cochineal dye from the crushed bodies of insects; crimson; scarlet; the colour of life; the colour of blood."

She put it rather well. Incidentally, it is a novel I would commend for bedtime reading.

My predecessor in office, the late James Elliot, held inquests into the deaths of the victims of the Shankill Butchers unaware that each was linked. The police officers investigating did not tell him – no doubt to protect sensitive lines of inquiry – and I remember him telling me how shocked he was to learn the truth. The murders carried out by the Shankill Butchers gang illustrate so well that unravelling, isolating and exposing the scarlet thread can be a most exacting task for a single human being and one that only a modern day Sherlock Holmes may be able to accomplish. If you require proof of this have a look at the "Shankill Butchers" entry in "Lost Lives" and follow the labyrinthine journey of the scarlet thread as it snaked its way through so many brutal murders.

I held inquests into the deaths of five Catholics who were murdered at Sean Graham Bookies on 5th February 1992. The youngest was only 15. The two gunmen believed to be responsible were Raymond Elder and Joe Bratty, both members of the UFF. Whilst there was no forensic evidence at that time linking them to the deaths, the dogs on the street knew who was responsible and Elder had been visually identified as having been there. Both were shot dead by IRA gunmen on 31st July 1994. Sometime before the massacre one of the guns used, a 9mm Browning pistol, had been in the custody of a UDA Quartermaster, William Stobie, who was also a Special Branch informant. He gave it to his Special Branch handler for deactivation. It was then deactivated and handed back to Stobie. However, it was then reactivated and used in the Sean Graham Bookie's massacre. The gunman who used it there was cool enough to reload it in the course of the shooting. (A total of 44 shots were fired.) Stobie was himself shot dead by a UDA gunman on 12th December 2001 and I held an inquest into his death. The history of weapons used in the troubles and paramilitary personalities can be fascinating. The 9mm Browning pistol had been stolen from the UDR barracks on the Malone Road by a UDA gunman, Kenneth Barrett, on 31st January 1989 and used by an unidentified UDA gunman to murder Aiden Wallace at the Devenish Arms on 22nd December 1991. I held that inquest too. It was then used at Sean Graham Bookies and eventually recovered by Police on 6th May 1992. Kenneth Barrett, also a Special Branch informant, was later convicted of the 1989 murder of the solicitor, Patrick Finucane in 2004. I also held that inquest.

Sometimes the scarlet thread has to be very long indeed and the colour of blood seems to be an appropriate one when the investigation relates to murder.

I have alluded to the quotation from "A Study in Scarlet" being a modern-day job description for a coroner. When I was appointed a deputy coroner in 1984 the scope of an inquest was much more restricted than it is now. The police provided the coroner with a selection of statements and a police inspector presented the evidence at the inquest. The late James

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Elliot, had a target of holding the inquest within 10 weeks of receiving the post-mortem report. Legal representation for bereaved families was unusual and families would be in ignorance of what evidence would be introduced until they heard it in the course of the inquest hearing. Usually the police investigation was ongoing. By and large that highly unsatisfactory state of affairs – "unsatisfactory" by the standards of today – was accepted by bereaved families. Now, the coroner expects to receive all documentation generated by the police investigation and so too does the family. Moreover, inquests tend to be held only when the investigation has concluded. There may be a series of criminal investigations – PSNI, Police Ombudsman, Historical Enquiries Team. Not surprisingly these may delay the holding of inquests for many years but families now appear to prefer that the inquest is held after the conclusion of all criminal investigations.

The statute De Officio Coronatoris of 1276 is generally considered to constitute the basis of modern coronial law in Ireland as well as England and Wales. Its provisions underline the paramount duty of the coroner to investigate.

> "That the coroner, upon information, shall go to the place where any be slain, or suddenly dead or wounded; and shall forthwith command four of the next towns, or five or six, to appear before him in such place, and when they are come thither, the coroner, upon the oath of them, shall inquire in this manner, that is, to wit, if it concerns a man slain, whether they know where the person was slain, whether it were in any house, field, bed, tavern or company, and if any who were there.
>
> …And also all wounds ought to be viewed, the length, breadth, and deepness, and with what weapons, and in what part of the body the wound or hurt is, and how many may be culpable, and how many wounds there be, and who gave the wounds; all which things must be inrolled in the roll of the Coroners…
>
> If any be suspected of the death of any man, being in danger of life, he shall be taken and imprisoned as before is said."

Interestingly, the mediaeval coroner was expected to make and record some form of medical assessment of what caused death and, clearly, his external examination of the body was not intended to be perfunctory as each wound found had to be described in some detail. Possibly, the mediaeval coroner was a forerunner of the forensic pathologist. Seven centuries would pass before this part of Ireland had a forensic pathologist, namely, Professor TK Marshall who was appointed as State Pathologist for Northern Ireland in 1958.[2]

Coroners were elected, the job was for life and during good behaviour. The coroner had to reside in the county and to be a "wise and discreet" knight and to be of substantial means. The rationale for the last requirement was that persons of wealth and status were less likely to succumb to corruption, but if they did their lands and goods would be forfeit to make good any resultant loss – an early form of indemnity insurance. Coroners were originally of such substance and station that, in the words of Blackstone, they would not "condescend to be paid for serving their country" in accordance with the common law "that none having any office concerning the administration of justice should take any fee or reward of any subject for the doing of his office". According to one commentator such lofty sentiments had been forgotten by the fifteenth century:

> "…with the waiving of the knighthood qualification, it was open to more, on some of whom it undoubtedly conferred a status to which they aspired and might otherwise not have attained. Also, by this time extortion had become firmly established, was consistently practiced and only rarely punished. The office therefore appealed increasingly to families which were struggling to rise and to the unscrupulous."

But there always have been a few good, honourable men.

As I have said the colour of the thread is not always scarlet and I will now give examples of that. Frustratingly, following extensive investigations I have held inquests into two deaths where my attempts to unravel the thread – the colour of which is undetermined at present - were thwarted by the present state of medical knowledge. Each inquest was concerned with the same issue, although the medical backgrounds were different, the post-mortem redistribution of morphine. How does a healthy human body and a dying human body metabolise morphine? Does a post-mortem analysis accurately reflect the ante-mortem position?

The first concerned a healthy body. Mrs A was admitted to hospital following the spontaneous onset of labour at 38 weeks gestation. It was her third pregnancy. Her previous two children had been born by vaginal delivery in April 2000 and February 2003 and are alive and well. She had no significant personal medical history. She had no history of allergies and she did not smoke or consume alcohol during her third pregnancy. The onset of fetal distress at full dilatation led to her third child being delivered by caesarean section. The baby was normal and healthy. Post-operatively pain relief was provided by morphine sulphate delivered by a patient-controlled pump. Eight hours after surgery she was found lying in bed in an unresponsive state and in spite of prompt resuscitative measures she failed to respond and was pronounced dead.

The Pathologist who performed the subsequent post-mortem examination found no evidence of significant natural disease to account for her death and there was nothing to suggest that any serious complication had arisen as a direct result of the pregnancy or the caesarian section. An examination of her heart by a specialist cardiac pathologist failed to reveal any evidence of underlying heart disease which might have explained the death. A toxicological analysis by Forensic Science Northern Ireland revealed the presence of morphine, a potent opiate painkiller, at a level significantly higher than the dose recorded in the medical records. The total level of morphine in the blood was 0.38 micrograms and the level of free morphine was 0.23 micrograms per ml. This contrasted with the clinical records which recorded that 12 mg was administered via the patient-controlled pump. (A leading forensic toxicologist who prepared a report for me cast doubt on the accuracy of that record.) The pathologist concluded that the cause of death was Morphine Intoxication.

However, not everyone who gave evidence agreed that this

is how the cause of death should be formulated and I had to consider alternative formulations, including that the cause of death was "unascertained" and should be recorded as such. The standard of proof in the coroner's court (with the exception of cases of suicide) is the civil standard of the balance of probabilities. I concluded that on the basis of the evidence before me, which included the broader clinical picture, the cause of death should be formulated as follows:

> 1(a) Opiod induced central nervous system depression and Upper Airway Obstruction due to 1(b) Morphine administration following general anaesthesia for caesarean section and epidural fentanyl administration in labour.

There was evidence, which I accepted, that Mrs A had been snoring heavily and I accepted the opinion of a consultant anaesthetist who prepared a report for me that this was indicative of an evolving upper airway obstruction rather than being merely indicative of her fatigue following childbirth. It should have resulted in the midwifery staff seeking advice from the duty anaesthetist, if for no other reason than reassurance, but that did not happen. An anaesthetic referral may have culminated in a reassessment of her condition and a fatal outcome may have been avoided.

My formulation of the cause of death made it clear that I concluded that, on the balance of probabilities, one of the underlying causes of this lady's death was morphine intoxication. However, I felt unable to discount the central nervous system depressant effects of fentanyl as the concentration of it in the epidural infusion and the additional dose for the caesarean section were in the upper range of acceptable dosage. I decided that "epidural fentanyl administration in labour" should be included as another underlying cause as I have noted that the central nervous system depressant effects of morphine and fentanyl are known to be additive.

I then went on to consider if I could reach a conclusion, again based on the balance of probabilities, which would explain the level of morphine found following the toxicological analysis. There was a divergence of views in the expert opinions I obtained and other possibilities were canvassed. These were:

a. She did not die from the effects of morphine intoxication but from some other cause of death, though what that was could not be ascertained;

b. the procedure used by the Pathologist to take a sample of blood from the body was flawed;

c. some unidentified error or mishap occurred in the course of the toxicological analysis;

d. a leakage from the sample bottle which occurred between the mortuary and the laboratory meant that the result of the subsequent toxicological analysis could not be relied on;

e. the level of morphine found was explainable by reference to the theory of post-mortem redistribution of morphine; (Whilst none of the experts discounted this theory the majority took the view that it could not account for the high level of morphine found.)

f. there had been a malfunction of the morphine PCA (Baxter-Half Day infusor) device which had been used for pain relief resulting in the infusion of an overdose of morphine;

g. the midwives who disposed of the residue of the morphine solution that remained in the syringe (which had been pre-filled with 60 mls of morphine solution), made an error in reading the amount remaining; (Their evidence was to the effect that only 6 mls had been used but a doctor involved in the attempts to resuscitate who saw the syringe stated that it looked half empty. To complicate matters further the medical records indicated she had not been in pain thereby obviating the need for any pain relief.)

h. some manufacturing error had been made by the pharmaceutical firm that made up the solution; and

i. the level of morphine found was due to some unidentified human intervention. (In relation to this the PSNI investigated, with negative results, whether the she had any history of drug abuse or whether someone might have supplied her with drugs whilst she was a patient in hospital.)

I considered some of these possibilities less likely than others and I was conscious of the understandable desire of all concerned, particularly Mrs A's family and the hospital staff, for an explanation for the level of morphine found. The need for an explanation assumed even greater importance as I concluded that morphine intoxication was one of the underlying causes of her death. I was satisfied that there was no evidential basis to allow me to hold that any of these suggested possibilities, whether singly or in combination, met the required standard of proof of the balance of probabilities. I had considered whether I should rank the possibilities I have mentioned to reflect my view of likelihood but I decided it would be wrong to do so as the evidential threshold of the balance of probabilities could not be met. I stated that I was satisfied on the balance of probabilities that death was due to the effects of morphine intoxication that occurred in circumstances which could not be ascertained coupled with the additive effects of the fentanyl.

The second inquest concerned a dying body. Mrs B, who was 56 years of age, suffered from severe chronic obstructive pulmonary disease, cerebral vasculitis and systemic lupus erythematosis. On admission to the hospital she was critically ill with acute respiratory failure due to the pulmonary disease. She expressed the wish that she did not wish for any active intervention to prolong her life. She was placed on the palliative care pathway and she died some six hours after being connected to a morphine infusion pump and this infusion continued for some 36 minutes after her death. Her death was reported to me only because of a suggestion that she may have received unspecified medical treatment from a family friend some months previously though the individual concerned denied that. However, a post-mortem was ordered to rule out any possibility that some form of treatment may have been given which may have contributed to her death.

The post-mortem examination failed to identify any connection between that medical treatment and her death but a toxicological analysis of a post-mortem sample of blood revealed a very high level of morphine that was well in excess

of the normal treatment range and at a level sufficient to cause death. It was found to contain 1.18 micrograms free morphine per ml and 1.26 micrograms total morphine (free morphine plus conjugates) per ml. The Pathologist ascribed death to "poisoning by morphine". He stated that her underlying medical conditions played no part in her death and that the morphine level detected was within the range where death in other cases had been attributed to morphine poisoning. No explanation for that level of morphine could be discovered. There was no evidence of untoward human intervention.

However, the Pathologist's formulation of the cause of death was not accepted by the hospital clinicians. One put forward an alternative formulation as 1(a) Chronic Obstructive Pulmonary Disease with Systemic Lupus Erythematosis as a contributory factor.

I obtained an independent expert report from a Biochemist and Senior Research Fellow in England. He stated:

> "One must be very cautious in interpreting postmortem opiod drug concentrations in blood from chronic pain or other patients being treated with opiods as meaning the same as similar levels in overdose deaths of persons not being treated for pain."

He concluded:

> "The concentrations of morphine found need not be the cause of death. What is confusing is the high percentage of free morphine to total morphine. On balance, it seems more likely that continued infusion of morphine (at concentrations 1,000-fold higher than found in blood) after the heart stopped beating, contributed to contamination of the post-mortem blood sample, producing a spuriously high free morphine figure.

Animal experiments, where drugs have been infused after death, support this conclusion. For example pigs infused intravenously with amitriptyline after death demonstrated high drug levels in blood samples from central vessels, heart, lungs as well as cerebrospinal fluid and vitreous humour. This implies that the presence of a lethal concentration of a drug in just one sample of heart blood can prove misleading in a case where agonal drug infusion may have occurred."

I sought advice also from Professor Dennis Johnston, Whitla Professor of Therapeutics and Pharmacology at Queen's University Belfast. In a letter to me dated 27th April 2010 he stated:

> "… if the infusion continued for a period of 36 minutes after death, it is impossible to make any judgement about the blood morphine levels. Free concentrations of morphine will clearly be higher since metabolism would have ceased and the distribution volume would have been dramatically decreased. Overall, this would result in much higher blood morphine concentrations than those occurring during life if we could rely on uniform distribution. This assumption cannot be relied upon and the normal variations at different sites within the body would be subject to even greater variation. Very high levels would be obtained near the infusion site and much lower concentrations would be obtained elsewhere."

Essentially he is making two points. First, as the morphine infusion continued for 36 minutes after death it is not possible to reach any meaningful conclusion based on the post-mortem blood morphine level found following a toxicological analysis. Second, an analysis of a single, isolated blood sample cannot be relied upon to give an accurate analysis of morphine concentration in the blood.

The Pathologist considered both views but, having done so he remained of the view that his original conclusions were correct. In a letter to me dated 13th May 2010 he stated:

> "It would be unwise to consider that the level detected was in some way a spurious result as I believe it has been rechecked and that the analysis would have been performed under strict laboratory conditions and guidelines. The accuracy of the level of morphine detected therefore seems unquestionable.
>
> Furthermore given the high level of morphine detected I feel unable, and that it would be foolish, to incriminate the conditions, namely chronic bronchitis and emphysema, from which she was suffering as having played a direct part in her death. That is not to say however that the decision to prescribe morphine to this terminally ill woman, who had serious irreversible chronic lung disease, was in any way unreasonable in an attempt to alleviate her anxiety, stress and suffering.
>
> In summary this is the case of a woman terminally ill with chronic lung disease with an as yet unexplained fatal level of morphine, most of which was free morphine, in the bloodstream. However despite our best efforts and seeking advice from elsewhere no robust, satisfactory explanation for the toxicology findings have been proffered. Whilst it may be that there is some as yet unidentified plausible natural/physiological explanation for the toxicological finding it may well be that there is not. Therefore one would caution against drawing any such conclusion lest some further evidence comes to light at some point in the future."

I felt his caution was understandable. Also, I accepted the accuracy of the toxicological analysis which was carried out by a Senior Scientific Officer attached to Forensic Science Northern Ireland.

In my verdict I stated that having considered all the available evidence and the competing opinions I was satisfied that present scientific knowledge is not capable of providing an answer to the conundrum posed by the circumstances of Mrs B's death. Despite the opinion of the Pathologist that her underlying condition played no part in her death and that she died from morphine poisoning, I concluded that the terminal condition for which she was being treated should not be ignored as it was the cause of her admission to hospital and the reason why she was on the palliative care pathway. On the balance of probabilities, I concluded that her terminal condition in combination with morphine toxicity caused her death. That being so I decided that the cause of death should be formulated as follows:

> I(a) Chronic Obstructive Pulmonary Disease and Morphine Toxicity

II Systemic Lupus Erythematosis.

Did I fudge it? You will note that I used the term "morphine toxicity" rather than the more emotive term of "morphine poisoning" which is associated more with a homicidal death. What I found perplexing were submissions on behalf of each hospital trust that I should ignore the toxicology results. It was put to me in relation to Mrs B that if I formulated the cause of death to include morphine toxicity the consequence would be that medical staff would become fearful of administering morphine – particularly to those patients on the palliative care pathway. But why would I ignore any toxicological analysis that showed the presence of morphine far in excess of any therapeutic level? Why should I and how could I possibly justify it? What about the families and their expectation that an inquest would provide an explanation for such a level? What about the aspersions that would be cast on the Toxicologist who carried out each analysis? What about the Pathologist whose formulation of the cause of each death was based on those analyses? Surely their professional reputations must count for something? For me the bottom line was that the toxicology could not be explained away by any proven scientific alternative thesis. Rightly or wrongly I took the view that the elephant in the room – the toxicology – could not be ignored.

Subsequently, I decided that it would be wrong not to initiate some action to see if the toxicological impasse could be resolved. I must confess I was unhappy with the unsatisfactory outcome to both inquests. I wrote to our Chief Medical Officer, Dr Michael McBride, giving chapter and verse in relation to each death and I provided him with a copy of all the expert reports. I copied that correspondence to the Presidents of the Royal College of Anaesthetists and the Royal College of Physicians and Professor Patrick Johnston, the Dean of the School of Medicine at Queen's University. Dr McBride has in turn referred the correspondence to the President of the Royal College of Pathologists. What I think Pathologists will say is that they rely on the results of the toxicological analysis and, in any event, the blood sample taken at autopsy is from a peripheral vein that is not proximate to the infusion site. That was the modus operandi in relation to these two women. Typically the blood sample is from a leg vein but not from the leg used for the infusion.

I am awaiting with bated breath the outcome of my referrals. Of course, if any of you have the answer please tell me.

What has surprised me is the absence of any research into how the human body metabolises morphine. I have already quoted from one of the expert reports submitted to me which referred to research involving pigs infused intravenously with amitryptyline. But is what may be true of the effects of amiptryline true of morphine? Both the Pathologist and the Toxicologist who carried out the analysis took the view that like is not being compared with like. So far as I can ascertain there has been no research on human beings. Surely such research must be possible if it is properly consented to? For instance terminally ill persons on the palliative care pathway who are in receipt of morphine could be asked to consent to a series of both ante-mortem samples and post-mortem samples. What would the Ethics Committee say to such a proposal? I have been told by members of the medical profession who know about these things that almost certainly the Ethics Committee would not approve such research. However, even if approval was given such research at best might only indicate how metabolisation in the dying body takes place. A Palliative Care Consultant I have spoken to informed me that by and large it is not known how the dying body deals with drugs and that it is likely metabolisation would be different to that in the healthy body.

Very few deaths of persons on the palliative care pathway are referred to the coroner (asbestos-related deaths excepted) as the vast majority of such deaths are from natural causes with a death certificate being issued. Post-mortems are rare and so the reservoir of knowledge, particularly in relation to the dying body and morphine is shallow indeed. The healthy individual in receipt of morphine as a short-term measure for pain relief invariably recovers without the opportunity or need for any morphine analysis. Thus, if Mrs A had, as expected, made a full recovery from the rigours of childbirth following a caesarean section, the morphine issue would never have arisen.

In summary are the issues these?

1. Is the theory of post-mortem redistribution of morphine scientifically valid?
2. Does metabolisation in the healthy body differ from metabolisation in the dying body?
3. Is what is true of a single healthy body true for all healthy bodies and, conversely, is what is true of a single dying body true for all dying bodies?
4. If the answer to that is No where does that leave us?

Two further points must be considered. First, criminal prosecutions take place – Dr Harold Shipman is one example – on the basis of a post-mortem blood analysis that shows a morphine level and which may culminate in someone being convicted of an offence and imprisoned. Is there not a problem in relation to this if medical science does not know how the human body metabolises morphine and the accuracy of any post-mortem level cannot therefore be relied upon? Second, if reliance cannot be placed on the post-mortem morphine analyses in relation to Mrs A and Mrs B does that now mean that all past analyses must be questioned? The consequences of the answer to that question being "Yes" are almost too dire to contemplate.

All of us have unfinished business and, I must confess, being able to solve the conundrum of the post-mortem redistribution of morphine is one of mine.

I hope this paper will provide you with food for thought and if you have the solution remember I am just a telephone call away. Unravelling the thread – scarlet or otherwise - can be as elusive as finding the crock of gold at the end of the rainbow. It is an exacting task and those involved would do well to remember the old adage that in any investigation what starts out as central may become peripheral and what starts out as peripheral may become central. All of us know the truth of that.

As an abuser of both morphine and cocaine Sherlock Holmes would have revelled in the challenge. You may remember the famous opening passage of "The Sign of Four":

> "Sherlock Holmes took his bottle from the corner of the mantelpiece, and his hypodermic syringe from its neat morocco case. With his long, white, nervous fingers he adjusted the delicate needle and rolled back his left shirtcuff. For some little time his eyes rested thoughtfully upon the sinewy forearm and wrist, all dotted and scarred with innumerable puncture marks. Finally, he thrust the sharp point home, pressed down the tiny piston, and sank back into the velvet-lined armchair with a long sigh of satisfaction."

The story ends with an exchange between Holmes and Watson with Holmes saying "For me there still remains the cocaine-bottle" and Sir Arthur Conan Doyle adds "And he stretched his long white hand up for it". (Some query whether Holmes had Marfan's Syndrome.)

POSTSCRIPT

To date I have heard nothing on the "science" from the Chief Medical Officer, the School of Medicine or the Royal Colleges which perhaps suggests it is much easier to pose questions than supply answers.

I have raised this issue with coroners in England and Wales and I now know of three who are investigating deaths where the post-mortem level of opiates bears no relation to the ante-mortem history. If you throw a pebble in a pond you do not know how far the ripples will extend.

This paper was given by the author at the combined meeting of the Ulster Medical Society and The Ulster Obstetrical and Gynaecological Society, on the 18th of November, 2010.

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1 © John L Leckey LL.M., Senior Coroner for Northern Ireland, November 2010.

2 See TK Marshall: "A National Forensic Pathology Service – the Northern Ireland Solution", (April 1968) Medicine, Science and the Law 73.

Letters

THE SWEET SOUND OF SCREENING?

Editor,

With a rising incidence of diabetes mellitus in the Northern Ireland population and the forthcoming review of a national screening programme we describe a pilot of diabetes mellitus type II screening. The pilot was carried out in the primary care setting, in three general practice surgeries throughout Northern Ireland; Lurgan, Ballyclare, and Cullybacky.

Diabetes mellitus Type II is one of the major causes of premature death and morbidity in the UK today, with the International Diabetes Federation estimating that the number of sufferers will only continue to grow. Approximately 70,000 people in the province have diabetes, 1000 of which are children[1].With the growing interest in diabetes in healthcare circles and an increase in litigation against doctors over the failure to diagnose diabetes we felt it was wise to look at methods of preventing this disease becoming such a physical burden to patients in future generations; early detection.

The purpose of this study is to appraise the need for a new screening system in general practice surgeries around the country, and to evaluate its effectiveness in the community setting. The study aims to see if the number of patients with diabetes detected by the screening programme is greater than the pickup of new patients by general practitioners, considering the current pickup rate by GPs to be equal to the national prevalence of the disorder, 3.9%[1].

The National Screening Committee announced in 2006, after several large scale studies, that screening for diabetes Type II on a national scale was not a viable option for the NHS to undertake. The purpose of this pilot was not to repeat the findings of previous studies but to select a smaller population of patients who exhibit risk factors for developing diabetes, such as obesity, to see if this increases the cost-effectiveness of screening by detecting a higher proportion of diabetics. Using patient records we developed a study group of patients at high risk of developing type II diabetes, and using a clinical screening setting tested a random selection of these patients for hyperglycaemia.

From a practice population of 28,250 a study group of 580 was drawn together from the criteria stated below. Of this 228 patients were invited to take part in the screening programme. Based on an initial audit and the guidelines laid down by the American Diabetes Association and by the Australian Diabetes Association, we devised the following inclusion criteria[2, 3]:

Patients with a BMI ≥25 kg/m2

Patients aged between 40 and 50

Individuals who had either a blood sugar test or urinalysis in the past two years (where documented) or were known diabetics were excluded.

Out of the 228 patients who were contacted and asked to take part, 111 responded and attended the screening sessions. Three positive results for hyperglycaemia were obtained. Using statistical analysis, we determined that although new diabetics were detected, the number was not statistically significant.

Whilst carrying out this study into the effectiveness of screening high risk group we also looked at the effects that the wording of a screening letter had on the attendance rates in each of the three centres. We found attendance rates differed greatly between practices, with an average attendance rate of 44%. Using statistical analysis a significant difference was found in attendance rates based on differing appointment types and terminology used in the appointment letters. It was found that the use of flexible appointment times, drop in clinics, and the use of 'high risk' terminology increased attendance rates.

Overall we found that there is minimum benefit to be gained from a targeted nationwide screening program for diabetes type II in patients, aged between 40 and 50, with a BMI of ≥25 kg/m2. With regard to increasing attendance rates using 'high risk' terminology in letters and flexible appointment times can bolster attendance rates at screening sessions.

The authors have no conflicts of interest.

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3. Dunstan D, Zimmet P, Welborn T, et al. *The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care* 2002; **25**: 829-834.

Ulster Med J 2011;**80(3):**166-174

Abstracts

14th Meeting of the Irish Society of Human Genetics, Friday 2nd September 2011

Health Sciences Building, University College Dublin

PROGRAMME:

10.00 – 10.55	Registration / Tea and Coffee.
10.55 – 11.00	Welcome.
11.00 – 12.30	Spoken Presentations: Plenary I.
12.30 – 13.30	**Keynote address: '**From childhood encephalopathy to lupus: Mendelian type I interferon-opathies**.' Prof. Yannick Crow,** University of Manchester, UK.
13.30 – 14.30	Lunch and Poster viewing.
14.15 – 14.30	Council Meeting.
14.30 – 15.30	Spoken Presentations: Plenary II.
15.30 – 16.15	Tea and coffee / Poster viewing.
16.15 – 16.30	Business Meeting.
16.40 – 17.40	**Keynote address**: 'Whole-genome sequencing and the detection of disease-causing mutations.' **Prof. Lynn Jorde**, University of Utah, USA.
17.40 – 18.30	Wine reception / Presentation of Prizes / Meeting Close.

SPOKEN PAPERS:

S01. Ptosis, arched eyebrows, hypernasal speech, obesity and mild learning disability - a clinical & mapping study.

SA Lynch[1], M Akram[2], N Goggin[2] M Earley[3], S Ennis[4], J Conroy[4].

[1.] NCMG, OLCHC, Crumlin Dublin 12, [2.] Paediatric Department. Waterford Regional Hospital, [3.] Dept of Plastic Surgery, Temple Street Children's Hospital, Dublin 1, [4.] School of Medicine & Health Science, UCD, Belfield Dublin 4.

We report 15 members of a three generation pedigree with ptosis, velopharyngeal incompetence, dysmorphism and a learning disability. The index case presented with nasal regurgitation & a dysmorphic appearance (medical flaring & arching of the eyebrows). Ophthalmological examination revealed a congenital ptosis, hypermetropia & a right convergent squint. He had grommets inserted for otitis media.

His mother has similar features. She has 6 children, 4 of whom are affected. The three older children & the mother, are obese. The maternal grandfather had ptosis & cannot read or write. He had 8 children, 5 affected & 3 unaffected. Five of this sibship have been assessed of whom two are unaffected. Two aunts of the index case have ptosis, obesity & learning difficulties. One has a son with ptosis.

Linkage analysis was performed on 7 of the samples including 6 affected individuals and 1 unaffected individual. Samples were genotyped on an Illumina Human-1M array. Parametric linkage analysis was undertaken using MERLIN. Two loci, on chromosomes 2p16.3-2q14 (14.4Mb) and 10q25.1-10q26.1 (13.5Mb), with LOD scores of 1.79 and 1.59 respectively were identified. Ninety-seven genes are contained within these regions. Additional samples (n=8) have been collected. Future linkage studies and mutation screening are ongoing.

S02. Familial catecholaminergic polymorphic ventricular tachycardia in Ireland.

Liyen Ng, Nicola Harper, Andrew Green.

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

Catecholamine polymorphic ventricular tachycardia (CPVT) is a rare inherited heart disease, which can predispose to ventricular arrhythmias and sudden death in young patients. Early detection of CPVT is crucial because opportune medical intervention prevents sudden cardiac death.

Mutations in the ryanodine receptor (RYR2) explain nearly 70% of the CPVT cases and cause the autosomal dominant form of the disease. Genetic analysis of RyR2 is available clinically and it has provided important insights into the mechanism underlying the disease.

Therefore in this retrospective study, we report the cases of CPVT families that have presented to the National Centre for Medical Genetics in OLCHC for genetic testing for CPVT. We discuss the phenotype of the CPVT carriers in our centre. Pathogenic variants in RyR2 have been identified in 2 families. 16 carriers have been identified and of these 8 (50%) have had symptoms prior to molecular analysis.

CPVT represents a clearly defined but still insufficiently recognised entity. The consequence of misdiagnosis is sudden death in children or young adults with an otherwise normal heart. There is wide range of phenotype for gene carriers from asymptomatic to syncope to sudden adult death syndrome (SADS). Better awareness may aid earlier diagnosis and appropriate medical treatments that can prevent sudden death.

S03. Incidence of I-cell disease (mucolipidosis type II) in the Irish population.

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Cases of I-cell disease diagnosed in Ireland over 13 years (1/1/1998– 31/12/2010) were identified in collaboration with the clinical diagnostics laboratory. A database documenting details of diagnosis, and clinical course where available was compiled. Results were correlated with published birth rates, including that of Irish Travellers (available only for the Republic).

Twenty infants from 14 families were diagnosed with I-cell disease during the study period. 18 were born to Irish Traveller parents, one to non-Traveller Irish parents and one to parents from Southern Europe. Mutation analysis was available for 7 cases, of whom 6 (all Travellers) were homozygous for the c3503_3504delTC mutation. Median age of death in patients of the Traveller community was 232 days (range 3-936).

Overall incidence, calculated using population data for the Republic (ROI) and Northern Ireland, was 1.56 per 100,000 live births. The incidence amongst Travellers (based on ROI cases and population data) was 114 per 100,000 live births, suggesting a carrier frequency of the common mutation in this group of 1 in 15. The carrier rate amongst Irish non-Travellers remains rare at 1 in 512. This high incidence and carrier rate found in the Irish Traveller population is relevant for genetic counselling of this consanguineous community.

S04. The Irish Giants: when truth meets fiction.

Lisa Bradley, Patrick J Morrison.

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Most countries and civilizations have stories about giants in their culture. In Northern Ireland, we have the Giant's Causeway, columns of hexagonal and octagonal basalt, built by a group of engineering-conscious giants who ran a combined operation with the giants of Scotland to facilitate easier access between the two sister countries. Another 'Irish Giant', Charles Byrne, was born in Littlebridge in 1761. His father was native to the area but his mother was Scottish. He was supposedly related to the Knipe brothers, the tallest identical twins (at 7ft 2in), from nearby Magherafelt. He grew rapidly and in his late teens featured in street shows in Ireland and London. After death his skeleton was acquired by the surgeon John Hunter and was eventually deposited in the Hunterian Museum in London. His enlarged pituitary fossa implied that his gigantism was due to a pituitary adenoma.

DNA studies have confirmed that mutations within the Aryl Hydrocarbon Receptor Interacting Protein (AIP) gene cause pituitary tumourigenesis, and can cause familial pituitary adenomas displaying autosomal dominant inheritance and variable expression. We present two families (one of whom is a proven descendant of Charles Byrne) with AIP mutations and discuss current recommendations for screening and predictive testing.

S05. An Overview of patients with Li-Fraumeni Syndrome and Li-Fraumeni-like syndrome in Northern Ireland.

Deirdre E Donnelly, Patrick J Morrison.

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Li Fraumeni Syndrome is a rare, autosomal dominant, cancer predisposition syndrome. Tumours can present at any age and, as the tumour spectrum is so wide, surveillance of at-risk individuals is difficult. We carried out a case note analysis of all families in Northern Ireland with this syndrome, two out of five of whom were positive for a TP53 mutation. The data obtained allow delineation of the phenotype, tumour distribution and age of onset and prognosis of specific tumours within the families.

We present the range of tumours and discuss screening implications for family members. This important condition is under-diagnosed and this analysis will allow better recognition of this disorder.

S06. A new locus for Episodic Ataxia.

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Episodic Ataxias (EA) comprise a genetically heterogeneous group of neurological conditions characterised by spells of ataxia, nystagmus & slurring of speech. The duration of clinical attacks vary from minutes to days. The various subtypes (EA1 to EA6) are differentiated by clinical presentation. Mutations in KCNA1, CACNA1A, CACNB4 and SLC1A3 are responsible for the development of EA1, EA2, EA5 and EA6 respectively. A locus has also been mapped for EA4 (1q42).

A three-generation Irish family with autosomal dominant EA was identified. Presentation occurred in early childhood and symptoms are controlled by Clonazepam (a GABA agonist).

Genome-wide linkage analysis was performed on 8 members of the family (6 affected, 2 unaffected) using the Illumina Human CytoSNP12 array. Following pruning the data, linkage analysis was performed using MERLIN on ~30,000 SNPs. Parametric analysis revealed three linkage regions on chromosomes 1, 7 and 20 with LOD scores of 1.8. These regions represent novel loci for EA. These results in addition to some of the novel features of the phenotype suggest that this family represent a new subtype of Episodic Ataxia.

S07. Identification of a novel disease gene for paediatric mitochondrial disorder.

Jillian Casey[1], Judith Conroy[1], Regina Regan[1], Ellen Crushell[2], SallyAnn Lynch[3], Sean Ennis[1].

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Mitochondrial disorders are amongst the most common inherited human diseases with a particularly high incidence in Ireland (1/9,000 births). We have studied a consanguineous Irish family that includes 3 children with clinical features consistent with a mitochondrial disorder. Molecular, biochemical and genetic analyses excluded all of the known causes of mitochondrial disease. It was concluded that the disease gene segregating in this family represented a novel cause of paediatric mitochondrial disorder.

We applied SNP homozygosity mapping (HM) and whole exome sequencing to investigate if a shared recessive mutation was common to this pedigree. The 3 patients and 5 unaffected relatives were genotyped for 1million SNPs (Illumina array). SNP HM identified

38 homozygous segments containing 134 genes that were shared by the patients.

On average, we detected 76,500 variants per patient exome. We identified 34 homozygous non-synonymous variants that segregated with the phenotype. Of these, only 2 were located within the 38 candidate regions of homozygosity, resulting in a 17-fold reduction in the number of putative disease variants for further investigation. Both candidate variants are located within the same gene, which belongs to a gene family previously implicated in mitochondrial disease. Limiting the search to the candidate homozygous intervals proved to be a powerful filtering strategy for the analysis of exome data and resulted in the successful isolation of the causative gene.

S08. The Role of Common Genetic Variation in Autism Spectrum Disorders.

Richard JL Anney on behalf of the Autism Genome Project and the Psychiatric GWA consortium. Institute molecular medicine, St. James' hospital, Dublin 8, Ireland.

Autism spectrum disorder has been established as a highly familial disorder with siblings of a proband showing at least 25-fold higher prevalence than that of the general population. Genome-wide association studies of ASD have highlighted signals on chromosome 5 intergenic to CDH9/CDH10 and SEMA5A/TAS2R1. As part of the Autism Genome Project (AGP) we have also previously identified strong association signals tagging the genes MACROD2, PLD5 and ST8SIA2. We present analysis from a follow-up of an additional 800 AGP families and preliminary data from the meta-analysis performed as part of Psychiatric GWA Consortia (PGC) Autism Study including data on approximately 4400 cases and 4400 pseudo-controls for greater that 1.25 million SNPs. The PGC Autism Study is comprised of GWA scans done by the AGP, The Autism Consortium in Boston, Johns Hopkins University, Children's Hospital of Philadelphia, and on samples collected by the Simons Simplex Collection and from Montreal and Finland. Using an additional 800 families from the AGP we do not observe significant validation of the previously GW-significant association signals from ours or others GWA of ASD.

However, we do see increased association signals in strong biological candidates for less noteworthy markers previously associated in the modest to strong range (p<10e-4). We observe a number of strong association signals for the PGC meta-analysis on chromosomes 5, 6, 7, 9, 16, 17 and 19 which are currently being followed up to validate their authenticity. We will present these data in the context of previous ASD findings and discuss the challenges faced and overcome in detecting loci that influence ASD susceptibility.

S09. Identification of a second dihydrofolate reductase activity in humans: the former annotated pseudogene *DHFRL1* is expressed and functional.

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Dihydrofolate reductase (DHFR) is a folate enzyme which reduces dihydrofolate into tetrahydrofolate in the presence of NADPH, ensuring a constant supply of biologically active folate. DHFR was previously thought to be the only enzyme capable of this reaction however we show that humans have a second dihydrofolate reductase enzyme encoded by the former pseudogene *DHFRL1* (dihydrofolate reductase like – 1), located on chromosome 3. We demonstrate that the *DHFRL1* gene is expressed and shares some commonalities with DHFR. Recombinant DHFRL1 can complement a *DHFR* negative phenotype in both bacterial and mammalian cells. Enzyme kinetics shows that the K_m for NADPH is similar for both enzymes but DHFRL1 has a higher K_m for dihydrofolate when compared to DHFR, indicating a lower affinity for the substrate. Localization of DHFRL1, visualized using confocal microscopy, shows that DHFRL1 has a strong presence in the mitochondria, indicating that mitochondrial dihydrofolate reductase activity may be optimal with a lowered affinity for dihydrofolate. We also found that DHFRL1 has the ability to bind its own mRNA in the same translational auto-regulation method as DHFR; with both enzymes capable of replacing each other. The identification of a second dihydrofolate dihydrofolate reductase enzyme will have a major impact on previous research surrounding DHFR.

S10. A genome scan for vesicoureteric reflux reveals a new recessive locus on chromosome 10 with an HLOD score >6.

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Vesicoureteric reflux (VUR), the retrograde flow of urine from the bladder towards the kidneys, results from a developmental anomaly of the vesicoureteric valve mechanism and has an incidence at birth of 1-2%. It often resolves with age, but ~8% of cases develop renal failure, accounting for ~25% of all renal failure. Several genome scans have been performed with conflicting results. We have performed a new scan on 530 cases and 435 other members of 246 families with 900,000 markers on the Affymetrix SNP Array 6.0. Linkage analyses have confirmed our previous non-parametric linkage peaks on 2q, 6q and 10q, all on a dominant model (highest with an HLOD of ~5 on 10q) and our previous peak on 7q is confirmed with HLOD >3 on a common recessive model, but also some linkage on a very rare dominant model. However, the most exciting finding is a very narrow recessive peak in a different position on 10q with an HLOD >6 that was previously missed because the markers were too far apart. There is also a dominant peak on 22q in one analysis. Numerous other smaller peaks remain to be examined. Our results did not replicate the findings of Briggs *et al.* (2009), Weng *et al.* (2009) or Conte *et al*. (2007). Analysis for association and copy-number variation is ongoing.

S11. HLA-A*3101 is a genetic marker for carbamazepine but not all anti-epileptic drug induced hypersensitivity reactions.

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Carbamazepine, phenytoin and lamotrigine are amongst the most commonly prescribed anti-epileptic drugs. However, their use can cause various subcutaneous adverse reactions; maculopapular exanthema (MPE), Hypersensitivity Syndrome (HSS) and Stevens-Johnson syndrome (SJS). A strong association between carbamazepine and phenytoin-induced SJS and *HLA-B*1502* exists in Asian populations however as *HLA-B*1502* is largely absent in European populations, the test is not applicable here.Through genome-wide association studies, we investigated whether genetic variants play a role in susceptibility to drug-specific hypersensitivity reactions when compared to drug-tolerant controls. We used genotype data to impute HLA types for our cohorts. *HLA-A*3101* strongly associated with carbamazepine-induced hypersensitivity and we confirmed *HLA-A*3101* as a risk factor for MPE (OR 8.3; 95% CI 3.6-19.4), HSS (OR 12.4; 95% CI 1.3-120.4), and SJS (OR 25.9; 95% CI 4.9-116.2). Neither HLA-A*3101 nor any other genetic marker associated with MPE resulting from phenytoin or lamotrigine. Due to low case numbers for HSS and SJS, we could not perform similar drug-specific analyses for the more severe phenotypes.

Our research provides the foundation for genetic testing of *HLA-A*3101* for all prospective European carbamazepine users. However, *HLA-A*3101* does not appear to be a genetic marker for lamotrigine and phenytoin-induced MPE reactions in Europeans.

POSTER PRESENTATIONS:

P01. Börjeson-Forssman-Lehmann Syndrome.

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Introduction: Börjeson-Forssman-Lehmann syndrome is a rare x-linked condition associated with learning disability, short stature, obesity, gynaecomastia, small genitalia and dysmorphic features, long ears, tapering fingers and short toes. The disorder is due to mutation of the PHF6 gene on the X chromosome.

Aims: The purpose of this report is to describe the phenotype in adolescence and In addition we wish to highlight the features useful for diagnosis of this underrecognised condition.

Methods: Clinical history, detailed physical examination and clinical photography were carried out for a 15 year old male presenting with obesity and learning disability. The diagnosis was confirmed by molecular genetic testing.

Results: He was born to non-consanguineous healthy Irish parents. He had a raised BMI of 29, height 3rd to 10th centile; physical examination is remarkable for gynaecomastia, large ear lobes, tapering fingers and hypogonadism. Endocrinological investigation revealed growth hormone deficiency. He has a learning disability and dyspraxia and is attending main stream school with assistance.

Conclusion: The fundamental key to clinical diagnosis is recognition of combination of obesity, learning disability and subtle dysmorphic features such as large ears and tapering fingers. These patients can gain significant benefit from symptomatic supportive treatment and counseling of family.

P02. Incidental finding of a beaked vertebra.

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[1.] National Centre for Inherited Metabolic Disorders, Children's University Hospital, Dublin, Ireland, [2.] Department of Radiology, Children's University Hospital, Dublin, Ireland.

Case: A 14 month old boy was referred for investigation of possible dysostosis multiplex associated with a storage disorder. Having presented with pectus carinatum, a lateral chest x-ray showed abnormal anterior "beaking" of the 2nd lumbar vertebral body (L2), confirmed on lateral spinal view (figure 1). He was the first child to non-consanguineous parents. He was otherwise well with normal growth and development. Examination showed pectus carinatum but no other abnormalities were found. There was no coarsening of features; skin, hair, joints, hands and spine appeared normal.

Skeletal survey did not reveal other skeletal abnormalities. Ophthalmology assessment was normal. Urinary mucopolysaccharides and oligosaccharides were normal, as were Leukocyte α-iduronidase, iduronate-2-sulphatase, galactose-6-sulphatase, α-mannosidase, and β-galactosidase.

Discussion: The finding of a beaked vertebra is rare and may be associated with lysosomal storage disorders (in particular the mucopolysaccharidoses), bone dysplasias, and neuromuscular conditions. Pectus carinatum, while occasionally the presenting feature of Morquio syndrome, is usually an incidental finding in healthy children. Increased prevalence in families suggests a hereditary origin.

Our case is unusual given the strong suggestion of initial radiographs, which self resolved. We hypothesise that delayed maturation of a growth centre may have lead to a temporary minor modelling abnormality in L2.

P03. Optimising the application of IHC in identifying germline MMR mutations in HNPCC.

Gillian Rea[1], Alex Magee[1], Maurice Loughrey[2].

[1.] Northern Ireland Regional Genetics Service, [2.] Department of Pathology, Royal Victoria Hospital, Belfast.

In the investigation of individuals with potential Hereditary Non-Polyposis Colon Cancer (HNPCC), immunohistochemistry (IHC) for mismatch repair (MMR) proteins may direct subsequent germline molecular genetic testing and need for screening endoscopy. Delays in the time taken to obtain IHC results will negatively impact the overall time taken to obtain mutation results.

The aims of this study were to assess current practice and streamline the use of IHC to enable an overall reduction in the time taken to obtain a molecular genetic result.

We carried out a retrospective case notes review of 32 cases with abnormal IHC results, examining the time at which IHC was requested. This audit of current practice revealed that IHC was requested at the time of surgery in 2/32 cases; at the time of referral to clinical genetics in 4/32 cases and after genetics clinic in 26/32 cases. To date 12 germline MMR mutations have been identified. The time taken to obtain IHC MMR results was variable but significant.

We have made a number of recommendations and actions to increase the frequency with which IHC is requested at the time of surgery or at the time of referral. We plan to re-audit our practice in 12-18 months.

P04 BRCA1/BRCA2 Mutation Negative Hereditary Breast Cancer in Ireland.

Fatima Al Oraifi, Trudi McDevitt, Nuala Cody, Marie Meanie, Cliona de Baroid, Rosemarie Kelly, James Geraghty, Andrew Green.

National Centre for Medical Genetics, University College Dublin.

The National Cancer Registry of Ireland statistics reveal that breast cancer is diagnosed in more than 2,000 women every year. Family history is an established risk factor for breast cancer. Studies on twins indicate that most of the excess familial risk is due to inherited predisposition.

The identification of the susceptibility genes BRCA1 and BRCA2 enhanced clinicians' ability to select high-risk individuals for aggressive surveillance, prevention, management, and led to the development of improved therapies. However, BRCA1, BRCA2 and several other identified susceptibility genes account for only 28% of hereditary breast cancer.

In Ireland, patients suspected to have familial breast cancer are referred to the National Centre for Medical Genetics (NCMG) for BRCA1 and BRCA2 mutation testing. Based on the Manchester scoring, we can predict the likelihood of familial breast cancer. As much as 84% are found to be negative to mutations in BRCA1/BRCA2 in Ireland. In this study, we aim to describe the clinical phenotype of affected breast cancer patients negative to mutations in BRCA1 and BRCA2 with a Manchester score of ≥16. We evaluate the proband's clinical status, including the age of onset, bilaterality, histological diagnosis, stage, receptor status, other affected relatives and presence of other cancers within the pedigree.

P05. Validation of Luminex xTAG™ Cystic Fibrosis 39 Kit v2 for Diagnostic Testing & Newborn Screening using Dried Blood Spots.

Melissa Rogers, Solvig Roring, Trudi McDevitt, David E Barton.

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With the National Newborn Screening Programme (NBS) for CF due to begin in July 2011, a method of detection is required which is amenable to analysis of dried blood spots (DBS), compatible with high sample through-put, and is highly sensitive in the Irish population.

Using the Luminex™ Liquid Bead Array Platform, we evaluated the xTAG™ Cystic Fibrosis 39 kit v2 which tests for 39 of the most common CF mutations found worldwide. The panel of mutations present in the xTAG CF 39 kit has an estimated detection rate in the Irish population of ~93.5%.

We have evaluated a panel of 130 DNA samples of known genotype from a range of sample material, including DBS. DNA was prepared from these samples using a variety of methods (Salting out, Qiagen EZ1 whole blood kit, Qiagen EZ1 tissue kit & phenol/chloroform extraction). DNA derived from DBS has proven difficult to amplify on multiplex assays in the past and is thus of particular interest for NBS.

All samples genotyped correctly indicating that the assay is both sensitive and specific. The assay performed equally well on all sample material including DNA extracted from DBS using the Qiagen EZ1. The system is now validated and in service ready for the CF NBS programme.

P06. Atypical "mild" Non-Ketotic Hyperglycinaemia in siblings.

Malikiwi Andra, Murphy Anne-Marie, Monavari Ahmad.

The National Centre for Inherited Metabolic Disorders, The Children University Hospital, Temple Street, Dublin 1, Ireland.

Nonketotic hyperglycinemia is a rare metabolic disorder that characteristically presents with hypotonia, refractory seizures and death in early infancy. Milder phenotypes presenting with developmental delay and hypotonia are occasionally encountered. Diagnosis is established by measuring CSF: plasma glycine ratio. Molecular characterisation is possible.

Natural history and clinical findings of 2 Irish sisters with atypical NKH are described.

A neonate presented with a history of poor head control and reduced feeding. Examination revealed truncal hypotonia and visual inattention. Brain imaging was normal. Plasma and urine glycine levels were noted to be elevated along with her CSF:plasma glycine ratio.

Her developmental milestones in the first 2 years of life were mildly delayed. Her older sister also previously had a history of poor feeding at birth and developmental delay.

Mutation analysis identified 2 missense mutations on exon 10 (L4221) and exon 23 (V905G) of the GLDC gene. They have learning difficulties with occasional behavioural disturbances and have required the care of a psychiatrist. Tremor and co-ordination difficulties are significant clinical features, seizure however is absent.

A mild form of NKH compatible with long-term survival exists. This diagnosis should be considered in children presenting with developmental delay and appropriate investigations should be implemented.

P07. Validation of the Asuragen Amplidex FMR1 kit for diagnostic Fragile X testing and further characterization of the WHO FRAX Reference Panel.

Michael Sweeney[1], Karen Meaney[1], David E Barton[1,2].

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Fragile X syndrome (FRAX) is the most common cause of inherited mental retardation and is caused by expansion of an unstable (CGG) n repeat in the FMR1 gene. In most diagnostic centres a PCR test is first performed and samples that fail to amplify (males) or show a single normal allele (females) proceed to Southern blot analysis, which is time-consuming and expensive. We have evaluated a fluorescent PCR assay using a panel of DNAs including the recently-certified WHO FRAX Reference Panel. The Asuragen Amplidex assay is based on gene-specific FMR1 PCR, CGG Repeat Primed PCR and employs 1/200th the amount of DNA required for Southern blot analysis, making the assay very amenable to robotic DNA extraction methods.

Following PCR optimization, the assay consistently identified all full mutations and could accurately size normal, intermediate and premutation alleles. All results were concordant with previous Southern blot and in-house PCR results. Overall, this assay is efficient, robust and greatly reduces laboratory workload and reporting times. The sensitivity of the assay will assist in detecting expanded alleles in prenatal samples and in cases with limited starting material. The results obtained have provided additional information on the sizes of normal and premutation alleles in the WHO Reference Panel, which will be valuable to labs calibrating their own assays.

P08. Familial occurrence of distal foregut atresia type I.

Li Yen Ng, Ian Robinson, Roisin Hayes, Harinder Gill.

National Centre of Medical Genetics; Radiology Department, Our Lady's Children Hospital Crumlin.

Aims: To investigate a family in which four members are affected with distal foregut atresia type I

To review cases reported in the literature and ascertain the pattern of inheritance and its pathogenesis.

Methods: 1. Information obtained from a variety of sources including the parents, medical records, radiological and histology reports, 2. Literature review pertaining to the pathogenesis of distal foregut atresia and previous familial cases was undertaken.

Results:

1. **Our Family:** Three female siblings, their maternal uncle and male second cousin were affected by distal foregut atresia. The age of presentation varied from 2 days to 43 months of age. The atresia ranged from complete to partial web, locating from the gastric antrum to preampullary duodenum.
2. **The Literature Review:** Cases reported from regions with high incidence of consanguinity suggesting an autosomal recessive pattern of inheritance. 2 pathogenic mechanisms have been proposed:
   i. failure of recanalisation of solid phase of duodenal development by Tandler in 1900
   ii. vascular theory by Louw and Bernard (Lancet 1995).

Conclusion: Familial distal foregut atresia is rare. It is inherited in autosomal dominant or recessive pattern. Improved knowledge and awareness may help in reaching an early diagnosis. Most children do well after corrected surgery.

P09. A three generation type 2 Stickler family with a multiexonic COL11A1 gene deletion.

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Stickler syndrome, with an estimated newborn prevalence of 1/7500-9000 has no consensus minimal clinical diagnostic criteria. It is a multisystem connective tissue disorder with ocular, auditory, craniofacial and skeletal features resulting in chronic morbidity.

10-20% of Stickler syndrome is attributed to mutations in COL11A1 gene. These individuals typically have more severe hearing deficit and type 2 congenital vitreous anomaly (beaded).The frequency of COL11A1 deletions is unknown. A multiexonic COL11A1 deletion was previously reported by Martin S *et al,* 1999.

The 14 year old female proband has a 9 year history of moderate myopia, joint hypermobility and chronic hearing loss and backache. Ophthalmic findings of congenital beaded vitreous anomaly suggested a type 2 vitreous phenotype. Radiology showed irregularity of end plates of several cervical, thoracic and lumbar vertebrae. A heterozygous COL11A1 deletion of exons 14-24 was detected which was consistent with Stickler type 2 phenotype.

Subsequent investigation identified at least three other affected relatives in 3 generations with variable phenotype. Further assessment of the family is ongoing.

This would appear to be the second but first 3 generation multiexonic COL11A1 Stickler syndrome type 2 family to be reported in the literature highlighting and further defining the phenotypic variability.

P10. 16p11.2-p12.2 microdeletion syndrome.

C Murphy[1], E Cullen[1], AM Murphy[1], M Mavinkurve[3], S Smith[1], N Irving[1], M O'Sullivan[1], SS Lim[1], SA Lynch[2], E Roche[1,3].

Department of Paediatrics, Trinity College Dublin, Ireland[1], National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Dublin 12, Ireland[2], AMNCH National Children's Hospital Tallaght, Dublin 24, Ireland[3].

Introduction: 16p11.2-p12.2 microdeletion syndrome is a rare condition associated with autism, developmental delay and obesity. This diagnosis is confirmed by array comparative genomic hybridization. The purpose of our report was to describe the adolescent phenotype and highlight diagnostic clues for rare undiagnosed causes of learning disability and obesity.

Methods: Clinical history, detailed physical examination and clinical photography were carried out for a now 16 year old female presenting to Paediatric services in childhood for developmental delay, speech delay and developmental dysplasia of the hip and in adolescence with obesity, learning disability and pubertal delay and

was diagnosed with a 16p11.2-p12.2 microdeletion syndrome by the Genetics service.

Results: The fourth child to non-consanguineous Irish Caucasian parents, physical examination is remarkable for short stature in 3rd to 9th centile and weight on 98th centile with stria on abdomen and webbing of neck. She has a history of headaches and benign intracranial hypertension. She is currently in mainstream school and has mild learning disability.

Conclusion: The early reports of this microdeletion syndrome describe children with autism. However more recently an association with obesity and primary amenorrhea has been identified which are fundamental clues in diagnosis. Further reports are required to delineate this condition.

P11. Next-generation sequencing of known and putative susceptibility genes for schizophrenia and autism spectrum disorders to detect rare high-penetrant risk variants.

EM Kenny, S Furlong, P Cormican, C Fahey, R Anney, G Donohoe, AP Corvin, L Gallagher, M Gill, DW Morris.

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

Schizophrenia (SZ) and autism spectrum disorders (ASD) are complex neurodevelopmental disorders that share certain phenotypes including cognitive deficits and some behavioural characteristics. Such similarities suggest that these disorders may share an underlying pathology and thus may share some genetic risk variants. This study involves next-generation sequencing of the exonic regions of 215 potential susceptibility genes in an Irish sample of 150 cases of ASD, 300 cases of SZ and 300 controls, in order to identify single nucleotide polymorphisms, indels and structural variants contributing to one or both disorders. A multiplex target enrichment method is used whereby DNA samples are multiplexed together using DNA indexes/barcodes and enriched for the exonic regions of these genes using the Agilent SureSelect target enrichment method. This is followed by 80bp paired-end sequencing in a single lane of an Illumina GAII. Gene selection comprised of five categories: 1) Interactors of NRXN1, 2) Interactors of DISC1, 3) Genes within the Glutamate Receptor Complexes; NMDA, mGluR5 and AMPA, 4) Cell adhesion molecules and 5) Functional and Positional Candidates. Analysis of the pilot set of samples indicates that the approach undertaken is successful with an even spread of sequence information for 24 indexed samples per lane, >8X coverage for 84% of target regions and overall SNP concordance with previous GWAS data (Affymetrix 6.0) of 99.3%. A preliminary SNP analysis of 219 SZ cases and 206 controls has identified an excess of rare (nonsense) mutations in the cases. We are currently validating these findings using capillary sequencing and details of these analyses will be presented.

P12. Genetic Determinants of Thromboxane and Prostacyclin – an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Sub-study.

Nina McCarthy[1], Ciara Vangjeli[1], Praveen Surendran[1,4], Achim Treumann[1], Cathy Rooney[1], Emily Ho[1], Peter Sever[2], Simon Thom[2], Alun Hughes[2], Patricia Munroe[3], Philip Howard[3], Toby Johnson[3], Mark Caulfield[3], Denis Shields[4], Eoin O'Brien[4], Desmond Fitzgerald[4], Alice Stanton[1].

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Introduction: The balance between two eicosanoids, prothrombotic thromboxane (TxA_2), and antithrombotic prostacyclin (PGI_2), regulates the formation of platelet plugs (thromboses). Thromboses prevent excessive bleeding when blood vessels are injured, but can also block blood vessels, causing heart attacks and strokes. This is the first study to investigate genetic determinants of TxA_2 and PGI_2 levels.

Methods: 544 participants in the HACVD substudy gave urine samples at two separate time-points. TxA_2 and PGI_2 were measured using LC/MS-MS, expressed as pg/mg creatinine to correct for urine concentration. Participants were genotyped on the cardiovascular-specific CVD50K chip, containing >50,000 SNPs. Linear regression analyses were performed assuming an additive model and adjusting for relevant covariates.

Results & Discussion: Nine loci were associated with either TxA_2 or PGI_2 at $P<1x10^{-05}$, two of which exceeded the Bonferroni threshold of $1.6x10^{-06}$. All nine loci were associated with effect sizes of ~0.5 standard deviations of the eicosanoid distributions per minor allele carried.

This study adds to the successes of the CVD50K chip in finding SNPs associated with cardiovascular phenotypes. SNPs associated with TxA_2 and PGI_2 in this study may be novel genetic biomarkers of thrombosis and bleeding risks, and/or provide a pharmacogenetic assay for therapies influencing thrombosis and bleeding.

P13. Characterisation of putative Autism Susceptibility Genes: Translating Genome Wide Analysis to Causation.

Graham Kenny, Richard JL Anney.

Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin.

Introduction: In a recent GWA of autism we identified an association within the gene MACROD2.[1] Establishing a functional consequence of association is required to determine a causal link between marker and disease. MacroD2 is a macro domain containing protein which may have a function in DNA silencing and sirtuin biology.[2]

Methods: Expression profiling using a human total RNA master panel. Exon-crossing primers were used to demonstrate the expression profile of MACROD2 across 21 tissues. Promoter mapping using luciferase reporter assays.Promoter mapping constructs were examined in SHSY5Y neuroblastoma cell lines. We observed differential expression of the various promoter lengths. From this data it would appear that an enhancer element of MACROD2 lies ~500bp upstream from exon 1.

Results: MACROD2 is expressed across mulitple human tissues, including brain, kidney, placenta, skeletal muscle, testis and thyroid gland. Promoter mapping constructs were examined in SHSY5Y neuroblastoma cell lines. We observed differential expression of the various promoter lengths.

Discussion: This project is structured to examine the biological

role of MACROD2 in humans, with the hypothesis that disruption of MACROD2 will impact on the structure and/or function of the neuron.

References: 1. Anney R, *et al*. A genomewide scan for common alleles affecting risk for autism. *Hum Mol Genet*. 2010;**19(20):**4072-4082. 2. Chen D, *et al*. Identification of Macro Domain Proteins as Novel *O*-Acetyl-ADP-Ribose Deacetylases. *J Biol Chem*. 2011;**286:**13261-13271.

P14. Heritability of subcortical brain structures in temporal lobe epilepsy.

Saud Alhusaini[1], Colin Doherty[5], Cathy Scanlon[2], Sinead Maguire[4], Gabor Borgualy[1], Paul Brennan[4], Mary Fitzsimons[2], Norman Delanty[1,3], Gianpiero Cavalleri[1].

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons. [2]Neurophysics, [3]Neurology, [4]Radiology Departments, Beaumont Hospital, Dublin.9. [5]Department of Neurology, St. James's Hospital, Dublin.8

Introduction: Temporal lobe epilepsy (TLE) exhibits a complex inheritance pattern and is likely caused by interaction of multiple environmental and genetic factors. As part of an ongoing effort to identify brain structural endophenotypes, we aimed to i) identify TLE-related changes in brain structural volume and ii) compare the heritability of such structures in TLE patients to published values calculated in neurologically healthy control populations.

Methods: MRI-based volume measurements of a number of subcortical brain structures were calculated in TLE patients, their unaffected siblings and healthy controls. Structural volume measurements of TLE patients were compared to those of the healthy controls. The heritability of the structures that displayed volume changes was calculated in the patients and their unaffected siblings.

Results: Significant reduction in hippocampal, amygdalar, and thalamic volume was found in TLE patients. Similar trends of volume reduction across the same structures were also observed in the unaffected siblings of TLE patients. High heritability value was observed for thalamic volume and was comparable to those previously reported; however, the heritability values for the hippocampus and amygdala were reduced.

Conclusion: Although a role for genetic factors in the development of TLE is likely, environmental factors (such as early brain insults and repeated seizure activity) seem to play a significant role in causing the observed volume loss in the hippocampus and amygdala. The reduced heritability of the volume of these two structures may affect their suitability as TLE-related endophenotypes. Given the observed volume reduction and high heritability of thalamic volume in TLE patients, the thalamus fits the profile for a novel TLE-related endophenotype.

P15. The interaction of vesicle associated membrane protein and sterol regulatory element binding protein and the implications for amylotrophic lateral sclerosis.

Karolina Weiner-Gorzel, Sein O'Connell, Maria Teresa Bengoechea-Alonso, Johan Ericsson.

School of Medicine and Medical Science, Conway Institute of Biomolecular and Biomedical Research, University College Dublin.

Vesicle associated membrane protein–associated proteins (VAPs) are endoplasmic reticulum membrane proteins implicated in diverse cellular functions. Recently missense mutations in the gene encoding the VAPB protein has been found in patients with familial neurodegenerative disorders such as amylotrophic lateral sclerosis. It has been shown recently that cholesterol and triglycerides levels could be a prognostic marker for ALS patients. However, data is limited with conflicting reports and conclusions as to whether hyperlipidemia or dyslipidemia can prolong the survival of ALS patients and whether a statin treatment regime would be beneficial. In order to determine the molecular mechanisms of this connection between VAPB and lipid metabolism, the interaction between VAPB and sterol regulatory element-binding protein (SREBP), a transcriptional regulator of lipid metabolism was investigated. This work identified a novel functional and physical interaction between SREBP and VAPB. VAPB knock-down and over-expression experiments indicated that VAPB may potentially be a negative regulator of SREBP. Whilst further analysis is required to determine the precise mechanisms involved in the interaction between SREBP and VAPB, our initial results suggest a potential role for deregulated lipid metabolism in neurodegenerative diseases.

P16. Galactosaemia, a systemic glycosylation defect? Biochemical and molecular aspects.

KP Coss[1], PP Doran[1,] JC Byrne[2], DW Murray[1], BA Adamczyk[3], PM Rudd[3], EP Treacy[4].

University College Dublin, Clinical Research Centre, Mater Misericordiae University Hospital [1], Royal College of Surgeons, Ireland, Molecular and Cellular Therapeutics[2], NIBRT Dublin-Oxford Glycobiology Group[3], and National Centre for Inherited Metabolic Disorders, and TCD[4], Dublin.

Classical Galactosaemia (Gal) is a rare autosomal recessive disorder of carbohydrate metabolism caused by GALT deficiency. It is screened for as part of the Irish National Newborn Screening Programme. Long-term outcomes of treatment with dietary galactose restriction are extremely disappointing as the pathophysiology is poorly understood.

Methods: We developed biochemical and molecular methods to study systemic glycosylation **(**HILIC fluorescence of *N*-glycans enzymatically released from whole serum and IgG) and gene expression (Affymetrix U133a plus2.0arrays from T-cell RNA) in adult Gal patients (n=12, 5 female and 7 male) with differing neurological outcomes. We also examined these parameters in patients undergoing supervised dietary galactose modification.

Results: HILIC of *N*-glycans released from serum glycoproteins (in particular IgG) demonstrated specific peak differences in informative patients with improvements noted with slightly higher galactose intake. Microarray and KEGG analysis demonstrated multiple pathway disturbances related to systemic glycosylation abnormalities (up to 67 KEGG pathway glycosylation genes affected) with specific central pathway genes also affected such as *SCL5A3* (myo-inositol co-transporter).

Conclusion: Our studies indicate Galactosaemia functions as a systemic glycosylation defect. We propose serum *N*-glycan analysis in combination with T-lymphocyte microarray data will provide improved biomarkers to understanding the pathophysiology of this and related disorders with a view to improving therapeutic options.

P17. Investigation of High Resolution Melting analysis as a tool for mutation detection.

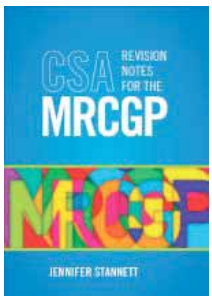
Ciara Fahey, Michael Gill, Aiden P Corvin, Derek W Morris.

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

High Resolution Melting (HRM) analysis using dsDNA-binding dyes and real-time PCR instrumentation is an attractive mutation detection technique due to its rapid, high-throughput and sensitive post-PCR analysis. HRM methodology is based on amplifying a region of interest using primer specific PCR, followed by gradual denaturing of the target region and generation of a melt curve, allowing successful detection of genetic variation in the sequence. In order to test the efficiency of HRM we applied it to exonic regions of the VIPR2 gene. Our two-stage approach to testing the HRM method was: (1) Analyse a proportion HapMap CEU samples of known mutation content based on online data (1,000 Genomes) to optimize performance of the method. (2) Blindly screen remaining HapMap CEU samples for mutations and compare results with online data. Stage 1: Melt curve analysis successfully identified a high proportion of expected mutations in tested HapMap samples. Stage 2: We will report on the specificity and sensitivity of the method when applied to remaining HapMap samples. If the method shows accurate performance, it can be applied to our large sample of schizophrenia cases and control samples. Along with subsequent capillary sequencing, it could potentially identify rare risk variants in patient samples.

Book Reviews

CSA REVISION NOTES FOR THE MRCGP



Jennifer Stannett, ISBN 978-1-904842-86-6, 186 pages, March 2011, £ 24-99, Scion Publishing ltd

Several years ago postgraduate training in general practice received a complete overhaul and the examination now consists of a written exam called the Applied Knowledge Test (AKT) and a Clinical Skills Examination (CSA). The CSA is an OSCE type exam where students deal with a series of clinical scenarios and are assessed in three key areas; data gathering, clinical management and interpersonal skills.

This book includes a wide range of clinical topics based on the MRCGP syllabus to help prepare prospective candidates. There are no glaring omissions of topics. For the current assessment there is not a detailed marking scheme and conceptual marking is used. The examiner arrives at a mark by weighing up observed behaviours which are positive indicators and other behaviours which are negative. Therefore it might have been helpful if the book had included some examples of negative behaviours.

Most of the evidence based references relate to NICE guidelines which is appropriate. The role plays that are provided would be useful for the prospective candidates to work through either in pairs or small groups, though at times the details for both doctor and role player are scant.

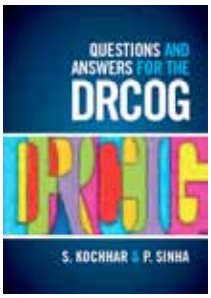
The Health Promotion scenarios involving smoking and obesity should have included some reference to the "readiness for change" consulting model. I also feel that in the meningitis station the hospital based investigations detailed are largely irrelevant with regard to general practice.

Some of the scenarios also simply list treatment options, while some reference to pros and cons of different treatments should be included e.g. HRT for managing menopausal symptoms.

This lack of balance in some of the scenarios may be due to the fact that the author appears to have written this book on her own and might have benefited from having an editorial panel to assist her. I also think that constructive feedback from readers should actively be sought as this would improve subsequent editions. However, this should not detract from the overall assessment of this book which will undoubtedly be a useful aid for candidates doing the nMRCGP and would also be helpful to GP Trainers not only for their continuing professional development but would also give them more of an insight of what is expected of their Registrars in this novel form of assessment.

Drew Gilliland

QUESTIONS AND ANSWERS FOR THE DRCOG



Suneeta Kochhar and Prabha Sinha. Scion Publishing, Pages 146, ISBN: 978-1-904842-87-3

This book is written by Suneeta Kochhar, a GP principal and Prabha Singha, a consultant obstetrician and gynaecologist in East Sussex. It is aimed at candidates preparing for the new style DRCOG exam. The book includes a brief overview of the new examination, the syllabus and three complete revision papers reflecting the current format of the exam.

Each revision paper is specifically designed to be answered under exam conditions and consists of 30 extended matching questions (EMQ), 18 single best answer (SBA) or 'best of five' questions and 40 multiple choice questions (MCQ). The questions are based on common clinical scenarios spanning a wide area of obstetrics and gynaecology, including contraception and termination of pregnancy.

The 'answers and explanations' section at the end of each exam paper is the real strength of this book. It gives a detailed explanation for each question, references and up to date evidence-based information where necessary. The explanations are thorough and emphasize the salient points while the references encourage self-directed learning.

There aren't many books for candidates preparing for the restructured DRCOG exam and the authors should be praised for their hard work in meeting the high demand. This book is concise, clearly laid out and user-friendly. It is an excellent revision guide, which enables the candidates to improve their knowledge, is relevant to general practice, and helps master the technique of answering the questions.

Although this book is primarily aimed at the candidates attempting the new style DRCOG exam, it can be equally beneficial to those who are preparing for the MRCGP Applied Knowledge Test and also to any other professionals with an interest in women's health, to update their knowledge in this field.

Janitha Costa

So you want to be a **Pharmaceutical Physician?**

Colin Hayward

Accepted 30 June 2010

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You want to what? How are you going to tell your boss that you are leaving the Health Service to join the dark side? Your mother will worry that she might not be able to continue telling her friends that you are a doctor.

You can tell them confidently that you are looking forward to a varied and stimulating career that could ultimately benefit more patients than you could ever treat in your own practice.

SO WHAT IS PHARMACEUTICAL MEDICINE?

Pharmaceutical medicine is one of the best kept secrets of the medical world. It is the specialty concerned with the discovery, development, evaluation, licensing and monitoring of medicines as well as the medical aspects of their marketing.

Pharmaceutical physicians work in different environments including regulatory agencies, drug companies and research organisations.

IS PHARMACEUTICAL MEDICINE REALLY A MEDICAL SPECIALTY?

Yes.

The need for involvement of medics in the development of medicines became increasingly recognised during the 1960s.. The role of the specialist evolved rapidly to provide an interface between pharmaceutical medicine and other medical disciplines. Creation of The Faculty of Pharmaceutical Medicine (FPM) within the Royal College of Physicians addressed demands for medicines to be developed and monitored to the highest scientific and ethical standards. The FPM was formally established in 1989 and in 2002, Pharmaceutical Medicine was officially recognised as a specialty in the UK. The FPM continues to set and maintain the highest standards of pharmaceutical practice.

WHERE IS PHARMACEUTICAL MEDICINE GOING AS A SPECIALTY?

Pharmaceutical medicine continues to grow. It is the 12th largest specialty based on the number of trainees, more than, for example, medical oncology. It is a dynamic specialty reflecting the need for an international collaboration between science and business. Half of FPM members are non-UK based, reflecting the global nature of Pharmaceutical Medicine.

The Faculty recognises qualifications from Belgium and Switzerland and in 2011the Diploma in Pharmaceutical Medicine examination will be held in the UK and overseas, in South Africa, simultaneously.

HOW ARE PHARMACEUTICAL PHYSICIANS TRAINED?

As with most specialties, the majority of training takes place on the job. Training takes 4 years and requires completion of the Diploma examination. In addition, you must provide evidence that you have reached the required standards in the following areas: regulation, pharmacology,

- statistics, development,
- healthcare marketplace, drug safety, role of the medical
- department, discovery of new medicines, therapeutics.

CAN I CARRY ON DOING SOME CLINICAL WORK WHILST WORKING IN PHARMA?

You could, and roles that require a more in-depth disease knowledge might even encourage this. My perspective is that you will be busy enough focussing on the one job.

NO ON-CALL SOUNDS GREAT – WHEN DO I START?

Hang-on a minute. Business is about ensuring a good return on investment.

Companies invest in you and will expect you to work in return. The pressures of life in industry are different from the clinic but there are pressures. To quote Dr Appleton (Appleton AL. Long hours not unique. BMA News May 14 2011: www.bma.org.uk/bmanews) “excessive hours are not the preserve of junior doctors”. New entrants expecting an easy ride should probably look elsewhere.

HOW DO I JOIN INDUSTRY?

The simple answer is you apply for a job, are interviewed rigorously and are judged on your merits.

Although I went into my first role somewhat naively, it provided a good starting point for a career as a Pharmaceutical Physician and I was able to work with some talented people in an innovative company. There are many roles for medics.

I recommend talking to physicians in industry to understand the options available and what might suit you best. Traditional starting roles include working in a contract research organisation reviewing the safety data from patients in trials; junior drug safety roles reviewing adverse events from your company’s drugs; medical manager (advisor) where you are the lead scientist working with the commercial team.

To enter specialist training in pharmaceutical medicine you need to have completed at least two years’ post foundation clinical training. While completing specialist training is not yet essential for being a Pharmaceutical Physician, it is desirable, particularly for senior UK roles.

Your specialty pre-industry may help you get roles that require expert knowledge, but as a medic, you already have the ability to pick up scientific concepts pretty quickly. Personal skills are also highly valued and in my opinion more important; requirements vary depending on whether your role requires a gregarious strategic thinker or a logical, critical data reviewer.

FINDING OUT MORE

Find out more by contacting the Faculty (www.fpm.org.uk) or BRAPP (www.brapp.org).

Who knows we may soon meet at a congress; as I have, you can have the opportunity to live around the world, work with talented people from different cultures and change disease paradigms. Not bad for a week’s work.

THE ULSTER MEDICAL JOURNAL

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