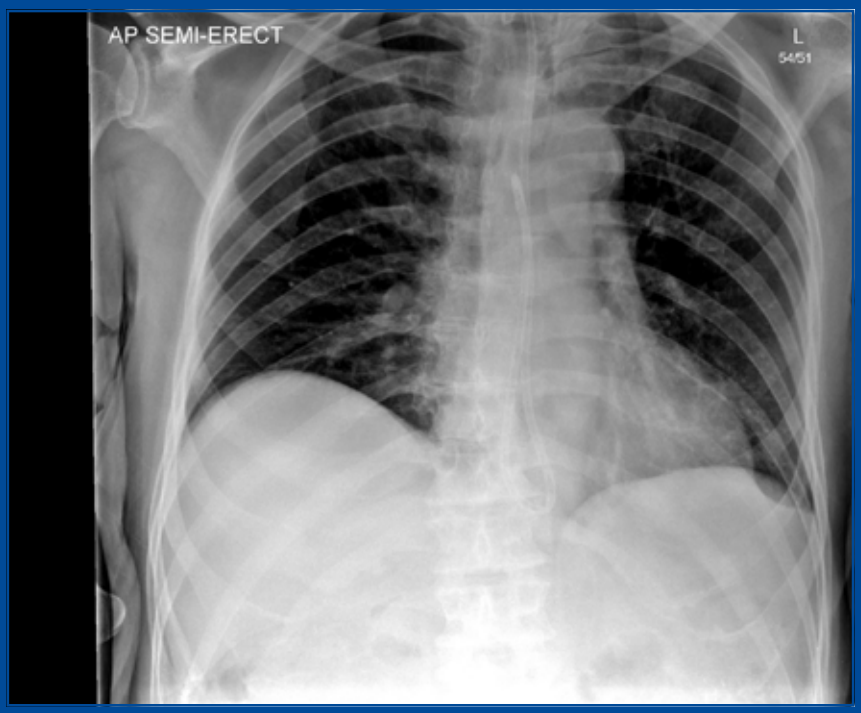
ISSN 0041-6193

THE ULSTER MEDICAL JOURNAL

Volume 81 (3) September 2012



Published in January, May and September by

THE ULSTER MEDICAL SOCIETY

www.ums.ac.uk

The Ulster Medical Journal

The journal of the Ulster Medical Society. First published in 1932.

Successor to the Transactions of the Ulster Medical Society (1862-1929), and the Transactions of the Belfast Clinical and Pathological Society (1854-1860)

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The journal is published in January, May and September, by the Ulster Medical Society, and typeset and printed in the UK by Dorman and Sons Ltd, Belfast. See inside back pages for institutional and personal subscriptions.

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Ulster Med J 2012;**81(3):**105-106

Editorial

Regarding Parnassus

"It's tough to make predictions", averred Lawrence 'Yogi' Berra, "especially about the future". The Danish physicist Niels Bohr, said the same. This edition considers, in our small way, the past, present and future. How we did things in the past needn't influence how they're done in the present; and how we practise now shouldn't dictate the future direction.

In 1912, at the Harvard College Observatory, a prodigiously talented lady named Henrietta Swan Leavitt noted that distant stars, Cepheid variables like Polaris, pulsated with a regular beat. Furthermore by comparing their relative brightness, she could calculate where they were in relation to each other. From this, she devised the term '*Standard Candles*'[1]. In 1913, Vesto Slypher, working at the Lowell Observatory, detected a red shift in distant stars and realised that they were moving away from us[1]. Consequently Edwin Hubble, utilising these standard candles and red shifts, postulated two things: the universe was much bigger than had been supposed, and that it was expanding[1].

In 1936, George Lemaitre, a Belgian priest, mathematician and physicist, posited 'A Day Without Yesterday'[2] as part of his Fireworks Theory. The universe, he calculated, had burst forth from a primeval atom, or singularity. Lemaitre, also suggested that there should be smouldering remnants of the explosion still out there -cosmic rays. No one paid much attention. In 1948, George Gamow in his landmark *'Alpha Beta Gamma'* paper[3] (surely one of the cleverest titles ever published), speculated that these residual traces would now be microwaves. His paper was also almost universally ignored. Nearly 20 years later, Arno Penzeus and Robert Wilson, researching at the Bell Antenna in New Jersey, and unaware of Gamow's paper, were bothered by a ubiquitous hiss detected by the antenna despite all their efforts to eliminate it. It was, of course, the final piece of the puzzle - microwave radiation left over from the Big Bang. For this they won the Nobel Prize in 1978. Penzeus and Wilson connected the dots between Swann Leavitt, Slypher, Hubble, Lemaitre and Gamow.

Let's return to Miss Swan Leavitt. Her occupation in Harvard was merely that of a *computer*; that is someone who studied photographic stellar plates and from them made computations[1]. She was unusual, and not merely because of her stellar intellect. Her gender placed her in a regrettable minority of influential scientists. Marie Curie was another and was the first woman to be awarded a Nobel prize; the first person to win two Nobel prizes and the only person to have been awarded Nobel Prizes for both physics (Radioactivity,1903) and chemistry (Radium and Polonium,1911). For many women, the playing field just wasn't level, and for countless others, playing wouldn't be an option at all.

In his Oration, Professor Jim Dornan reviews the lot of women in history. I can recall, as a medical student, noting that all the consultants in what are now termed *craft specialties* seemed to be men. Even then I wondered, with the greatest respect to those great and good men, particularly in gynaecology, there surely had to be anatomical and physiological limits to their empathy? Professor Dornan and his generation were perfectly placed to amend this gender imbalance, and to their great credit, amend it they did.

This edition's Review paper is by Professor Tony Gallagher, an acclaimed international authority on simulation and an idea whose time has surely come. Professor Gallagher makes a compelling case for the future training direction of craft specialties, and how skills must be acquired and measured. The historical medical aphorism " See One; Do One; Teach One" won't pass muster. There is a viable alternative. Please read this edition's review paper to learn more.

QUICK RESPONSE CODES

Sharp-eyed readers will observe that the journal's back cover now includes a small black and white square. This is a 'Quick Response' (QR) code. Its purpose, we envisage, is to facilitate access to the journal from your smartphone. It's a work in progress, but if you have the software (and it's readily available as a download), please try it. In successive editions we will increase its functionality.

EDITORIAL APOLOGY

As happens on occasion, a busy, and much in demand contributor was unable to meet our current publication deadline, and his apology was fulsome. Consequently, as the 'Grand Rounds' piece was already entitled, 'The Chest Radiograph' and would form part of a greater sequence, I elected to write, at a minute to midnight, something myself. I hope it will be of some use to students and examination candidates.

Please keep sending me your good papers.

Barry Kelly

Honorary Editor

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NORTHERN IRELAND
RARE DISEASE PARTNERSHIP

The Northern Ireland Rare Disease Partnership (NIRDP) is a unique partnership of those living with a rare disease and organisations representing them, with clinicians and other health professionals; science and industry; health policy makers and academics.

A disease is "rare" if it affects 5 or fewer in 10,000 of the general population. There are over 6,000 recognised rare diseases; as medical science advances, more are identified. 1 in 17 people in the UK is likely to be affected by a rare disease at some point in their lives; that's almost 106,000 people in Northern Ireland.

Collectively, rare diseases are NOT "rare"!

Although these conditions are all individually rare, we find that affected individuals share many of the same experiences. Patients with rare disorders can face a very long and convoluted diagnostic journey. They may see many doctors and other health care professionals before getting a diagnosis. When they do receive a diagnosis they often find that very few healthcare professionals have heard about their condition, or know much about it.

And from the doctor's perspective, managing a patient with an unknown condition, or a rare disease can be a complicated, even daunting task!

Some aspects of diagnosis, care and treatment can be very highly specialised, and may even be available in only one or two localities in the UK- even in the world. But much of the support and help that is needed by patients day to day can be relatively routine, and can be provided from existing services. We know, too, that the patient experience is greatly improved (even transformed) by a willingness on the part of their doctors and other health care professionals to listen to them, and to their carers: to find out something about the condition and to seek advice and help from the specialist or specialist centre, even if he, she, or it is "across the water" or even further afield.

The NIRDP aims to advocate, educate and innovate for those living or working with rare diseases. We aim to work together to find practical ways of improving the quality of life, treatment and care for those living with rare diseases right across NI- in every GP practice and political constituency, in towns and townlands. Our membership includes people with over 30 different rare conditions, ranging from the very rare disease to the relatively well recognised, like Motor Neurone Disease, Spina Bifida, Muscular Dystrophy or Huntington's disease; and a range of specialist nurses, physicians, researchers, and organisational representatives. This mix facilitates information and knowledge transfer, and mutual support- whether that is families facing similar difficulties; families supporting their clinicians to promote improvements to service delivery; or clinicians adding weight and expert knowledge to calls for policy changes.

Membership is free. It gives access to a growing network of knowledge, information, help and support; and to ways of influencing and making views known and heard. Please encourage your families with rare diseases to make contact with us; please contact us yourself if you feel we can be of any help; and most especially if you would like to contribute to any aspect of our work. We are stronger together!

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Ulster Med J 2012;**81(3):**107-113

Review

Metric-based simulation training to proficiency in medical education:- What it is and how to do it

Anthony G Gallagher

Accepted 25 July 2012

ABSTRACT

High profile error cases and reduced work hours have forced medicine to consider new approaches to training. Simulation-based learning for the acquisition and maintenance of skills has a growing role to play. Considerable advances have been made during the last 20 years on how simulation should be used optimally. Simulation is also more than a technology learning experience for supplanting the traditional approach of repeated practice. Research has shown that simulation works best when it is integrated into a curriculum. Learning is optimal when trainees receive metric-based feedback on their performance. Metrics should unambiguously characterize important aspects of procedure or skill performance. They are developed from a task analysis of the procedure or skills to be learned. The outcome of the task analysis should also shape how the simulation looks and behaves. Metric-based performance characterization can be used to establish a benchmark (i.e., a level of proficiency) which trainees must demonstrate before training progression. This approach ensures a more homogeneous skill-set in graduating trainees and can be applied to any level of training. Prospective, randomized and blinded clinical studies have shown that trainees who acquired their skills to a level of proficiency on a simulator in the skills laboratory perform significantly better *in vivo* in comparison to their traditionally trained colleagues. The Food and Drug Administration in the USA and the Department of Health in the UK have candidly indicated that they see an emergent and fundamental role for simulation-based training. Although a simulation-based approach to medical education and training may be conceptually and intellectually appealing it represents a paradigm shift in how doctors are educated and trained.

BACKGROUND

During the Annual meeting of the American Surgical Association (ASA) in April 2002 at the Homestead (VA, USA) researchers from Queen's University Belfast and Yale University (USA) reported the results from the first prospective, randomized, double-blinded trial of virtual reality (VR) training for the operating room (OR). Surgical residents randomized to the VR training arm of this study subsequently performed the actual dissection of the gallbladder from the liver bed portion of a laparoscopic cholesystectomy (LC) 26% faster than traditionally trained surgical residents and made six times fewer objectively assessed intra-operative errors[1]. This study (or VR to OR as it has become known[2]) was important because for the first time it unambiguously demonstrated the potential of (VR) simulation as a powerful training methodology for the acquisition of procedural skills outside the OR which directly impacted on *in vivo* OR performance. Previous studies had compared VR training to no, or traditional approaches to training (i.e. on real patients), but these studies were conducted wholly in the skills laboratory and not on real patients.[3-7]

Although simulation had been used in other industries such as aviation for decades[8] and in medical disciplines such as anaesthetics for many years[9] its potential as a training device in surgery and procedure-based medicine was not taken seriously until a series of high profile and impactful events forced medicine and surgery to consider a new way of training. High profile error cases in the UK[10] and the USA[11] as well reduced work (and training) hours[12, 13] forced medicine to consider new training paradigms. Bad experiences following the introduction of minimally invasive surgery (MIS) ensured that surgeons were already sensitised to the need to improve training.. The introduction of MIS, particularly LC, was accompanied by an increased frequency of complications, many life-threatening, particularly during the early experiences.[14] That these problems could occur when experienced surgeons, well versed in open techniques and with knowledge of anatomy and pitfalls embraced new techniques, heightened concerns about the training of novices who lacked such a background in open surgery. But the agenda was now set, surgery needed to develop new methods for training the novice in surgical techniques in general and for training experienced surgeons in the newer techniques.[15]

Dr. Richard Satava, a US army general surgeon first proposed the idea of VR simulation for the acquisition of surgical skills in the early 1990s whilst on secondment to the Defence Advanced Research Projects Agency (DARPA).[16] Until the VR to OR study results were reported his proposal was at best considered 'eccentric' and VR simulation a technology of marginal significance. In March 2002 at a closed door meeting in Boston College, hosted by Dr. Gerry Healy (President of the American College of Surgeons 2007 – 2008) and the American College of Surgeons (ACS) and in light of the imminent VR to OR study report at the ASA, the decision was

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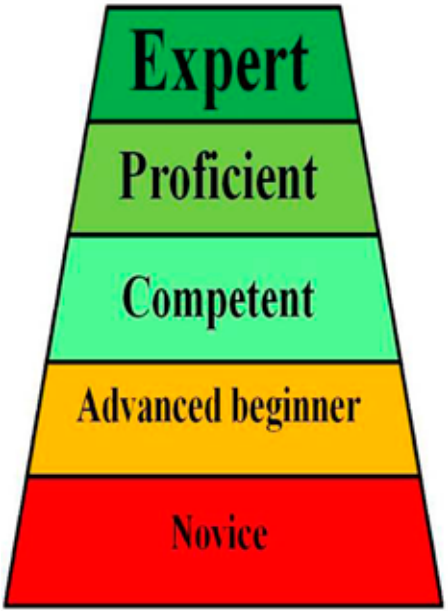

STAGE	PERFORMANCE CHARACTERISTICS
Expert	• Source of knowledge and information for others • Continually looks for better methods • Work primarily from intuition • Being forced to follow rules degrades performance
Proficient	• Seeks to understand larger context • Frustrated by oversimplification • Can self-correct performance • Can learn from experience of others
Competent	• Can troubleshoot problems on his/her own • Seeks out expert user advice • Develops conceptual models
Advanced beginner	• Starts trying tasks on his/her own • Has difficulty troubleshooting • Begins to formulate principles, but without holistic understanding
Novice	• Has little or no previous experience • Doesn't know how to respond to mistakes • Needs rules to function

Fig 1. Dreyfus & Dreyfus Figure[23]

taken for the ACS to 'champion surgical simulation'.[17] The impact of this brave and enlightened decision was enormous. True to its word the ACS championed simulation based training which has led to the establishment of Accredited Education Institutes (within the USA and globally) of which simulation is an important pedagogical component.[18]

WHAT IS SIMULATION?

Simulations have been given many definitions over the years but it is fair to say that 'simulation' is usually thought of as VR. In 1993 Satava[16] originally proposed that "Virtual reality [simulation] is a fully three-dimensional computer-generated "world" in which a person can move about and interact as if he actually were in this imaginary place."... "A world can be anything from a kitchen to an automobile to an abdomen -- anything which can be drawn can be experienced three dimensionally". In contrast, high fidelity simulations in disciplines such as anaesthetics utilized very realistic materials and equipment to represent the task(s) that the candidate must perform[19]. Anaesthetic simulations centred on computerized, interactive, life-sized manikin that could be programmed to provide realistic patient responses and outcomes. Low fidelity simulations would be ones in which the candidate is presented with a verbal description of a hypothetical work situation and then asked to describe how he/she would deal with the situation rather than having the candidate perform the actions he/she would take.[20] Thus, simulation fidelity has been construed by trainers and educators as the degree of similarity (and apparent technical sophistication) of the simulation to the real world situation that was being trained. Inanimate simulation tasks such as animal tissue would be low fidelity and increasing sophistication and or face validity of the simulation represented increasing simulation fidelity. This issue will be returned to when the concept of metrics is discussed. It suffices to state at this point that both of these views of simulation fidelity are now incomplete in light of a more sophisticated and comprehensive theoretical understanding of what a simulation is and how it is configured and implemented for the efficient and effective learning of skilled performance.

WHAT IS SKILL?

One of the most important functions of a simulation is to facilitate the effective and efficient training of skill outside the clinical situation thus minimising the risk to the patient from at least part of the novice's learning curve. But what is skill? Failure by medicine to explicitly answer this question has been one of the major impediments to the development of good simulations and simulation-based training. When United States Supreme Court Justice Potter Stewart was asked describe his threshold test for obscenity in the case of Jacobellis v. Ohio (1964) he infamously ruled that 'he knew it when he saw it'.[21] Similarly, most doctors have an opinion as to what skill is but few can robustly define it. A parsimonious definition of skill might be 'it is what skilled individuals do'. However, this definition does not advance a specific testable model of skilled performance that could be used to characterise performance. In contrast, psychologists have tackled the same problem by subjecting the 'skill' to be characterised to a detailed task analysis and then operationally defining (not describing) important aspects of performance which constitute skill.[15, 22] They then quantitatively validate whether their characterisation fits with what is known about the skill they have analysed. Do more skilled individuals perform better on their assessments than less skilled or experienced individuals (construct validity)? Do individuals who perform well on their evaluations also perform well on a variety of similar and related tasks (concurrent validity)? Do their assessments predict future skilled performance (predictive validity)? These task-analysis derived characterizations of skilled performance do not have to capture every aspect of performance but should at least allow for ordinal differentiation between different levels of performance as described by Dreyfus and Dreyfus[23] and summarised in **Figure 1**[15].

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Table 1:

Metric Errors

Metric errors/criteria of injury assessment	**Operational Definition**
Procedure **START**	first contact of diathermy with tissue
Procedure **END**	last attachment is divided
FAILURE TO PROGRESS	No progress made in excising the gallbladder for an entire minute of the dissection. Dealing with the consequences of a predefined error represents lack of progress if no progress is made in excising the gallbladder during this period.
GALLBLADDER INJURY	There is gallbladder wall perforation with or without leakage of bile. Injury may be incurred with either hand.
LIVER INJURY	Necessitates capsule penetration and may have bleeding.
BURN NONTARGET TISSUE	Any application of electrocautery to non-target tissue with the exception of the final part of the fundic dissection where some current transmission may occur.
TEARING TISSUE	Uncontrolled tearing of tissue with the dissecting or retracting instrument.
INCORRECT PLANE OF DISSECTION	The dissection is conducted outside the recognized plane between the gallbladder and the liver (i.e. in the sub-mucosal plane on the gallbladder, or sub-capsular plane on the liver).
INSTRUMENT OUT OF VIEW	The dissecting instrument is placed outside the field of view of the telescope such that its tip is un-viewable and can potentially be in contact with tissue. No error will be attributed to an incident of a dissecting instrument out of view as the result of a sudden telescope movement.
ATTENDING TAKEOVER	The supervising attending surgeon takes the dissecting instrument (right hand), or retracting instrument (left hand) from the resident and performs a component of the procedure.

WHAT ARE METRICS?

Based on the task analysis process outlined above, the units of performance that have been identified (and validated) as integral to skilled task performance are the metric units of task execution. This means that these performance units should be used to define and shape the configuration of any simulation developed to train skilled task performance. Metric units must be unambiguously defined so that they can be scored as occurring or not occurring. These metric units should capture the essence of procedure performance and might include the steps that the procedure should be performed in, the instruments used and what should be done with them. Crucially, the metrics should also describe for each procedure step what should not be done thus characterising performance that deviates from optimal performance (or errors).[24] Metric errors are some of the most important performance units for simulation based training.[15] Training should concentrate on what should be done and the order in which it should be done but it should also target performance errors for at least reduction, preferably elimination. This means that operational definitions of performance units or metrics need to be unambiguous. For example, **Table 1** shows the operational definitions of metrics for the dissection of the gallbladder from the liver bed portion of a LC including a start and end point procedure markers.[1] They unambiguously 'define' rather than describe when each metric error has occurred. This approach considerably facilitates the reliable scoring of metric-based performance units across a variety of functions from skills training[25-28] at different experience levels.[29, 30] It has also been shown that this approach works well as part of the process for selection into higher training[31] and considerably enhances assessment reliability levels in comparison to Likert-scale assessments.[32]

In discussions with different groups of physicians and surgeons from around the world there appears to be a consensus appears that reaching agreement on performance metrics is all but impossible. This may however, only apply to agreement on 'everything'. The majority of doctors very experienced and proficient in the performance a specific procedure can very quickly identify and agree what should be done, how it should be done and what most certainly should not be done for most parts of a procedure. The problem is that doctors rarely think about procedures in that level of detail. Practitioners who are 'proficient' in the performance of a procedure (with average to good outcomes) will already exhibit many if not all of the important performance characteristics to perform the procedure well. They have

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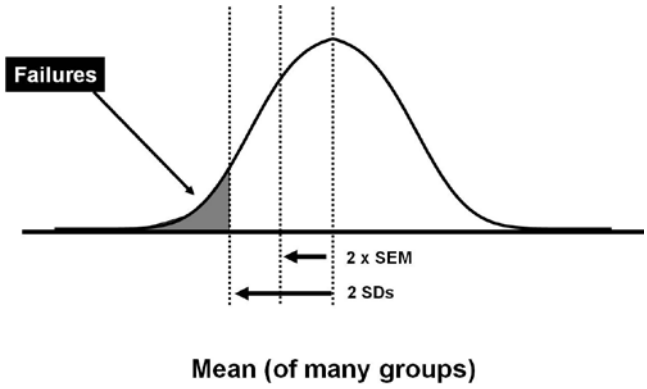

Fig 2a. the Wijen method of competency assessment

however, automated to many of these and how it is they are performed (much like the complex skills required to ride a bicycle). A primary function of the task analysis process is to identify and define what these performance characteristics are. This should be done initially for a 'reference procedure', i.e., a straightforward procedure that can be performed without complications or deviations under ideal circumstances. (An optimal approach to learning should ensure that trainees are capable of performing an uncomplicated procedure before they have to deal with procedure variations). The task analysis should seek consensus (not necessarily agreement) between procedure experts on the characteristics of the reference procedure and instruct them to characterise the reference procedure and not unusual or interesting variants of it. Procedure performance should be guided by a) professional guidelines, b) manufacturer guidelines on device usage and c) results from empirical studies. In the absence of a consensus between the experts on the items (a) to (c) above then individual procedure practices that they may have developed from years of practice wisdom should be employed. Errors are defined as procedure actions which deviate from optimal practice and are not necessarily bad but are potentially unsafe. Critical errors in contrast are procedure actions which are most certainly unsafe but may not always lead to a bad outcome.[15] The underlying philosophy of this approach is that bad outcomes do not happen by accident but usually from the coalescence of deviations from optimal procedure protocol.[33] The task analysis stage of the development of a simulation is crucial as metrics are the fundamental building blocks of a good training program. Metrics thus define how the simulation should be characterised and performed by the trainee and must afford the opportunity for meaningful performance assessment. Assuming that the metric identification and definition process, simulation operationalizaion and implementation goes well these performance characteristics should be easily validated, as distinguishing between experts and novices (i.e., construct validity) and predictive of acquired skills post training (predictive validity). Other validation processes are necessary but these two are probably the most important for training purposes. The construct validity study will inform the training process which metrics best distinguish between experienced/expert and novic performances and will guide the skills benchmarking process or 'proficiency level' which trainees should acquire before progressing to *in vivo* practice.[15, 34]

SIMULATION DEFINED

Equipped with an understanding of the importance of metrics for the characterization and configuration of a simulation, simulation can thus be defined as i) an artificially created or configured 'learning' situation that allows for the practice or rehearsal of all or salient aspects of a procedure. The artificial learning situation must ii) provide the span of appropriate sensory responses to learner physical actions that are behaviourally consistent with what would be experienced in real life (including the opportunity to enact both appropriate and inappropriate learner actions (i.e., errors)). The simulation should also afford the opportunity to iii) perform the procedure iv) in the same order and v) with the same devices that the procedure would normally be performed. Crucially, it should also afford vi) reliable and valid metric-based assessment of performance. Assessments must at a minimum vii) allow summative but preferably formative feedback on procedure performance proximate to task execution, particularly for metric errors.

WHAT IS PROFICIENCY-BASED TRAINING?

Traditionally medicine has trained doctors to be 'competent' and this fact has been reinforced by high profile medical errors cases, e.g., The Bristol Case.[10] However, what is probably less well known outside of (academic) medicine is that this level of competency is in fact 'minimum' competence. Indeed over the years medicine has developed robust statistical processes for the definition of minimum competency levels (**Figure 2a**).[35] As shown in Figure 3a competency definitions can vary considerably between and even within institutions using these statistical methods. The concern that many surgeons, interventional cardiologists and radiologists and other procedurists express is that this level of skill may be too low. Also of concern to them is the variability in competence thresholds. They also express concern about the failure of medicine to define a measured skill level that is objective, transparent and fair. Furthermore, they believe that training practitioners to a level of proficiency[23] may be a more conservative but superior approach. They are however faced with the same problem of benchmark definition.

The "I know it when I see it" approach does not work well for understanding and operationally defining what skill is but, it will serve more than adequately for helping to define a proficiency benchmark, i.e., proficiency is the level of performance exhibited by proficient individuals. Thus, validated metric-based simulations can serve as benchmarking devices. The philosophy being that individuals who are very experienced at performing a specific task or procedure e.g., a consultant/master surgeon, are at least competent, probably proficient and some will be expert.[15, 34] This means that a level of proficiency benchmarked on the mean performance level of these individuals on the validated metric-based simulation is a fairly conservative criterion level. Furthermore, it has considerable face validity. Rather than benchmarking on some abstract performance level reached by consensus in a committee the training pass level is defined on the performance levels of individuals who are actually very experienced at performing the procedure clinically. This does not imply that individuals who demonstrate this benchmark in training have the same 'performance capacity' as the individuals on whom the level was established. It simply means that they were

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able to demonstrate that performance level (e.g.., technical or knowledge or both) on consecutive trials. They will not (yet) have acquired the procedural wisdom of the experienced operator. This approach to training ensures a much more heterogeneous skill set from trainees as ALL trainees must reach AT LEAST the proficiency level (on two consecutive trials) before progressing to *in vivo* practice (**Figure 2b**). The other advantage of this approach (summarized in **Figure 3**) is that it eliminates the issue of number of training trials or time in training before progressing. It also puts the onus on the trainee to demonstrate proficiency before progressing. The onus on the trainer is to provide the facilities and access to training to demonstrate proficiency. The results from this approach to training skills have shown that proficiency-based progression trainees significantly outperform traditionally trained doctors,[1, 25, 36] even for advanced procedures.[28]

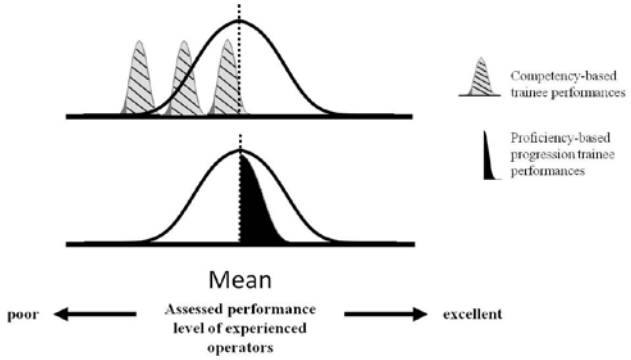

Fig 2b. Competency Vs Proficiency

WHAT IS THE DIFFERENCE BETWEEN REPEATED AND DELIBERATE PRACTICE?

Medicine is currently grappling with the mechanics of a proficiency-based progression approach to training (e.g., development of metrics, metric validation, proficiency definition etc).[15] It circumvents some very sticky problems such as how to define competency? If an individual has demonstrated a proficiency benchmark they must by default have demonstrated competency as proficiency is a more advanced skill level as proposed by Dreyfus and Dreyfus.[23] It has also forced medicine to define precisely what is meant by 'skill' (for a reference approach at least). Another benefit from the process of defining skill and deviations from optimal performance, i.e., metrics, has been the evolution of an understanding how metrics could be used to define, shape and configure a specific simulation. Thus a simulation becomes a vehicle for the delivery of metric-based training rather than some abstract entity. Furthermore, metric-based simulation training can be configured in such a way as to make training much more efficient and effective. Traditionally skills in medicine have been acquired through repeated practice in the clinical setting. How quickly they learned depended on how frequently they encountered the learning situation, whether they have the opportunity to implement or practice their skills and whether their supervisor had the opportunity (or inclination) to use the setting as a training occasion. Thus, the learning accrued from such opportunities could be very variable. Simulation affords the trainee to acquire their skills in the simulation laboratory in a much more systematic way. It also means that each time the trainee engages with a metric-based simulation their learning can be optimized. Each time the trainee performs the procedure they will receive feedback on their performance. Summative feedback at the end of the procedure will facilitate learning but metric-based formative feedback on performance is a much more powerful aid. This will inform trainees if they are performing the procedure incorrectly or in the wrong order and it should let them know if they are using the devices inappropriately. Trainees should receive this feedback proximate to the performance error. This approach to learning is called deliberate practice.[37]

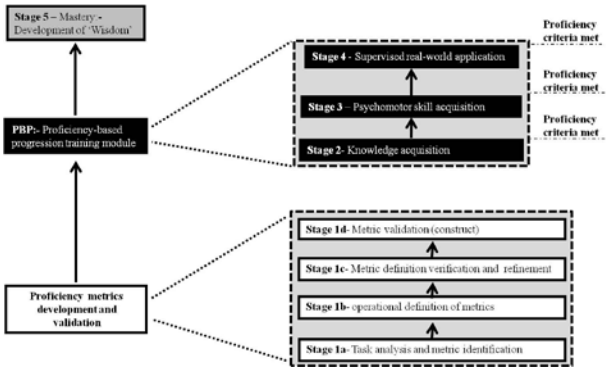

Fig 3. the Proficiency-based progression method

The extended, structured and motivated practice by trainees first described Ericsson, Krampe and Tesch-Römer[37] were important explanations of learning skilled performance but one crucial aspect of their accounts to training was missing, i.e., performance feedback. In addition to engaging in deliberate practice the trainee musicians studied by Ericsson and colleagues also had access to immediate feedback from their tutor. They would have been informed by their tutor (or recognised themselves) when they played a note wrong. Engaging in frequent practice sessions would mean that the trainee had ample opportunity to practice and rehearse their playing with equivalent opportunities to correct and improve performance. Implicit to this process and presumed performance improvement (i.e., learning) is the concept of performance feedback. The same is true for the acquisition of skill in medicine. This approach to learning is more efficient and effective than the traditional approach of repeated practice and is made possible with metric-based simulations. The pre-requisites for this approach to simulation training are the identification and definition of optimal and sub-optimal performance by procedural experts and the capability of the simulation to model the procedure and operator performance interaction in real-time. It is then simply a matter of benchmarking proficiency using the actual performance of proficient doctors. Thus the experienced doctor is the starting point for the development of a simulation and the quality assurance of it by benchmarking on their performance thus circumventing some potentially complicated, convoluted and thorny issues such as what is competence or how is it defined?

THE FUTURE (NOW)

Metric-based simulation ensures that training sessions are more than just simulated clinical 'experiences'. It ensures that there is no ambiguity about the progress of training for the trainee (and the trainer). Simulation-based training in medicine now has a quantitatively validated

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clinical function. This foothold is considerably better than even a decade ago. So much so that the Food and Drug Administration in the USA now requires simulation based training as part of device approval[38, 39] and the Department of Health in the UK have issued guidance which appears to suggest that trainees should not be performing a procedure on a real patient the first time they perform the procedure.[40] Implementation of simulation based training will continue to evolve but for certain, simulation based training will form a fundamental part of acquisition and maintenance of skills in medicine and healthcare. In time it will also (probably) be part of the General Medical Councils reaccreditation process. It is therefore essential that medicine has a thorough understanding of what simulation is and the imperative of metrics. Quantitative characterization that has been validated for a proficiency-based progression training function is not a million miles away from quantitative assessment of performance by experienced doctors, i.e., re-validation.

SUMMARY

Proficiency-based progression training works and it works because of well proven principles and practices of learning.[15] To ensure the optimal effectiveness of a proficiency-based progression training program does not require a radical change in the current curriculum content. However, what it does require is a radical change in how that curriculum is delivered and implemented. Simulation is very powerful training tool for the delivery of deliberate practice coupled to formative and summative metric-based feedback on performance. In the absence of computer generated simulation, formative metrics on training performance need to be delivered by a trainer who is very experienced at performance assessment. A training program that has a clear end point (i.e., level of proficiency) must provide the facilities and opportunities for the learner to meet the level of proficiency. A deliberate practice training regime affords the opportunity for independent pacing of skill acquisition; a coherent curriculum with appropriately sequenced learning material and a variety of learning experiences. Although this approach to medical education and training may be conceptually and intellectually appealing it represents a paradigm shift in how doctors are educated and trained.

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Ulster Med J 2012;**81(3):**114-117

Paper

Obtaining the MRCP diploma – difficult Olympic hurdles or a straightforward triple jump?

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Accepted 9 May 2012

INTRODUCTION

The Royal Colleges of Physicians of the United Kingdom have a common membership examination in general medicine and successful candidates are eligible for the award of the MRCP (UK) Diploma[1]. This important postgraduate qualification is achieved after passing three separate examinations typically known as MRCP Part 1, MRCP Part 2 and MRCP PACES. Attaining the MRCP (UK) Diploma or "full membership" has become a necessary prerequisite for successful completion of UK Core Medical Training (CMT). Attaining the MRCP (UK) Diploma is now essential prior to commencing training in any of the medical specialties at Specialist Trainee year 3 (ST3) level. For many doctors, acquiring this essential qualification proves to be a long, arduous and expensive process. Pass rates for trainees in the component MRCP examinations vary widely between UK postgraduate medical deaneries[2]. This variation in attainment of the MRCP, and other postgraduate medical examinations, reflects many factors including pre-medical school admission qualifications, UK medical school attended, gender, ethnicity, organisational skills of trainees and the different emphasis placed by deaneries on the optimal "timing" of examinations with respect to junior doctors within Foundation Year (FY) and Core Medical Trainee (CMT) programmes[2-7]. This article aims to provide FY and CMT doctors with some practical guidance on the optimal timing of taking MRCP examinations and pragmatic advice to UK and overseas medical graduates and their clinical supervisors on effective preparation for these important postgraduate career milestones.

PURPOSE OF THE MRCP

A popular misconception about the MRCP (UK) Diploma award is that memorising excessive amounts of obscure detail is needed to pass the written exams. This is not the case. The MRCP Part 1 examination tests an understanding of the important basic science principles that underpin day-to-day clinical practice. MRCP Part 2 is a more clinically oriented written examination with questions focused on clinical scenarios. The exam tests whether candidates can consider various clinical factors in deciding on the most appropriate investigation or treatment. The candidate answers "single best answer" multiple choice questions in the both the MRCP Part 1 and Part 2 examinations. The MRCP Practical Assessment of Clinical Examination Skills (PACES) explores the ability of trainees to integrate a number of clinical skills with the aim of demonstrating safe management of patients allied with appropriate communication to allay patient concerns. Passing these three MRCP examination components and appointment to an ST3 post following interview allows the trainee to enter higher specialty training in various medical specialties within the UK.

COST OF THE MRCP

In 2012, the total cost of a UK-based trainee applying to sit each part of the MRCP (UK) Diploma would be £1456[1]. This sum excludes any books, online question banks, exam preparation courses or travel expenses which are required by a candidate. The true cost of taking the MRCP examinations in the UK is arguably closer to £2500, none of which is tax deductible and relatively little of which can be reimbursed. A candidate who needs to resit MRCP examinations will spend even more money and unfortunately some trainees may eventually spend several thousand pounds negotiating PACES. For an overseas-based clinical trainee the cost of sitting each component of the MRCP (UK) Diploma is at least £2330[1]. Clearly, having an efficient plan to get the "full membership" is vital to minimising costs associated with resitting component MRCP examinations.

FOUNDATION YEAR PROGRAMME AND MRCP

UK postgraduate deaneries have provided variable advice to candidates on when they should sit the MRCP examinations. Those deaneries that promoted preparation for MRCP during the Foundation Year Programme and encouraged an early attempt at MRCP Part 1 appeared to have higher pass rates than deaneries which have actively discouraged MRCP exam preparation during the Foundation Year 1 and Year 2 (FY1 and FY2) years. Part of this inter-deanery variation in MRCP examination success may stem from regulations in place from August 2007 to August 2009 when only MRCP Part 1 was required to be eligible for appointment to an ST3 post. These earlier regulations arguably had reduced the sense of urgency trainees had to progress through the component exams of the MRCP (UK) Diploma during the Foundation Year Programme and Core Medical Training years. For instance, for those trainees attempting the MRCP Part 1 examination during 2010-11 the pass rate was 77.4% (ranging from 57.7% to

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TABLE 1:

Pros and Cons of studying for and sitting MRCP examinations early

Pros	**Cons**
More confidence in managing medical patients	Uncertainty regarding medicine or a medical specialty as a long term career pathway
More constructive input into ward rounds and daily ward reviews	Pressure of studying for postgraduate exams so early in career after starting work as a junior doctor
More competitive applications for clinical posts and at interview; demonstrates commitment to specialty, or in studying for a postgraduate exam	Potentially diverts focus from obtaining Foundation Year competencies
Reduces stress at the end of Core Medical Training when applying for ST3 posts in medical specialties.	Expensive to sit examinations if poorly prepared or motivated and therefore more likely to fail first attempt
Broader knowledge base augments the educational value of workplace based assessments.	Exam burnout
Improves quality of referrals made to other specialties	
Sense of achievement and progression in career	
Allows time for resitting examinations if needed or a break	

95.0% in the sixteen UK postgraduate medical deaneries) by the end of year 1 of Core Medical Training (*unpublished data from Royal College of Physicians examinations department and JRCTB, September 2011 Update*).As outlined previously, success in MRCP examinations is associated with certain background factors including the medical school a candidate attended, gender, ethnicity and time management skills of trainees[2-7]. There are several other reasons for disparate MRCP pass rates. Firstly, those who delay attempting the MRCP examinations find, in the worst case, that they have 18 months or less in which to sit and pass all three parts. This generally leads to cramming revision, superficial learning, and often several examination resits with consequent delay in entering ST3 level medical specialty training.

Secondly, the FY1 period, immediately after graduation from medical school, may be viewed as a relatively quiet year in terms of academic endeavours whilst the graduate makes the transition from medical student to junior doctor. Some deaneries have emphasised the importance of the Foundation Years for obtaining curriculum competencies and sampling different clinical specialties rather than studying for postgraduate examinations. Nevertheless, studying for the basic science component during FY1 and passing the MRCP Part 1 examination in early FY2 actually enables the trainee to concentrate on learning the clinical material tested in the MRCP Part 2 and PACES exams from an earlier point in their career. This clinical learning is more readily integrated and reinforced when trainees are not dedicating their mental energy to revising basic science principles. As a greater proportion of their FY2 and core medical training experience is used to assist preparation for MRCP Part 2 and PACES exams then the likelihood of passing is increased.

Finally, due to specific local factors in each deanery some trainees may have different levels of commitment to their ultimate specialist career pathway and this may impact on when MRCP exams are attempted. A deanery encouraging attendance at high quality MRCP examination revision courses or the local organisation of focused clinical teaching for MRCP PACES are also likely to improve trainees' preparation for these examinations.

TIMING MRCP

The MRCP is a medical "triple jump" that needs to be carefully planned. A timeline of when these exams might be taken in relation to training grade is outlined in Figure 1. Presently, the full MRCP (UK) Diploma is required before an individual can take up an ST3 post in a medical specialty. The concern is that a candidate without PACES may be offered an ST3 post to begin in August pending a pass in PACES but may fail the June/July diet of exams and thus be ineligible to take up their ST3 post. Ideally junior doctors should attain the full MRCP (UK) Diploma award before applying for ST3 positions.

A trainee appointed to a core medical training post from August 2009 onwards who does not pass the full MRCP (UK) Diploma award by the end of 24 months has not completed core medical training. There has been some variation in interpretation of this regulation at Annual Review of Competence Progression (ARCP) meetings but this may result in a trainee being given an ARCP outcome 3 (unsatisfactory outcome: inadequate progress by the trainee – additional training time required) and core medical training period extended by 6 months in the first instance. This may also impact upon the availability of entry points for core medical training for new trainees.

In order to maximise the chance of passing all the component MRCP examinations comfortably within the given timeframe, even allowing for resit exams, it seems prudent to consider taking the MRCP Part 1 exam in October or January of the FY2 year. The MRCP Part 2 examination could then be

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attempted in April or June of FY2. If both parts are passed then the whole Core Medical Trainee Year 1 (CT1) year can be used to prepare for MRCP PACES exam which could be taken in June of CT1 or September of CT2 with opportunity for a resit prior to the ST3 post applications. Having a full year or more to prepare for MRCP PACES allows active clinical skill development whilst allowing time to undertake audits, projects and teaching in order to improve the quality and competitiveness of an ST3 application.

WHAT CANDIDATES SAY IS NEEDED TO PASS MRCP

Passing MRCP Part 1 is highly dependent on both the number and quality of multiple choice questions attempted in revision texts or online question banks. Clinical experience *per se* was rated as relatively unimportant in whether one passed the MRCP Part 1 exam. In contrast, clinical experience plays a much more important role in dictating the outcomes of both MRCP Part 2 and MRCP PACES. The successful PACES candidate is likely to have spent a good deal of time in both outpatient and acute care settings and will have managed a variety of medical problems before a successful PACES attempt. Time is needed to not only integrate a broad base of clinical material but also to refine the communication and counselling skills which are usually critical determinants of success in PACES. It seems likely that there is a direct correlation between the volume and quality of clinical encounters a candidate has had and their subsequent success in the MRCP PACES examination

TAKING MRCP EXAMINATIONS EARLY VERSUS LATER IN TRAINING

The previous discussion outlines many of the benefits of taking MRCP examinations early in clinical training. However, there are some potential disadvantages of tackling these postgraduate examinations prematurely. Table 1 lists some of the pros and cons of sitting MRCP exams early in training. There are two major hurdles that doctors face in deciding to take MRCP early. The first is their own personal uncertainty regarding their future career path and the second is the perceived insurmountable difficulty of taking the MRCP examinations in the earlier stages of clinical training. Arguably career pathway indecision should not preclude consideration of studying for and attempting MRCP Part 1. Clinical therapeutics and the basic sciences (such as statistics, genetics and cell biology) together account for around 45 out of 200 multiple choice questions (22.5%). These are topics that are covered in the postgraduate exams of many other specialties and are themselves highly relevant to clinical work during the Foundation Years. Additionally, knowledge of the pathophysiology underlying common medical conditions that is tested in the MRCP Part 1 examination is highly desirable for all trainees regardless of later medical career specialism. Even if Core Medical Training is not pursued after FY2, the fact that a postgraduate exam has been attempted and passed demonstrates personal commitment, discipline and capability

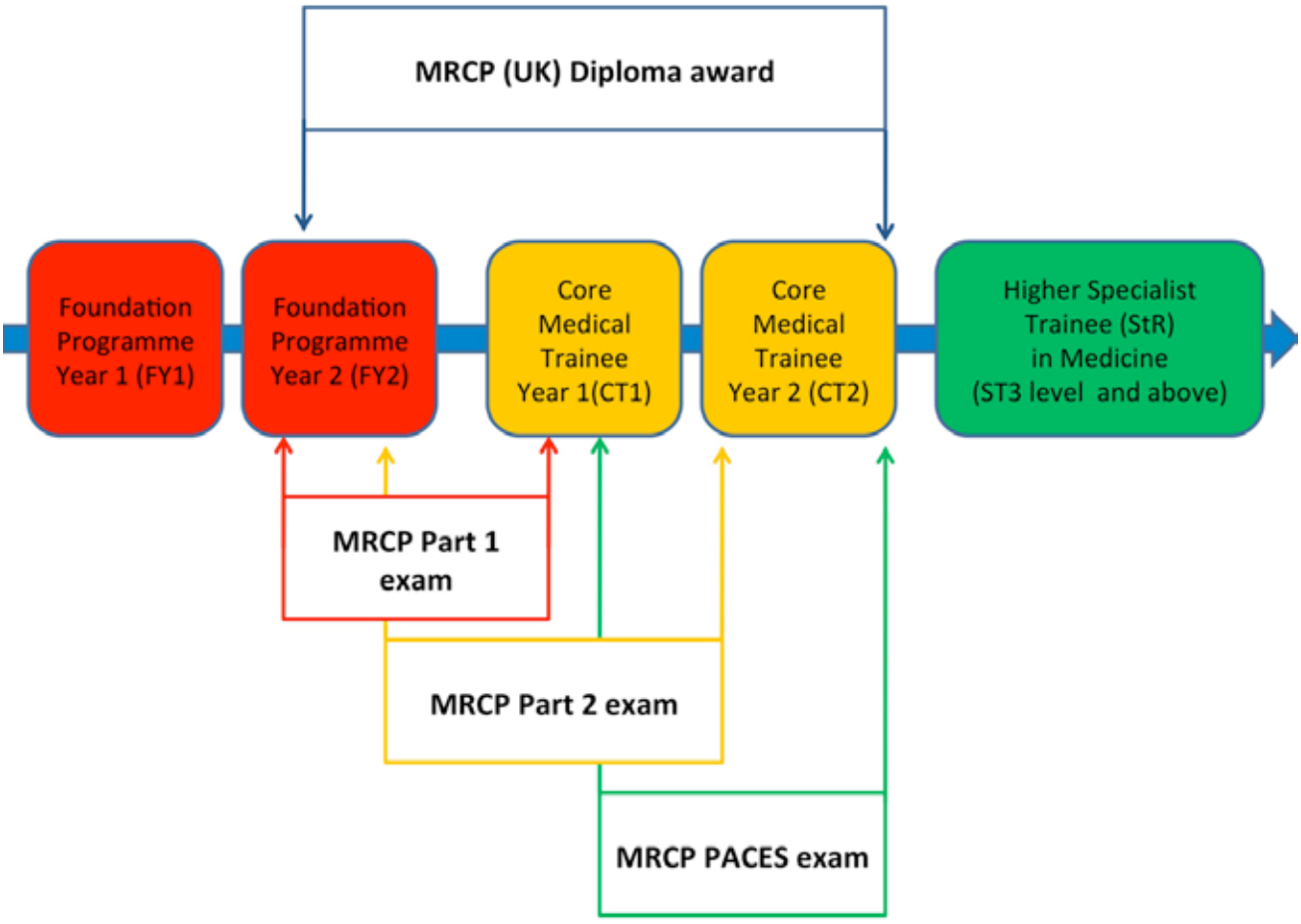

Fig 1. Linking the junior doctor training year with an optimal timetable for sitting MRCP examinations

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that will be often be rewarded at short listing and interviews, especially in those specialties in which exams can only be taken after appointment to a training post.

The perceived difficulty of the MRCP Part 1 examination is arguably a "cultural" phenomenon. The content of the MRCP Part 1 may prove challenging because the basic science concepts tested were usually covered in medical school curricula during the earlier years of the medical course and inadequate time is dedicated by candidates to revising these areas. The changes in working patterns occasioned by the European Working Time Directive mean that the FY1 year is actually a very good time in which to prepare for the basic science components of not only the MRCP but also other postgraduate clinical exams, so long as sufficient time is given to refresh and integrate the material studied. For those that are clear on their intention to proceed to Core Medical Training they can 'hit the ground running' with MRCP Part 1 passed early in their FY2 year and continue preparation for MRCP Part 2 and PACES examinations during FY2, CT1 and CT2 years.

Concerns that studying for MRCP will compromise attainment of Foundation Year (FY) Programme competencies are unfounded. Instead of seeing MRCP preparation and FY competencies as mutually exclusive they should be viewed as opportunities to develop a richer FY programme experience. Having a broader knowledge base improves the quality and validity of workplace based assessments.

A STRATEGY FOR MRCP SUCCESS

Each individual brings their own learning style to studying for MRCP examinations but we suggest a number of practical "tips for success" as follows:

- Studying vast blocks of exam-related material at a time is wearying. Focus on small specific areas, especially those in which you have no or limited experience. Test your own knowledge with multiple questions and concentrate on those subjects which you have found to be most challenging.
- Ask Core Medical Trainee and Specialist Trainee colleagues which books and online question banks they used. Purchase a small number of good exam revision resources and set aside time every week to study them. This is especially helpful for MRCP Part 1 exam preparation.
- Many Core Medical Trainees and Specialist Trainees will be more than happy to coach MRCP PACES candidates (especially if there's a nice meal at the end of it for them!)
- Make sure, having encountered a new disease or concept; you can actually recall some salient facts about it the next day, and then the next week!
- Make your studying part of your day-to-day job. Does this patient have an unusual disease, or taking an unfamiliar drug, or is he/she experiencing a complication of their condition? Not only will some targeted reading later that day or night (again, digest small chunks, not textbook chapters) consolidate what you've seen but will make you a better, safer and more interested doctor.
- Be active in your learning. Consider what complications could develop; are there interactions with the drug you have just prescribed? How will you answer the patient if you are asked about their prognosis? Search out and use scoring systems, calculate the CURB65 and ABCD2 scores, assess the anion gap (smartphones leave most doctors without excuse for doing this) – practising what you have learnt is key to creating a longer term memory for the clinical context.
- Studying for the MRCP examinations does not occur in a vacuum. You will encounter many patients with rare diseases. You will come across patients whose laboratory results or physical examination suggest a serious potentially treatable disease – you may be the first and perhaps only doctor that person has contact with. MRCP PACES examiners are not looking for virtuosic displays of diagnostic brilliance but safe, competent doctors who are ready to proceed to higher specialist training. What you study for MRCP will keep patients safe; on some occasions you will have learnt something that may save a life.

CONCLUSIONS

A junior doctor interested in a long term career in a medical specialty should consider sitting the written MRCP Part 1 (and if successful) Part 2 examinations during the Foundation Years Programme. Active studying from early on in the Foundation Years Programme allows integration of clinical material into daily patient care thus improving both safety and quality. A combination of careful planning and thorough preparation will maximise the chances of success in these expensive postgraduate examinations. Those applying for Core Medical Training should aim to have passed the MRCP Part 1 examination by that time and possess full MRCP (UK) Diploma by the time of medical specialty ST3 application. The MRCP examinations should be seen as a feasible medical "triple jump" rather than impossible Olympic hurdles.

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Ulster Med J 2012;**81(3):**118-122

Paper

Clinical phenotypes of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy seen in the Northern Ireland paediatric population over the last 30 years.

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Accepted 09 May 2012

ABSTRACT

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyendocrinopathy syndrome type 1, is a rare autosomal recessive disorder with a variable and evolving phenotypic course. It is caused by mutations in the autoimmune regulator (AIRE) gene. APECED syndrome is diagnosed clinically by the presence of 2 from 3 major criteria; chronic mucocutaneous candidasis, primary hypoparathyroidism and primary adrenocortical insufficiency. Many of the patients develop all three before the age of 20 years. There is also a wide spectrum of other associated conditions including endocrine and non endocrine manifestations. This paper reviews the clinical phenotypes seen in the paediatric population of Northern Ireland during the last 30 years detailed from a retrospective review of clinical notes. Eight patients were identified with APECED and all patients were found to be homozygous for the c.964del13 mutation.

A wide clinical variation is apparent within APECED syndrome. Paediatricians should be vigilant of the diagnosis when they encounter any of the features described and consider the future development of associated diseases. In confirmed APECED syndrome, clinical and laboratory investigation is essential to initiate early treatment in the patient and other affected members of the family.

Key words: APECED, c.964del13, candidiasis, hypoparathyroidism, adrenal insufficiency.

INTRODUCTION

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or autoimmune polyglandular syndrome type 1 is a rare and debilitating disorder of childhood. It is inherited in an autosomal recessive manner with mutations in the autoimmune regulator (AIRE) gene. Clinical diagnosis requires the presence of two from three major criteria; chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism and autoimmune adrenal failure[1-6]. If a sibling has the syndrome only one of the above manifestations is required[1].

Mucocutaneous candidiasis is the most common first presenting feature, typically developing in infancy or early childhood. Hypoparathyroidism usually develops around the age of 7 years with adrenocortical deficiency developing by the age of 13 years [4,7,8]. All three cardinal features usually occur by the age of 20 years with additional manifestations developing until at least the fifth decade[1]. The diagnosis of APECED can be challenging as it can present with one major and several minor manifestations or with several minor manifestations and characteristic ectodermal dystrophy[9].

This paper highlights the age of presentation of each of the major criteria and the range of minor criteria seen in the paediatric population of Northern Ireland in the last 30 years.

PRESENTATION AND CLINICAL COURSE

Patient 1 (male) was found incidentally at the age of 4.8 years to have hypocalcaemia secondary to hypoparathyroidism (serum calcium 1.46mmol/L, parathormone (PTH) <5pg/ml) and was commenced on alfacalcidol and calcium supplements.

He later presented at the age of 5.4 years with a hypoglycaemic seizure following an anaesthetic. Serum cortisol was 1082nmol/L. He was advised to avoid prolonged fasts and to take hydrocortisone if unwell or if requiring a general anaesthetic. He has had several further episodes of hypoglycaemia for which no cause has been identified despite extensive investigation. At 5.8 years he presented with photophobia due to punctate epitheliopathy possibly secondary to vitamin A deficiency. At this time genetic testing revealed the c.964del13 mutation. Aged 6.2 years he was found to have candidiasis of his oral mucosa, finger nails and toenails and at 10.2 years he developed small patches of alopecia. Isolated mineralocorticoid deficiency (serum sodium 127mmol/L, plasma renin activity elevated at 24.2ng/ml/

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hr and aldosterone 183pmol/L) presented at 11.4 years and he commenced fludrocortisone treatment. Cortisol response to Synacthen has to date been normal. Adrenal antibodies changed to positive when rechecked aged 11.2 years, having previously been negative 21 months earlier.

Patient 2 (female, sister of patient 3) presented at 1.7 years with stridor and a seizure secondary to hypocalcaemia (serum calcium 1.1mmol/L, PTH <3pg/ml). Initially she was commenced on alfacalcidol. At endocrine review aged 2.5 years oral candidiasis was found and adrenal antibodies were positive. She was found to be homozygous for the c.964del13 mutation.

At 3 years she was noted to have 2 small areas of hypopigmentation. At 5.2 years she presented acutely with vomiting and dehydration and gave a clear history of craving salty foods. She was diagnosed with mineralocorticoid deficiency (serum sodium 125mmol/L, serum potassium 5.8mmol/L, although random cortisols (1287nmol/L and 876nmol/L) were normal). Treatment with fludrocortisone and hydrocortisone was started.

At 6.3 years she was diagnosed by the ophthalmologist with a 'dry eye condition'.

Patient 3 (male, brother of patient 2) was screened for APECED at the age of 1.6 years. He was found to carry a homozygous mutation in the AIRE gene. He had attended previously with chronic idiopathic urticaria and recurrent candidiasis. At 1.9 years he was admitted to the paediatric intensive care unit with a lower respiratory tract infection secondary to influenza A. Following several episodes of septicaemia he was diagnosed with IgG-2 subclass deficiency and commenced subcutaneous immunoglobulin infusion 2 weekly. He is now 4.5 years old and has had no further problems attributable to APECED.

Patient 4 (male) presented at 3 years with a hypocalcaemic seizure (serum calcium 1.24mmol/L, PTH <3pg/ml). He had a history of standing on his tip toes appearing to have muscle cramps and intermittent spasms in his arms consistent with tetany. He was commenced on calcium supplements and alfacalcidol. Around 6 years he was found to have increased pigmentation of a scar on his abdomen and right arm. At 6.4 years he was diagnosed with Addison's disease by his general paediatrician (serum sodium 133mmol/L, potassium 3.6mmol/L, aldosterone 209pmol/L, random cortisol 29nmol/L) and commenced replacement treatment with hydrocortisone and fludrocortisone. At 10.3 years adrenal antibodies were positive and he was found to be homozygous for the c.964del13 mutation. At 11.6 years he was noted to have buccal candidiasis and at 13 years vitiligo. He experienced wide fluctuations in serum calcium levels from symptomatic hypocalcaemia to hypercalcaemia requiring frequent inpatient treatment. The possibility of non compliance with treatment was raised so he was changed from alfacalcidol, half-life 30-35 hours, to calcitriol, half-life 5-6 hours, which allowed blood monitoring of the medication and more rapid correction of high or low calcium concentration. Renal ultrasound showed nephrocalcinosis.

Patient 5 (female sibling of patient 8) experienced measles encephalitis at 1.9 years but recovered well. She then presented aged 2.9 years with cough, tetany of hands and feet and stridor. She was found to be hypocalcaemic (serum calcium 1.65mmol/L). She was noted to have candida infection of her thumb nail and mouth requiring frequent antifungal treatment.

Exocrine pancreatic insufficiency was diagnosed and treated from 5.4 years after a 3 month history of bulky pale loose motions and high faecal fat content. Sweat test and jejunal biopsy were normal. Further testing aged 12.5 years confirmed deficiency of trypsin and only very small amounts of amylase and lipase in duodenal juices. When 7.3 years she showed decreased height velocity, weight loss, skin pigmentation, nausea, vomiting and abdominal pain. Maximum cortisol (260nmol/L) response to Synacthen was suboptimal, baseline ACTH >800pg/mL, serum sodium 122mmol/L and potassium 4.1mmol/L. She was commenced on hydrocortisone and fludrocortisone replacement. An oral glucose tolerance test was normal. Vitiligo and keratitis of the cornea were identified at 11.1 years. At 11.7 years she was diagnosed with type 1 diabetes. Poor height velocity noted at 13.4 years prompted a pituitary stimulation test which found high levels of growth hormone. Repeat jejunal biopsy was normal. When she was 15.6 years she was diagnosed with primary ovarian failure (early breast development around 14.3 years had not developed further and a small amount of pubic hair had been noted at 15 years with no progression). Investigations showed high gonadotrophins (FSH 61u/L, LH 28.3u/L) and low 17β-estradiol (<50pmol/L). Ultrasound showed a slight increase in uterine size and ovaries appeared normal. Adrenal and ovarian antibodies were present. She was commenced on ethinylestradiol which was subsequently changed to Cyclo-Progynova.

At 16 years old she experienced light headedness, blurred vision and hypertension which was felt to be attributable to acute nephritis and nephrocalcinosis . A renal biopsy revealed patchy scarring. She was commenced on enalapril and bendrofluazide. Around this time she also had further seizures not attributable to biochemical disturbances. Electroencephalogram was abnormal and she was commenced on carbamazepine.

Patient 6 (male) was diagnosed with asthma when 4.8 years old. He then presented aged 5.5 years with a hypocalcaemic seizure (serum calcium 1.44mmol/l, PTH 6pg/mL). He also gave a history of having a 'funny' feeling in his arms and legs intermittently for a few weeks prior to admission. He was commenced on alfacalcidol and calcium supplements. Genetic testing showed he was homozygous for the c.964del13 mutation. A decreased height velocity was noted aged 7.6 years (height had fallen from the 50th to the 25th centile over 2.5 years). Glucagon and insulin stimulation tests revealed a low growth hormone response (maximum growth hormone 4.3ng/ml) and low IGF-1 5.1mmol/L. Growth hormone treatment commenced at 8 years. MRI showed no evidence of any abnormality in the pituitary gland or adjacent structures. He was diagnosed with isolated mineralocorticoid deficiency at 8 years (serum sodium 132mmol/L, renin 22.63ng/ml/h, aldosterone 152pmol/L, positive adrenal antibodies) and commenced on fludrocortisone replacement. Synacthen testing revealed a normal cortisol response (maximum cortisol response 517 nmol/L, baseline ACTH 53ng/L).

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Patient 7 (male) was admitted to hospital aged 0.9 years with a lower respiratory tract infection complicated by a small pleural effusion and erythema multiforme requiring 12 days intravenous antibiotics. At review aged 1.1 years he was reported to have poor energy, decreased appetite and abdominal distension. Examination identified 3-4cm of hepatomegaly and 2-3cm splenomegaly. Investigations revealed thrombocytopenia and elevated liver enzymes (ALT >150OU/L, AST 1508U/L). Bone marrow examination was normal. Autoantibody screen revealed a smooth muscle antibody titre 1:80, antimitochondrial antibodies positive, titre 1:40 and liver/kidney microsomal antibody titre 1:320. Liver biopsy was performed and the diagnosis of autoimmune hepatitis type 2 made. He was commenced initially on prednisolone aged 2 years and subsequently on azathioprine 5 months later. He was found to have decreased bone density and prednisolone was stopped but after 5 months restarted due to an acute rise in liver enzymes.

He was admitted to the paediatric intensive care unit aged 4.5 years with severe dehydration and salt loss (serum sodium 105mmol/l, aldosterone <70pmol/L, renin 14.64ng/ml/hr, adrenal antibodies positive). Fludrocortisone was commenced. At 5.3 years he was noted to have marked oral candidiasis.

Two years later he experienced mid back pain and thoracolumbar spine xray showed generalized slight reduction in bone density, partial collapse of the body of T9 and minimal reduction in height anteriorly of the body of T8. Further investigations revealed serum calcium 2.53mmol/L, PTH <5pg/ml and he was found to be homozygous for the c.964del13 mutation. At 8.8 years he was diagnosed with severe autoimmune keratitis with significant involvement of both cornea requiring a corneal graft.

MRI scan performed at 9.2 years showed further vertebral changes on a background of osteoporosis most likely as a result of his ongoing need for high dose glucocorticoids. He was commenced on bisphosphonates.

Patient 8 (female sibling of patient 5) had experienced transient hypocalcaemia as a neonate which resolved until 2.4 years when she presented with tetany (serum calcium 1.5mmol/L, phosphate 3.22mmol/L). She commenced alfacalcidol. Prophylactic ketoconazole was required from 3.5 years as candida of her nails and mucous membranes became a recurring problem.

At 6.8 years she developed glycosuria. An oral glucose tolerance test was normal but following intermittently raised random plasma glucose levels she commenced insulin aged 7.3 years. At this time vitiligo and grey streaking of her hair and eyelashes were observed.

Aged 8 years she was investigated for a history of steatorrhoea which confirmed exocrine pancreatic insufficiency. Creon was commenced. At 9 years slightly raised liver enzymes were detected which persisted. There was no autoantibody consistent with autoimmune hepatitis. Prophylactic ketoconazole was stopped. Aged 10 years she developed a macrocytic anaemia, positive intrinsic factor antibody, low serum B12 and megaloblastic bone marrow. She responded well to Neo-Cytamen injections 3 monthly. Autoantibodies to ovarian tissue were detected from an early age. She was commenced on low dose ethinylestradiol aged 9.9 years with the hope that oestrogen may have a beneficial effect on the ovaries. This treatment continued for 5.3 years by which stage pubertal signs were progressing and menarche reached at 14.6 years with subsequent regular menstruation. Aged 13.8 years she required a mastoidectomy for cholesteatoma. Recurrent ear infections continued to be a problem. Positive adrenal antibodies were recorded from early childhood. At age 14 years routinely performed investigations showed plasma ACTH 274ng/L and cortisol 165nmol/L but cortisol response to Synacthen stimulation remained normal, as did electrolytes. Due to symptoms of persistent lethargy hydrocortisone replacement was commenced. Initially fludrocortisone was given but withdrawn when she developed fluid retention and hypokalaemia. The slightly abnormal liver function tests returned to normal on physiological hydrocortisone replacement.

Aged 15.9 years she was admitted with frank haematuria and hypertension. Investigations revealed mild nephrocalcinosis and high urinary calcium to creatinine ratio. Renal biopsy demonstrated chronic tubulointerstitial disease. Cystoscopy was normal. Although an autoimmune disorder could not be excluded, the more likely cause was felt to be hypercalcuria secondary to alfacalcidol treatment. Blood pressure gradually settled and antihypertensive treatment (enalapril) discontinued.

DISCUSSION

Major Criteria (Figure 1)

Mucocutaneous candidiasis was present in seven of eight patients. The youngest age of presentation was 1.7 years in a patient tested for the APECED mutation as his other sibling was affected. Age range for the diagnosis of candidiasis varied from 1.7 to 11.6 year (mean 4.8 years old) in contrast to previous reports of it typically being seen within the first year of life.

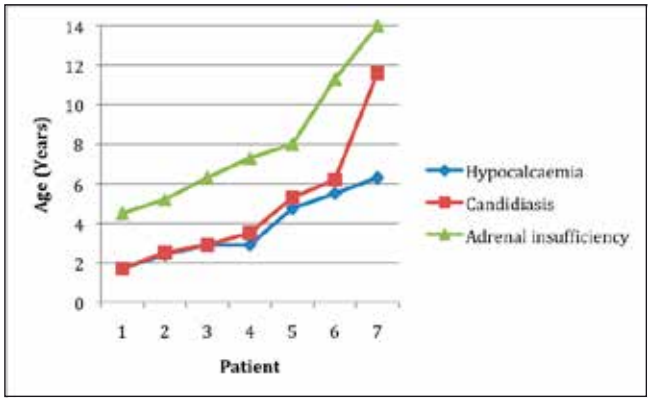

Fig 1. Number of patients affected and age of first presentation of each major criterion

Hypoparathyroidism was detected in 7 patients. In 5 patients this was the initial major feature diagnosed and in one it was diagnosed at the same time as candidiasis. Age range for diagnosis was 1.7- 6.3 years (mean 3.8 years). Hypoparathyroidism is reported in the literature to have a peak incidence between 2 and 11 years old and this was

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TABLE 1.

Age (years) at presentation of major and minor criteria for each patient

Patient (number)	Hypocalcaemia	Candidiasis	Mineralocorticoid deficiency	Glucocorticoid deficiency	Pancreatic insufficiency	Visual problems	Vitiligo	Type 1 diabetes	GH Deficiency	Primary ovarian failure	Nephritis/renal disease	Hepatitis	Dental	Pernicious anaemia	Alopecia	Urticaria
1	4.8	6.2	11.3			5.8							8.2		10.2	
2	1.7	2.5	5.2			6.3	3.1									
3		1.7														1
4	2.9	11.6	6.4	6.4			13				14.2					
5	2.9	2.9	7.3	7.3	5.4	11.1	11.1	11.8		15.6	16.2		6			
6	5.5		8						8							
7	6.3	5.3	4.5	4.5		8.8						1.1				
8	2.4	3.5		14	8		7.3	7.3			15.9		5.7	10		

largely seen in this review with only one presenting before 2 years old.

Seven of the group studied had positive adrenal antibodies and developed glucocorticoid and/or mineralocorticoid insufficiency at the time of review between 4.5 to 14 years (mean 7.5 years). In 3 patients mineralocorticoid deficiency preceded glucocorticoid deficiency[9]. Patients can be very sensitive to small doses of fludrocortisone causing hypokalaemia[6]. Autoimmune adrenal failure is usually the last of the major features to present and has a peak incidence around 13 years[1-7], later than found in our patients.

Minor Manifestations (Table and Figure 2): -

Visual problems were seen in half of the patients (keratitis in 2, one 'dry eye condition' and one possible vitamin A deficiency). Renal disease with nephrocalcinosis was detected in 3 patients most likely secondary to treatment with alfacalcidol. Two showed additional features of nephritis and renal tubular disease. Four patients had vitiligo and one had alopecia. Three patients had dentinogenesis imperfecta and one had the rarely associated chronic idiopathic urticaria.

Within the group 2 patients developed exocrine pancreatic insufficiency, 2 with type 1 diabetes; primary ovarian failure, growth hormone deficiency, autoimmune hepatitis and pernicious anaemia were each seen in a single patient.

The number of manifestations affecting each patient varied from 2 to 10 (3 patients demonstrated 5, one patient 6 and 2 patients with 10 components). The age at presentation and spectrum of disease is illustrated in the table and figure 2.

Of note patient 3 was diagnosed with IgG2- deficiency; to the authors' knowledge this has not been described before in APECED, however Bereket et al[10] confirmed IgA deficiency in 1995.

Brown and Holland[11] describe 'one of the puzzling components of APECED is severe chronic mucocutaneous candidiasis (CMC).' They confirmed the authors' findings that APECED patients are not susceptible to other overt infections.

Brown and Holland report the work of Puel et al[12] and Kisand et al[13] who have described the functions of autoantibodies to IL-17 and IL-22 in CMC in APECED. This may herald new treatment strategies for the future in APECED.

APECED runs a variable and unpredictable course. The importance of early recognition of the differing components is vital. In patients presenting with any of the major criteria the diagnosis of APECED should be considered and other features actively sought. Perheentupa[6] found the classic criteria to be fulfilled by 5 years of age in only 22% of cases, by 10 years in 67%, by 20 years in 89% and by 30 years in 93.5%. Clinicians need to be aware of the diversity and presentation of the various manifestations of APECED. A fall in height velocity in one patient identified isolated growth hormone deficiency, a relatively rare feature of the syndrome. In addition, failure of pubertal progression may indicate primary gonadal failure as seen in one patient.

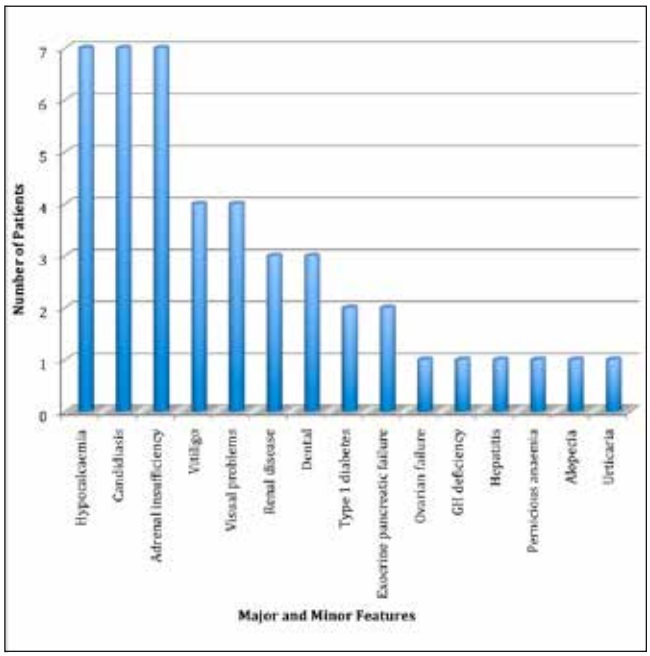

Fig 2. Number of patients affected by each manifestation of APECED

Early and correct diagnosis ultimately allows for intervention and management to prevent potentially life threatening events. Investigations are tailored to treatment and the development of new signs and symptoms with annual laboratory testing for evolving endocrine deficiencies. Families should be made aware of the potential later manifestations of the syndrome.

Any siblings of known affected individuals require clinical assessment. If the genetic mutation is not known or not

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requested, family members should be followed up clinically. APECED is a rare disease but important to recognize and treat early to avoid significant morbidity and mortality. As well as the physical impact of the diagnosis, the psychological and emotional burden placed on families and patients should not be underestimated. Long-term follow-up is essential which includes an effective transition from paediatric to adult care.

ACKNOWLEDGEMENT

The authors thank the following consultant paediatricians for referring patients: Des Brown, Joanne Hughes, John Glasgow, Paul Jackson, Joanne Nelson and Charles Shepherd.

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Ulster Med J 2012;**81(3):**123-126

Paper

Hip fracture in Northern Ireland, 1985-2010. Are age-specific fracture rates still rising?

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Accepted 02 May 2012

ABSTRACT:

BACKGROUND: The aims of this study were to review and update previous projections of the number of proximal femoral fractures in the Northern Ireland population and to ascertain if the trend of increasing age-specific fracture incidence was continuing.

METHODS: Data from 1985 to 1997 was obtained from hospital theatre records to ascertain the number of surgical procedures for proximal femoral fracture. Data for the years 2005 and 2010 was obtained from Northern Ireland's Fracture Outcomes Research Database (FORD) and locally held records in one region not then using FORD. Demographic details were obtained from data published by the Northern Ireland Statistics and Research Agency. Age-specific fracture rates were calculated for males and females in 5 year age brackets and for populations aged 50+ and 65+. Updated projections for the number of proximal femoral fractures by 2020 were made assuming the continuation of the same age-specific fracture rates observed in 2010.

RESULTS: From 1997 to 2010 the age-specific fracture incidence has fallen or plateaued across most observed age and sex sub-groups. Over the period 2010 to 2020, male and female fracture numbers are projected to increase by 23% and 21% respectively which equates to approximately 400 extra proximal femoral fractures.

CONCLUSION: Over the next decade there will be an increasing burden on Northern Irish healthcare resources attributed to a rise in the number of proximal femoral fractures. The age-specific fracture rates in this population are no longer rising and hence the expected increase in healthcare costs is primarily a consequence of the anticipated changing demographic trends.

INTRODUCTION

Hip fracture is a common injury with high morbidity and mortality. Fracture risk is multifactorial and reflects the patients' falls risk, frailty and underlying bone fragility. This frailty is reflected in poor outcomes with approximately 10% of sufferers dead within one month and one third dead within a year.[1] The clinical resources required for acute care are considerable with costs estimated at over £12000 for each individual inpatient stay.[2] With additional need for rehabilitation and longer term community support this rises to an estimate of over £25000 for the first year for the significant percentage of people requiring longer term residential care.[3]

Approximately 75000 proximal femoral fractures occur annually in the UK and with predicted demographic changes in the number of elderly people this is projected to increase to 91,500 by 2015 and 101,000 in 2020.[1] Previous studies within the Northern Ireland population demonstrated the number of proximal femoral fractures was increasing faster than that anticipated by demographic change alone.[4] The purpose of this study is to ascertain if age-specific fracture rates (the rate of fracture for specific age groups) have continued to rise within Northern Ireland or if they have levelled off or fallen as has been witnessed in other European[5-9] and North American populations.[9-12] Updated projections of proximal femoral fracture incidence are important in health care planning and provision of resources in Northern Ireland.

METHODS

Data was extracted from the Fracture Outcomes Research database (FORD) for the years, 2005 and 2010. For the year 2010, data was also collated from a separate database in Craigavon Area Hospital which opened a trauma and orthopaedic service in 2008 but was not then inputting data on FORD. Analysis of these data sources ensured capture of all proximal femoral fractures presenting for care throughout Northern Ireland. The incidence of proximal femoral fracture was recorded by sex and age in five year age bands for individuals aged 50-90+ years. A previous study collated similar information for the years 1985, 1991, 1994 and 1997 by surveying all theatre records in Northern Ireland hospitals undertaking operative management of proximal femoral fracture.[4]

The population of Northern Ireland at the different sampling times and future population projections were obtained from data published by the Northern Ireland Statistics and Research Agency.[13,14] This allowed the age and sex-specific hip fracture

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Table 1:

Annual incidence rates for fractures of the proximal femur by age group over the period 1985-2010 and total fracture numbers

Age group (years)	Males (rate/100,000)						Females (rate/100,000)					
	1985	1991	1994	1997	2005	2010	1985	1991	1994	1997	2005	2010
50-54	26	29	17	28	18	20	55	43	30	39	22	40
55-59	23	46	28	49	47	31	97	88	71	47	71	39
60-64	37	53	47	56	71	82	101	97	134	80	118	121
65-69	99	88	59	133	94	118	168	185	170	196	139	203
70-74	190	173	151	202	167	177	382	387	393	414	370	435
75-79	243	242	386	412	401	324	741	833	833	912	785	775
80-84	662	610	803	643	626	699	1247	1419	1666	1527	1539	1477
85-89	1207	1207	1386	1298	1344	985	2175	2278	2541	2607	2567	2363
90+	1930	1576	1878	2101	1630	2083	2623	3292	3381	4714	3209	3141
50+	128	137	147	169	168	170	374	432	479	500	474	476
65+	262	257	303	339	341	340	663	759	853	926	893	903
Total fracture No.	230	257	292	348	398	445	870	1037	1182	1275	1323	1438

rates in 5 year age bands to be calculated from age 50 to 90+ years.

RESULTS

The annual age specific rates of proximal femoral fracture for males and females are recorded for the years 1985, 1991, 1994, 1997, 2005 and 2010 (Table 1). Published data on this cohort based on figures up to 1997 demonstrated a 1.6% (95% CI 1.0-2.2) increase in incidence per annum with the rate increasing with age. The trend was noted in both males and females.[4]

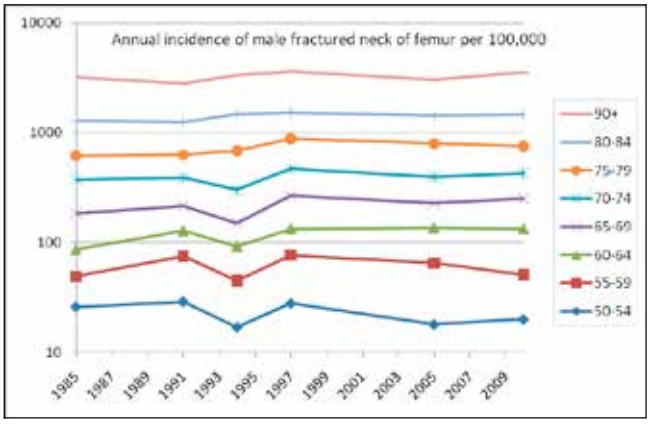

Fig 1.

Data obtained for the years 2005 and 2010 shows a continued increase in total fracture numbers which is in line with expectations from an ageing population. However, in most age groups a small reduction in the age-specific incidence of hip fracture is seen between 1997 and 2010. This trend can be observed in figures 1 and 2. Similarly, fracture incidence has been calculated and tabulated in table 1 for the age 50+ and 65+ cohorts. In males aged 50+ fracture incidence/100000 population has remained static with a rate of 169 in 1997 and 170 in 2010. Over the same period the female age 50+

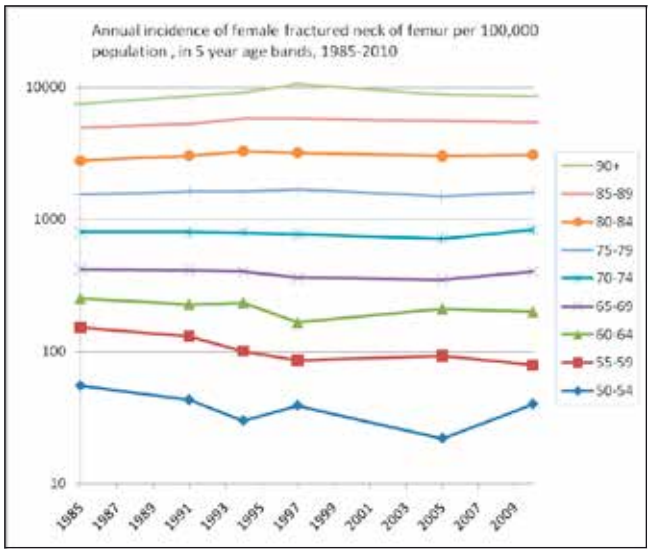

Fig 2.

fracture incidence rate/100000 has fallen from 500 to 476. In the age 65+ cohort the male fracture incidence/100000 has not changed being 339 in 1997 and 340 in 2010. In females the rate has fallen from 926 to 903 fractures/100000 population over the same time period.

From data obtained for 1985 to 1997, projections were made using three different assumptions. Firstly, that age standardised rates present in 1997 remained static. Secondly, that the secular increases in each age and sex sub-group would continue and thirdly, based on exponential growth (i.e. linear growth on a log scale or equivalently, a constant percentage increase per annum). These projections, previously published in 2000[4] have been plotted in figures 3 and 4 alongside the observed data from 2005 and 2010 and demonstrate that growth in fracture numbers has been slower than originally projected as a consequence of the levelling off in age-specific fracture rates.

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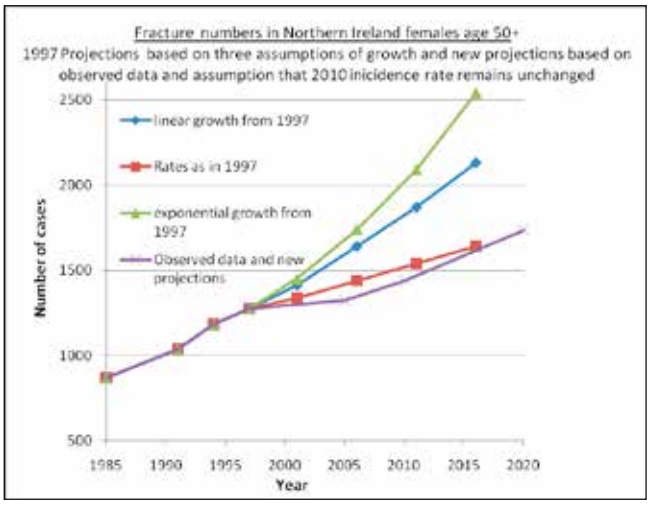

Fig 3.

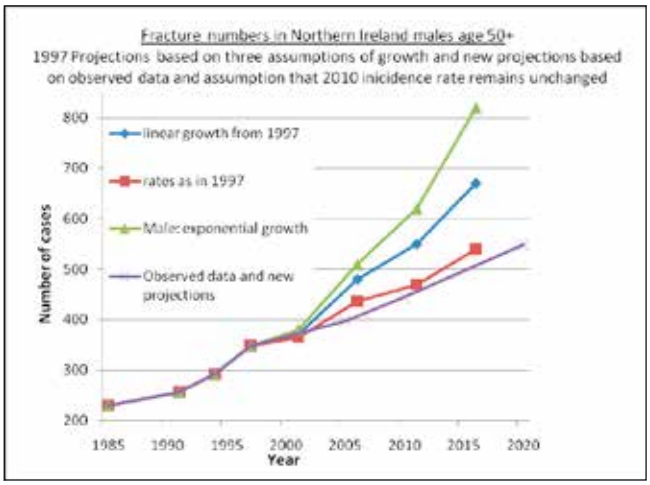

Fig 4.

New proximal femoral fracture projections have now been calculated based on the assumption that the 2010 age-specific incidences will remain unchanged in males and females. These suggest an increase in the number of male fractures from 445 to 548 (23% increase) and female fractures from 1438 to 1736 (21% increase) from the year 2010 to 2020.

DISCUSSION

This updated analysis of proximal femoral fracture incidence in Northern Ireland demonstrates that previous projections of total fracture numbers and age-specific rates have not been realised. Indeed age-specific fracture rates have levelled off or fallen in most age groups and consequently, projections of increased health care costs attributable to the rise in the number of proximal femoral fractures should be revised. Nevertheless, based on the assumption that the 2010 age-specific incidence remains unchanged and adopting population projections, in 2020 there will still be an extra 401 proximal femoral fractures in Northern Ireland (298 female and 103 male) representing a 21% increase from the number in 2010.

Similar levelling off or reductions of proximal femoral fracture rates have been observed across several European[5-9] and North American[9-12] populations. The potential explanations for this trend are numerous and varied. A study from Canada[16] observed a substantial increase in the number of bone mineral density scans and prescription rates for osteoporotic medication during the study period. This trend was followed by a true reduction in wrist and hip fracture rates despite the increasing age of the observed population. A study from Denmark[16] also observed a reduction in hip fracture rates between 1997 and 2006 alongside a significant increase in usage of anti-osteoporotic medications. This study however demonstrated that the decreased risk in men was nearly the same as in women despite a six times lower treatment prevalence and hence the authors could only attribute a small percentage of prevented hip fractures to this intervention. This study also reported reduction in smoking habits of the observed elderly population, increases in body mass index, and an increase in those reporting that they took regular exercise, all of which potentially had greater effects than the use of anti-osteoporotic medication. Nevertheless, development of fracture liaison services has been reported in West Glasgow[17] to significantly increase the proportion of patients with a fragility fracture receiving the required osteoporosis treatment, with resultant cost-effective prevention of fractures including hip fracture. A similar fracture liaison service was successfully established in Belfast in 2003[18] and remains in place to ensure uptake of appropriate treatment for osteoporosis in patients with fragility fracture.

A review of studies of hip and other fractures worldwide[9] reported that osteoporotic diagnosis and treatment does not fully explain the temporal reduction in hip fracture incidence. It postulated that as well as factors affecting risk late in an individual's life-course, additional risk factors encountered by differing birth cohorts contribute in later life to fracture rates. Such cohort effects have also been put forward to account for changing fracture rates in Finland where increased average body weight and functional ability was observed in an ageing population.[8] A study in the United states proposed that a cohort effect was likely to account for much of the observed change in fracture rates due to improved nutrition, the protective effect of raised BMI, a reduction in usage of psychoactive drugs and a reduction in falls risk.[10] The authors suggested further research to identify unknown factors which they thought may be present and contributing to the changing incidence.

SUMMARY

Proximal femoral fracture numbers continue to rise in Northern Ireland in line with the ageing population. Compared with the period 1985 to 1997 when the age-specific fracture rates were seen to be on the rise we now observe that between 1997 and 2010 the age-specific fracture rates have seen a plateau or slight reduction which is in keeping with findings in populations in North America and Europe. Reasons for the change are not identified by this study but are likely to embrace a range of influences including birth cohort, nutrition and falls risk as well as identification and treatment of low bone mineral density and other lifestyle factors.

Previous projections of inpatient health care costs associated with proximal femoral fractures had predicted, assuming a cost of £12000 per fracture,[2] that costs would rise to £33.6 million by 2016 to treat the 2800 fractures anticipated in

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Northern Ireland.[4] These projections have not been realised due to the described change in age-specific fracture incidence and current projections of 2284 fractures in the year 2020 at the same cost of £12000 per fracture would result in a revised annual inpatient cost of proximal femoral fractures of £27.4 million (An increase of 21% from 2010 to 2020). Though less than previous projections this still represents a £4.8 million per annum increase by 2020 which has significant implications for healthcare planning and resourcing. This highlights the need to adopt interventions which may prevent fracture and its associated morbidity and mortality as well as reducing healthcare costs.

ACKNOWLEDGMENTS

We acknowledge the assistance of Ruth Murphy in obtaining information for admissions to Craigavon Area Hospital.

The Authors have no conflict of interest.

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Ulster Med J 2012;**81(3):**127-129

Paper

Is the "red flag" referral pathway effective in diagnosing colorectal carcinoma?

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Accepted 8 March 2012

ABSTRACT

Introduction: In 2000-2004 there were, on average, 938 new cases of colorectal cancer (CRC) diagnosed per annum in Northern Ireland, accounting for 13.9% of all cancers. The two week "red flag" referral system aims to detect 90% of patients with CRC for prompt treatment. The aim of this study is to examine the impact of the "red flag" referral system on identification of patients with CRC, time to treatment and stage of disease.

Methods: A random sample of 200 patients referred via the "red flag" system was identified from the local cancer patient tracker database. Data pertaining to demographics, time to hospital appointment, appropriateness of referral and diagnosis were collected. For patients identified with CRC, the stage of disease and time to first definitive treatment were also documented.

Results: Of the 200 patients, 56% were female. The age range was 27 - 93 years. Eighty three percent were seen within 14 days of referral. Referrals adhered to the guidelines in 45% of cases. There were 4 pancreatic cancers, 1 endometrial cancer, 1 ovarian cancer and 1 myelodysplasia diagnosed. Three patients were diagnosed with CRC (1.5%). Of these, 1 was palliative and the remaining 2 commenced definitive management within 6 days of decision to treat.

Conclusion: The "red flag" referral system does not appear to be effective in identifying patients with CRC but did identify patients with other types of cancer. Less than half of the referrals adhered to the guidelines. A review of this system should be undertaken.

Key words: Colorectal cancer; Referral criteria; Diagnosis; Guidelines

INTRODUCTION

Colorectal carcinoma is the second commonest malignancy in women and third commonest malignancy in men in the United Kingdom[1,2]. In 2000-2004 there were 938 new cases of colorectal cancer diagnosed per annum in Northern Ireland, accounting for 13.9% of all cancers. The overall 5 year survival rate is 53.7%[3].

The two week "red flag" referral service arose from the NHS Cancer Plan in 2000 and the intention was to detect 90% of patients with colorectal cancer for prompt treatment[1,2,4-7]. This referral system was introduced in Northern Ireland in May 2007. To facilitate these referrals, guidelines have been established detailing high risk criteria for patients with suspected colorectal cancer[8,9]. (See Table 1). Previous studies have shown that when the guidelines are adhered to, the diagnostic yield for colorectal cancer is greater[6,10,11].

Patients referred via the "red flag" pathway must be seen by a hospital specialist within 14 days of referral and 95% of these patients who are identified as having colorectal cancer should begin their definitive treatment within 62 days of referral[8].

The aim of this study is to examine the impact of the "red flag" referral pathway on identification of patients with colorectal cancer, time to treatment and stage of disease.

METHODS

All consecutive adult patients with suspected colorectal cancer referred via the "red flag" referral pathway to a single unit over a one year period (1 April 2009 – 31 March 2010) were identified retrospectively from the local cancer patient tracker database. A total of 522 "red flag" referrals were identified. A random sample of 200 patients was selected by the audit department for analysis. Information was collected retrospectively from the medical notes. Time to be seen by a hospital specialist was calculated from the date of the GP referral letter to the date of first specialist outpatient appointment. Data was collected from the referral letters and compared with referral guidelines (Table 1) to establish if the "red flag" referral was appropriate. For those patients diagnosed with colorectal cancer, the stage of disease and time to first definitive treatment were also analysed.

A literature search was performed using Medline (key words "two week rule" and "colorectal cancer") and backward chaining from articles obtained.

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RESULTS

Of the 200 patients included in the study, 112 (56%) were female and 88 (44%) were male. The age range was 27 - 93 years with a median age of 68 years. Eighty three percent of patients were seen within 14 days of referral with a median time to appointment of 7 days. Referrals were consistent with the guidelines in only 45% of cases. Fourteen patients (7%) had normal investigations. One hundred and ninety patients (95%) had a benign diagnosis, the most common of which was diverticular disease (26.5%). The most common benign diagnoses are detailed in Table 2. Four patients had pancreatic carcinoma, 1 patient had endometrial carcinoma, 1 had ovarian carcinoma and a further patient was diagnosed with myelodysplasia. Three patients were diagnosed with colorectal carcinoma (1.5%). Two of these patients had a left sided malignancy (Duke's C & Duke's D). The remaining patient had a tumour in the right colon (Duke's B). Of these, 1 patient was palliative and the remaining 2 patients started treatment within 6 days of the decision to treat.

DISCUSSION

The two week "red flag" referral service was implemented to try to detect patients with colorectal cancer for early treatment[1,2,4-7] and guidelines were implemented to facilitate this[8,9] (see Table 1). This study shows that a large proportion of referrals do not adhere to the guidelines and the diagnostic yield for colorectal carcinoma is low. This lack of adherence to the guidelines is reflected in other studies in this area with non-compliance rates varying from 37.9 - 49.6%[6,10-12]. There may be several reasons for this including lack of time in the primary care consultation, less familiarity with colorectal history taking or a change in the patient's recollection of their symptoms[13].

The low diagnostic yield of "red flag" referrals for suspected colorectal cancer is well documented with pick-up rates of 3 - 14% being quoted in the literature[2,4,6,7,10,12-15]. This may be due to the referral of a large number of patients who do not adhere to the guidelines[4].

Of note, when the guidelines are adhered to, the diagnostic yield for colorectal cancer is greater. In a study carried out by Flashman *et al*[6] looking at all patients referred to a "two week rule" clinic in a 1 year period, 9.4% of patients were diagnosed with colorectal cancer, comprising 26.1% of all colorectal cancer diagnoses made in that time period. The diagnostic yield was greater in the "two week rule" clinic compared with the routine clinic (9.4% vs 2.2%; $p<0.0001$). The authors also found that 85% of the colorectal cancers referred fulfilled at least one of the referral criteria therefore suggesting that the guidelines are valid if adhered to.

Similarly, Debnath *et al*[10] found that a colorectal cancer diagnosis was of higher frequency in those referrals that complied with the guidelines. Eccersley *et al*[11] found that 25% of those patients that fulfill the referral criteria are diagnosed with colorectal cancer, supporting the view that the criteria must be firmly adhered to[7]. This may be improved by improving education in the primary care sector with regards to the high risk criteria for colorectal cancer and the importance of not referring patients with transient symptoms or symptoms lasting longer than 18 months via this referral pathway[10]. Also, an increased awareness of the diagnostic value of rectal bleeding without anal symptoms[6] and the importance of digital rectal examination may increase diagnostic yield. In a study carried out in North Middlesex University Hospital[1], 45% of referrals had no documented evidence of clinical examination. Just over half (56.7%) had no documented digital rectal examination and, of these, one third were found to have a palpable rectal tumour at outpatient appointment. Also worryingly, 30.6% of those with a documented normal digital rectal examination had a palpable rectal tumour at clinic. Other methods to improve adherence to referral guidelines may include triage of the "red flag" referral letters by clinicians although this will add to an already heavy workload and may not screen out unnecessary referrals if the information provided is inaccurate. Specific referral letter for colorectal cancer could be introduced[10] but this may only add to an already overwhelming amount of paperwork in the general practitioner's workload.

In our study, 3.5% of patients were diagnosed with other malignancies, lending some support to the view that the guidelines do appear to be effective in identifying a malignant process in the patients referred[11].

Table 1:

Red flag referral criteria

	Symptoms & signs for red flag referral
1	Persistent rectal bleeding for 6 weeks without anal symptoms (>60 yrs)
2	Change in bowel habit to looser stools/increased frequency for 6 weeks (>60 yrs)
3	Change in bowel habit to looser stools/increased frequency and rectal bleeding (>40 yrs)
4	Palpable right iliac fossa mass
5	Palpable rectal mass (intraluminal)
6	Unexplained iron deficiency anaemia (Hb<11g/dL men, <10g/dL non-menstruating women)

Table 2:

Common diagnoses

Diagnosis	Number of patients (%)
Diverticular disease	53 (26.5)
Haemorrhoids	39 (19.5)
Colonic/rectal polyps	17 (8.5)
Functional/IBS	17 (8.5)
Constipation	16 (8)
Normal investigations	14 (7)
Outlet bleeding	8 (4)
Inflammatory bowel disease	7 (3.5)
Diverticular abscess	1 (0.5)
Diverticular bleed	1 (0.5)

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Eighty three percent of patients in this study were seen within 14 days of referral which is comparable with figures quoted elsewhere[11]. The age range of patients is similar to that seen elsewhere[6] and again reflects a non-compliance with the referral guidelines.

CONCLUSION

The "red flag" referral system does not appear to be effective in identifying patients with colorectal carcinoma and had a greater yield for patients with other types of cancer. Less than half of the referrals adhered to the guidelines highlighting a need for improved education in the primary care sector with regards to the high risk criteria for colorectal cancer. Other solutions may include introducing a specific proforma for suspected colorectal cancer referrals or perhaps vetting of referrals by clinicians and the letter redirected with an explanation of why the patient does not meet the "red flag" criteria. A review of this system should be undertaken.

The authors have no conflict of interest.

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Ulster Med J 2012;**81(3):**130-133

Case Report

Left Bundle Branch Block morphology Ventricular Tachycardia in a marathon runner

Emily C Hodkinson, Kerry Aston, Simon J Walsh

Accepted 21 March 2012

A 41-year-old male presented to the accident and emergency department with a 3-hour history of palpitations and mild chest discomfort that had woken him from sleep. There was no history of previous episodes; indeed he had no past medical, surgical or family history of note.

He was an Iron Man marathon competitor.

The admission ECG showed a broad complex tachycardia (figure 1). Atrio-ventricular dissociation was evident with negative QRS concordance across the chest leads, fusion beats were also visible. The presence of a left bundle branch block, superior axis morphology further supported a diagnosis of ventricular tachycardia originating from the apex of the right ventricle.

Synchronized DC cardioversion was performed and his resting ECG was abnormal with extensive anteroinferior T wave inversion and Epilson waves in the leads III and aVF (figure 2).

On transthoracic echo the right ventricle was severely dilated and hypokinetic (figure 4). A coronary angiogram confirmed normal coronary arteries. On signal averaged ECG (SAECG), late low-amplitude ventricular potentials were evident.

The combined findings of sustained left bundle, superior axis ventricular tachycardia, repolarisation abnormalities on resting ECG, depolarisation abnormalities on Signal averaged ECG and regional structural abnormalities on 2d Echo fulfilled the revised Task Force criteria for diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)[4] (Figure 3).

A cardiac MRI was performed and demonstrated the classical imaging findings of ARVC. The right ventricle was dilated, the apex and right ventricular (RV) outflow tract were dyskinetic and there was an aneurysmal segment in the basal inferior wall of the right ventricle. Abnormal gadolinium contrast enhancement was seen at the RV apex and also in the left ventricle reflecting disease severity and a higher risk of heart failure and arrhythmias[8] (figure 5).

The patient was commenced on bisoprolol, and given the high future risk of sudden cardiac death, a dual chamber single coil defibrillator was implanted. Electrophysiological testing was not undertaken, as it has not been shown to be useful in risk stratification of ARVC[9].

Definitive diagnosis of ARVC is dependent on histological findings. However, transvenous endomyocardial biopsy has

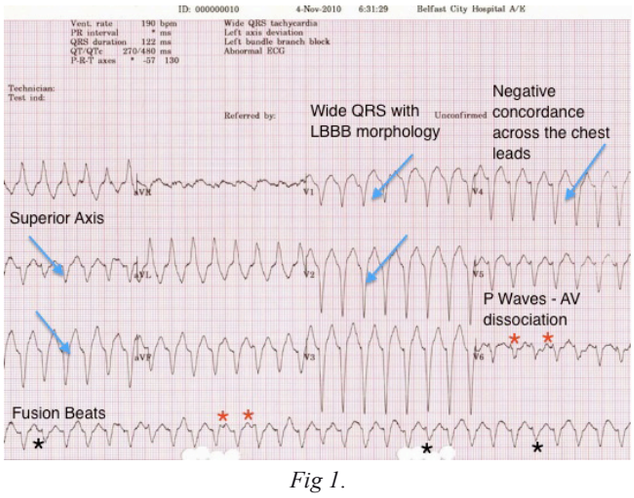

Fig 1.

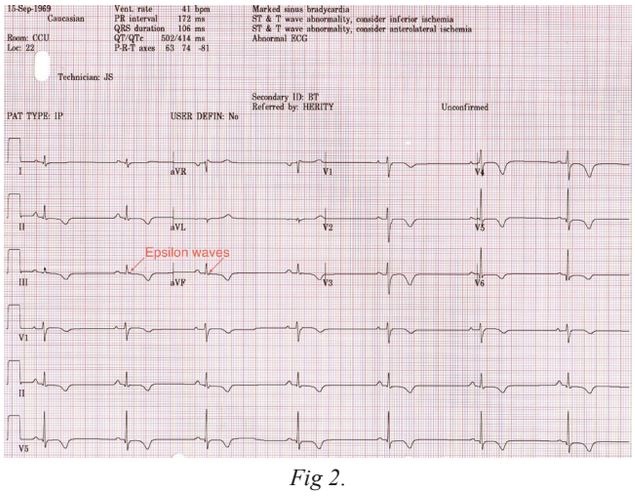

Fig 2.

diagnostic limitations; the fibrofatty change of ARVC is often patchy and, as biopsies are taken usually taken from the septum rather than the RV free wall (to reduce the risk perforation), diagnostic yield can be low[2]. As the Taskforce diagnostic criteria had already been fulfilled in this case we elected not to undertake a biopsy.

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Fig 3. 2010 ESC revised Task Force Criteria for the Diagnosis of ARVC

1. RV on Imaging	
Major	**By 2D echo:** • Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): - PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) - PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) - *or* fractional area change ≤33 percent
	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) - *or* RV ejection fraction ≤40 percent
	By RV angiography: • Regional RV akinesia, dyskinesia, or aneurysm
Minor	**By 2D echo**: • Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): - PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) - PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) - *or* fractional area change >33 percent to ≤40 percent
	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) - *or* RV ejection fraction >40 percent to ≤45 percent
2. Histology	
Major	Residual myocytes <60 percent by morphometric analysis (or <50 percent if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	Residual myocytes 60 percent to 75 percent by morphometric analysis (or 50 percent to 65 percent if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
3. ECG - Repolarization abnormalities	
Major	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block
4. **ECG - Depolarization/conduction abnormalities**	
Major	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)
Minor	Late potentials by SAECG in ≥1 of the following 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG - Filtered QRS duration (fQRS) ≥114 ms - Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms - Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
5. Arrhythmias	
Major	Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
6. Family History	
Major	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutationΔ categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Definite diagnosis = 2 Major or 1 Major and 2 Minor criteria or 4 Minor from different categories

Borderline Diagnosis = 1 Major and 1 Minor or 3 Minor criteria from different categories

Possible Diagnosis = 1 Major or 2 Minor criteria from different categories

PLAX: parasternal long-axis view; RVOT: RV outflow tract; BSA: body surface area; PSAX: parasternal short-axis view; aVF: augmented voltage unipolar left foot lead; aVL: augmented voltage unipolar left arm lead.

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He has been referred to medical genetics and is undergoing genetic testing and family screening.

The diagnosis had major implications for his life as he had been advised to cease all high intensity activity.

DISCUSSION

ARVC is an inherited cardiomyopathy[5] characterised RV dilation, thinning & dysfunction. Histologically, the RV myocardium is replaced by fibrous fatty tissue[4]. It is a disease of the desmosomes; the mechanical connections between myocytes are disrupted hence the predilection for thin RV and the observation that the disease is more severe and presents earlier in athletes[4].

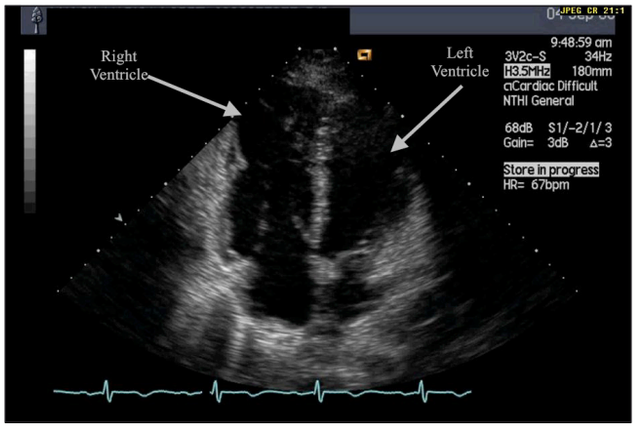

Fig 4. Dilated and Hypokinetic Right Ventricle

The prevalence of ARVC is estimated at 1:1000[1]. It is an autosomal dominant condition with variable penetrance.

Most patients present between the ages of 10-50 years[1]. The main presenting symptoms of ARVC are dizziness, palpitations, atypical chest pain and syncope[1,3,8,]. It is estimated that ARVC accounts for 20% of sudden cardiac deaths with an overall mortality rate of 2.5% per year[2]

A definite diagnosis of ARVC requires the presence of a combination of major and minor clinical criteria as set out by the 2010 ESC revised Task Force Criteria[4].

Many patients are asymptomatic and the diagnosis is often only considered due to non-specific ECG or echocardiographic abnormalities of the right ventricle. Clinicians are encouraged to consider a diagnosis of ARVC in these patients and to refer on to cardiology for further investigation.

VT with a left bundle branch block morphology and an inferior axis commonly originates from the RV outflow tract (RVOT). In contrast to Arrhythmogenic Right Ventricular Cardiomyopathy, RVOT VT occurs in structurally normal hearts (occasionally the RVOT is dilated and RV regional wall motion abnormalities are seen on CMR[10]) and is readily treatable with verapamil and betablockers or radiofrequency ablation. The ECG in sinus rhythm in RVOT VT is normal as is the SAECG. In contrast to ARVC, there are no family screening implications with RVOT VT.

Other differentials to consider include idiopathic dilated cardiomyopathy (IDCM)[8] and Uhl's anomaly. Patients with IDCM usually have a progressive decline in left ventricular function, in contrast to ARVC where the right heart is primarily affected. In Uhl's anomaly the RV myocardium is paper thin and devoid of myocardium. There is no replacement of muscle by fatty tissue. It usually presents in childhood [1.]

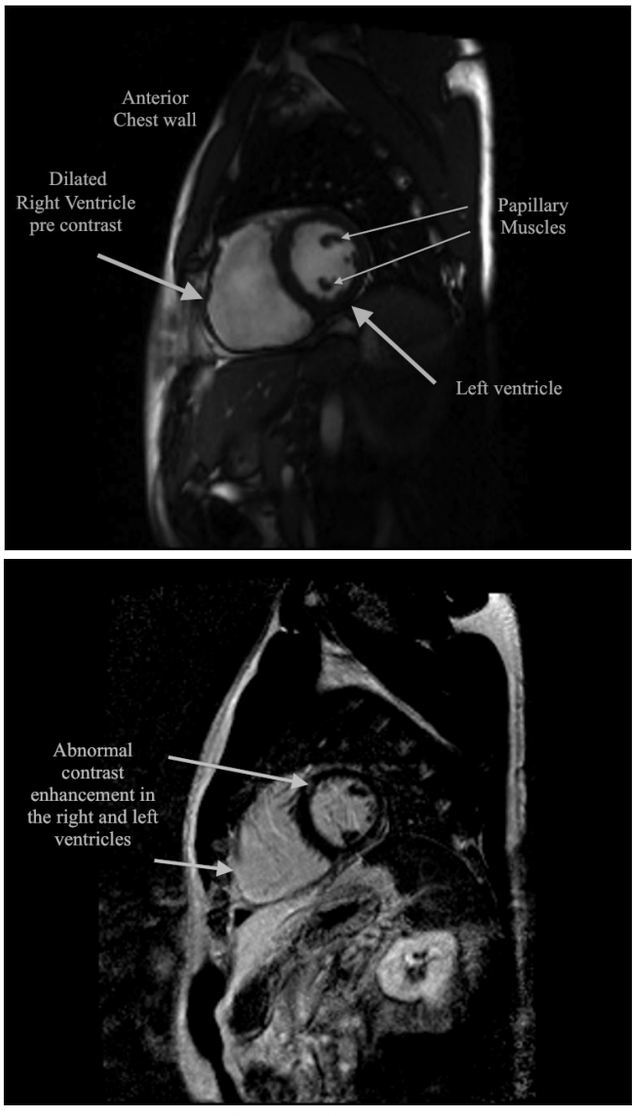

Fig 5. Short Axis Cardiac MRI images before and after Gadolinium contrast showing abnormal uptake at the RV apex and the anteroseptal region of the LV.

Epsilon waves are characteristic of ARVC but are only found in around 30% of cases[6,4]. They are distinct waves seen between the end of the QRS and start of the T wave and represent low amplitude potentials caused by delayed conduction through the abnormal right ventricle[7].

The treatment of ARVC is that of a cardiomyopathy. The goal is prevention of sudden cardiac death. Right heart failure occurs late. Anything more than moderate-intensity activity is strongly discouraged[4,5].

CONCLUSION

ARVC is a recognised cause of sudden cardiac death. Left bundle branch block morphology ventricular tachycardia or an abnormal right ventricle on echo in an otherwise well patient should prompt onward referral to cardiology.

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With Thanks to Dr Nicola Johnston, RVH who kindly provided the cardiac MRI images

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Ulster Med J 2012;**81(3):**134-135

Case Report

An Unusual Cause of Reversible Cardiomyopathy

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Accepted 8 March 2012

A 58-year-old male presented with a two month history of paroxysmal nocturnal dyspnoea, 2 pillow orthopnoea and bilateral ankle swelling. He was a 15 pack year smoker. His past medical history was unremarkable. Clinical examination revealed features of congestive cardiac failure, including a raised jugular venous pressure, peripheral oedema and bilateral lung crepitations. Blood pressure was 137/56 mmHg. Electrocardiography showed rate controlled atrial fibrillation (AF), QRS duration was within normal limits. Chest radiograph revealed cardiomegaly and increased pulmonary vascularity. Brain natriuretic peptide (BNP) was raised at 660 pg/ml (Normal Range: 0-100). Serum troponin I and inflammatory markers were normal. Transthoracic echocardiogram showed severe, global, dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) of 25% (biplane simpson's method). There was no significant valvular heart disease. He was treated with intravenous furosemide with clinical improvement. Cardiac catheterisation demonstrated angiographically normal coronary arteries. Extensive investigations for autoimmune, infective and infiltrative causes of cardiomyopathy were negative; cardiac Magnetic Resonance Imaging (MRI) with gadolinium enhancement showed no areas of delayed contrast enhancement to suggest cardiac amyloidosis or myocardial fibrosis and there was no evidence of myocardial oedema (Fig.1). The patients reported alcohol intake was limited to 4-5 units per week. There was no known family history of cardiomyopathy.

The patient was treated with full standard heart failure medication, including ACE inhibitors, beta blockers and aldosterone antagonists. Ambulatory ECG monitoring revealed paroxysmal rate controlled atrial fibrillation. The patient was warfarinised. At routine follow up clinical features of heart failure had resolved but left ventricular systolic function remained severely impaired on follow up echocardiogram.

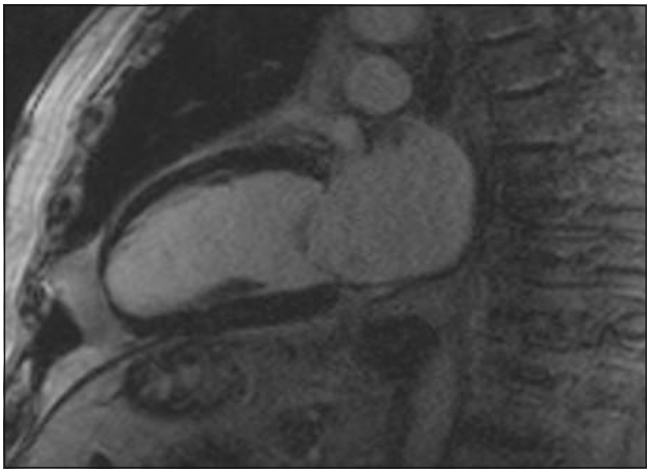

Fig 1. Cardiac Magnetic Resonance Imaging with gadolinium, demonstrating no areas of delayed contrast enhancement.

Two years after initial presentation his clinical condition had deteriorated with recurrent decompensated heart failure, severe proximal muscle wasting and debilitating lethargy complicated by newly diagnosed type 2 diabetes mellitus (fasting plasma glucose 7.7 mmol/l, HbA1c 7.8%) and bilateral femoral deep vein thrombosis. Blood pressure was 125/75 mmHg. On examination he was noted for the first time to be clinically cushingoid, with rounded facies, centripetal adiposity and supraclavicular fat pad accumulation. Subsequent investigations confirmed hypercortisolism biochemically with an elevated urine free cortisol (897 nmol/24h) and failure of suppression of 8am serum cortisol (239 nmol/l) after a 1 mg overnight dexamethasone suppression test. A diagnosis of ACTH-dependent Cushing's syndrome was confirmed with elevated plasma ACTH concentrations of 70-80 ng/l. A high dose dexamethasone suppression test (2 mg qds for 48 hrs) showed partial suppression (74%) of serum cortisol to 134 nmol/l. He was subsequently transferred to the regional centre for further investigations for tumour localisation to guide surgical treatment. No definite source of the excess ACTH was found following bilateral inferior petrosal sinus sampling (central to peripheral ACTH ratio of 1.6 : 1 after administration of corticotropin-releasing hormone). Pituitary gadolinium-enhanced MRI was normal, computerised tomography (CT) chest, abdomen and whole body PET-CT scan were unremarkable.

Because of the urgency of the deteriorating clinical situation, arising from the effects of severe hypercortisolism, a decision to proceed to bilateral adrenalectomy for definitive treatment was agreed. Initially, he was commenced on metyrapone 1 gram twice daily, which blocks cortisol synthesis through inhibition of 11β-hydroxylase, until bilateral adrenalectomy was performed three months later without complication. Four

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TABLE 1

Serial echocardiography measurements at initial presentation and 4 months after bilateral adrenalectomy

Variables	At presentation	4 month post bilateral adrenalectomy
Left Ventricular dimensions		
LVIDd (cm) (4.2-5.9)	**6.4**	**4.9**
LVIDs (cm) (2.0-3.8)	**5.9**	**3.5**
IVSd (cm) (0.7-1.2)	**1.3**	**1.3**
LVP wall thickness (cm) (0.6-1.2)	**1.2**	**1.2**
Left Ventricular function		
Ejection fraction* (%)	**25**	**63**

*using Biplane Simpson's method

LVIDd, left ventricular internal diameter end-diastole; LVIDs, left ventricular internal diameter end – systole; IVSd, interventricular septal wall thickness at end-diastole; LVP wall thickness, left ventricular posterior wall thickness at diastole.

months post operatively and thirty five months from initial presentation his symptoms have improved with no clinical evidence of heart failure, normalised serum BNP and normal left ventricular dimensions and function on echocardiography (Table 1). His ejection fraction had improved from 25% at presentation to 63%, four months post bilateral adrenalectomy. At follow up the patient had remained in normal sinus rhythm on ambulatory ECG monitoring.

Cushing's syndrome is an uncommon but potentially reversible cause of dilated cardiomyopathy, most often reported in patients with hypercortisolism arising from an adrenal adenoma[1-2]. Common causes of reversible cardiomyopathy include alcohol, tachycardia-related cardiomyopathy, myocarditis and ischaemia, all of which were effectively excluded in this case. Previous studies examining the relationship between hypercortisolism and cardiac dysfunction, suggest that cardiac remodelling occurs in Cushing's syndrome, independently of hypertension[3-4]. It is believed that cortisol may act directly on myocardial tissue as glucocorticoid receptors have been shown in animal[5] and human heart tissue[6]. The striking change in cardiac function after resolution of hypercortisolism in the present case after bilateral adrenalectomy suggests that the cardiomyopathy was attributable to hypercortisolism and responsive to a eucortisolaemic state, despite an initial delay in recognition of the underlying diagnosis.

This case highlights the importance of considering Cushing's syndrome in the differential diagnosis of cardiomyopathy. It also demonstrates the benefits of definitive treatment with bilateral adrenalectomy in patients without a definite source of ACTH secretion. This patient remains under careful long-term surveillance for emergence of the source of the ACTH secretion. However, with stabilisation of his cardiac status following bilateral adrenalectomy, longer term follow up will be achievable.

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Ulster Med J 2012;**81(3):**136-142

Annual Oration

The Fall and Rise, of (some) Women

James Dornan

Accepted 9 May 2012

"Gentlemen – it has fallen to my lot, in accordance with an old established custom, to inaugurate the academic session 1852-1853 at this hospital".

These were the words uttered by Dr A G Malcolm, the Orator of the day, during his opening lecture to The Belfast Medical School, at a time when the General Hospital was in Frederick Street. There was no mention of women, as there were none in the audience. The 1850's were a low point for women in the history of Homo sapiens. A point from which some have managed to find the road back to the summit, but worldwide, most have failed to get back from whence they started. It was 1890 before an Orator was able to say, "Ladies and gentlemen – it has fallen to my lot to inaugurate this academic year".

There were three Queen's Colleges in Ireland in the latter part of the nineteenth century, in Belfast, Cork and Galway, and in 1856 we saw the opening of the Dublin Catholic College. Intriguingly, and amazingly in retrospect, in 1856 an Act of Parliament debarred women from attending any university throughout the Celtic Islands. This act was only repealed some twenty years later. However, the decision to repeal the act was not supported by all of the apparently learned fraternity. The Professor of Midwifery in Belfast was particularly unhappy, commenting, "the culture and refinement of the age should have forbidden such a transformation". Indeed, Sir William Jenner, of typhus and typhoid fame, although a man of great breadth and vision, had said at the time, "I have one daughter, and sooner than see her at the dissecting table, I would see her dead before me". By now the reader will be developing an understanding as to why the women's liberation movement of the twentieth century was needed, and sadly, is still required in much of the world. Some women, I am delighted to report, overcame the odds. Dr Joy Darling (nee Pedlow) was born in Belfast in 1886. Her father had told her that "medical school is no place for a woman". She was therefore encouraged to study languages, but by translating private documents at night she was able to raise enough money to put herself through medicine (personal communication). Not only that, she won most of the academic and sporting prizes on the way through, including becoming the Irish tennis champion. She also married, had four healthy children, and at the same time as being a General Practitioner, she was both an anaesthetist and an obstetrician in Belfast for many years, before retiring in the 60's. Dr Darling seems to have invented multitasking, for whilst also running a nursing home on the Antrim Road, providing private maternity care in order to raise money to enable her to care for destitute women that they would give birth safely, she also provided a shelter for injured servicemen returning from war. I was delivered by her, though my mother assures me that she was one of the private patients, rather than one of the destitute ones.

In 2004, I was elected Senior Vice President of the Royal College of Obstetrics and Gynaecologists based in London. I had responsibility for Education and also International Women's Health, working in the latter field for the next three years, and indeed beyond, as presently I remain a member of the International Executive Board. Internationally, it became very obvious to me very quickly that women are not in a good place. Let me present the reader with a multiple choice question : what do the following statements have in common? Failing to be born because of your gender. Having the labia and clitoris removed by a sharp stone at the age of eight years old. Forced into marriage at first menstruation. Non-consensual sex from your first encounter. No access to contraception or termination ever. Forced to abort your girl fetus. Dying in a field, guilt ridden and infected from unsafe home abortion. Being one of the 50% of women in the world with no antenatal care. Being one of the 95% of women in the world who deliver outside the birthing centres. Being an Afghan girl with a 1 in 8 chance of dying in pregnancy. Being shunned by all as a harlot if not delivered before sunset. Dying twelve hours after convulsing continuously during labour for the lack of exposure to Magnesium Sulphate, which is cheaper than table salt. Dying from uncontrollable bleeding just after giving birth to the beautiful baby for which you have always longed. Dying after 72 hours of obstructed labour because of immature pelvic development associated with no sunlight and Vitamin D deficiency. Dying from overwhelming pelvic infection, which could have easily been halted in its tracks by the simple application of first generation antibiotics. Allowed to die in labour by your partner as it is cheaper to take a new wife than to pay for a caesarean section. Being constantly wet with urine leakage, and rejected as a consequence of obstructed labour. Suffering from constant physical abuse and to be considered to be of less value than a domestic animal. Well sadly, in all parts of the world, the answer to the multiple choice question is that all the above only happen to women, and are silently happening to a lot of women, a lot of the time, right now. A mixture of man and nature is a heady mix indeed for women to endure, especially if the women in question are uneducated. The good news for womankind is that historically not all our accoucheurs, or midwives, appear to have been anti-woman. One such was Bartholomew Mosse, who a century before the Belfast General Hospital opened, was so affected by the plight of women in famine-ridden

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Ireland, that following the death of his own wife in labour, and seeing the plight of women in dire straits and in great need of warmth, food, shelter and medical care, built one of the world's first lying-in hospitals at the end of O'Connell Street in Dublin.[1]

At the Rotunda Hospital, Bartholomew Mosse's mothers were provided solace, support and simple obstetric remedies. He also was 300 years ahead of his time, by attaching the Gate and the Ambassador Theatres within the grounds of the hospital, where artistic productions by local artists would raise funds to pay for the running of the hospital. Bartholomew Mosse and Joy Darling were truly part of the true Big Society-well ahead of their time.

Bartholomew Mosse was the first Master of the Rotunda, and to this day there has still been no female appointed to this post. He was English by birth, being the son of the Rector to King William III and he was a unique man indeed. I would contend that his co-genderists were just coming to an end of a 3000 year experiment in patriarchy. However, when I say "coming to an end", I speak in hope rather than expectation for it surely must come to an end if women are to regain their position in society worldwide.

Having babies in much of the world is still a very risky business. Nature is a tough obstetrician and in many ways believes in survival of the fittest. It has indeed been a pleasure to work in this part of Europe where we practice, to a greater or lesser extent, socialised medicine which, contrary to nature some may say, believes in survival of the weakest. However, half of the world's population are women, and they are the only ones with the 'where-with-all' to use their bodies for reproduction. Sadly, most of these women have little input into the decision as to whether to do so, nor equally importantly, indeed do not have the sexual rights associated with the process. Pregnancy for many women in the world is a death sentence.[2,3]

Working with the Liverpool School of Tropical Medicine, we in the RCOG have established a Life Saving Skills Emergency Obstetric Care Package, which provides a three day course for midwives and medical officers on how best to address the ten main causes of maternal mortality.[4] Maternal mortality is extremely high in Africa, South East Asia and the less economically developed parts of the world.[5] Indeed the global gap between rich and poor countries has actually increased in the past decades.[6] Africa, as a whole, has a maternal mortality rate of 830 per 100,000. Sweden's is 4 per 100,000. In Africa, if a mother has six children, she has a 1 in 20 chance of dying.[7] Yet, by addressing the main causes of maternal mortality within the country where the infrastructure problems have been addressed, success can be achieved very quickly. Malaysia and Sri Lanka have both done this over the past forty years.

The major killers of women in their reproductive years are childbirth, followed closely by HIV/AIDS, tuberculosis and malaria.[9]

The major causes of death associated with pregnancy are haemorrhage, sepsis, unsafe abortions and pre-eclampsia, all of which can generally be addressed successfully by the attention of a skilled birth attendant at the woman's bedside, armed with knowledge and simple drugs.[10] However, this modest goal is much simpler to suggest, than to deliver. To address these and other problems traditionally considered primarily to be associated with poverty, the Millennium Development Declaration was signed by 189 countries in 2000 when they set targets for Global Action Against Poverty, that were to be addressed by 2015.[6] The health related millennium goals are ; To eradicate extreme poverty and hunger. To achieve universal primary education. Promote gender equality and empower women. Reduce child mortality. Improve maternal health Combat HIV/AIDS, malaria and other diseases. Develop a global partner for development. Obstetricians tend to focus on millennium goals 4 and 5. In developed countries throughout the world there is an abundance of well-budgeted, earnest groups of government and non-government departments and management organisations that work with the United Nations and the World Health Organisation, and indeed many other groups, to try to "trickle down" help to the most needy in the under resourced world. Indeed, there is good evidence that maternal, child and infant survival can be shown to be directly proportional to the density of health workers on the ground.[11.12]

America has 10% of the world's disease yet employ 35% of the world's workforce. Europe has 15% of the world's disease, and 18% of the world's workforce. Africa, which has a quarter of the world's disease, has only 3% of the healthcare workforce. It has been calculated that 36 African countries have a one million deficit of doctors, nurses and midwives.[13] Many of those reading this paper may be indirectly involved in "trickling down" to help the needy, but others will also be involved in "trickling up" through civil society or missionary work, offering consultancy, guidelines development, formal in -country assessments, building facilities and so forth. Indeed, "trickling up" is now considered to be at least as efficient and effective as "trickling down". From my relatively short time working with others to help reduce child mortality and to improve maternal health, increasingly I have become more convinced that the answer to millennium goals 4 and 5, is in fact millennium goal 3, which is the "promotion of gender equality and empowerment of women".[6] By empowerment, I mean that : Women have necessities such as food and clothes. Their psycho-social needs have been addressed and they are in control over their own lives. She has political empowerment by having a voice.

I believe strongly that if we empower and educate women, they themselves could then decide whether to get pregnant, to whom, and to ensure that they maximise their and their offspring's chances of survival before, during and following childbirth.

The indicators for millennium goal 3 are ; The ratios of girls to boys in primary, secondary and tertiary education. The ratio of literate women to men in the 15-20 year old age group. The share of women in waged employment in the non-agricultural spectrum. The proportion of seats held by women in their national parliament. The ratio of girls to boys in primary education in Africa and South East Asia is actually improving.[14] Indeed in the last 15 years there has been a statistical improvement with over 85% of girls now having primary education. However, the ratio against boys in tertiary education is not so encouraging. Indeed girls comprise only a

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third of the very few places in tertiary education in Southern Asia and sub Sahara Africa.[15] The reader may not be overly shocked by these statistics from the under- resourced world, but it has been suggested recently by Joan Smyth, writing in the Independent on Sunday, that the overall pay gap in the UK itself is 21% in the private sector, and that it will be 100 years before parity is reached. So it's mostly a matter of degree.

The reader will not be surprised to learn that Norway is one of the leaders in "giving women a voice" and 46% of Norway's MPs are female. However, more surprisingly, in Rwanda the figure is 52%, and indeed a recent article in the Lancet suggests that Rwanda is one of the few African countries that has the potential to achieve millennium goals 4 and 5 by the year 2015, suggesting a direct correlation between the empowerment of women and maternal mortality.[16] A SWOT analysis, (strengths, weaknesses, opportunities and threats) on Millennium Goal 3 proves revealing. The strengths and weaknesses are internal factors, which are those factors within the millennium development goals themselves. Opportunities and threats are external factors that have an external influence outside the millennium goals. The strength of millennium goal 3 is that it was welcomed by the feminist movement, and the MDGs provide a common language for the work of governments, United Nations Agencies and International institutions. The inclusion of maternal mortality, universal education, HIV and malaria, suggested that on these areas in particular, there was a commitment to gender equality.[17]

The weakness of millennium goal 3, however, was that the MDGs were silent on security and dignity unless they were affecting economics. They were also silent on women's human rights and all gender based violence. Particularly sadly, they were silent on sexual reproductive rights - a perfect example of an opportunity lost. The reader will have to consider the world politicians in power at the time of the conception of the MDGs and make their own judgement on the reasons.

Millennium goal 3, however, did provide opportunities. There have been many international conferences to address population, development and women's rights.[17] Several women's groups and organisations have been established with government support around the globe and advocacy has increased.[18] An example would be the recently established White Ribbon Alliance, which is supported by many female leaders, and partners of leaders, around the globe. Many countries are slowly, steadily and surely bringing in laws to protect women and women's rights.

There are also threats to millennium goal 3. There are too few secure paid jobs and there are still huge wage differentials and occupational segregation.[17] Poor health conditions of women throughout the world are widespread and women have higher unemployment rates. Perhaps, most important of all is the fact that women do not have the ultimate power to decide, in all circumstances, with whom they wish to be sexually active; whose baby to carry; whether to carry the baby; where to have their baby; how to have their baby or how to avoid dying while trying to do so. If all women had these rights, then they truly would be empowered. Sadly most women remain poor, powerless or pregnant. It seems ironic that in Britain we have spent the last two decades concentrating only on one of the above list, "How and where to have your baby". We really must try harder as a society to prioritise.

At the new millennium, the Native American Indians have decreed that in the last three thousand years, Mother Earth has been a "man's world" and that life is "out of balance". The word that they use for this is "koyanisqatsi". They have also made four major observations on the present state of the world. They have suggested that for the last three thousand years the male ego has run unchecked, that we have had far too many testosterone fuelled wars, that there has been a plethora of mysogenistic societies, and that homosapiens have shown s huge disrespect for Mother Earth. A powerful quartet that warrant a period of quiet contemplation.

Man has much of which to be to be proud in the last three millennia, as well as much of which to be ashamed. Changez Sultan is a Pakistani artist of note, and is someone I have grown to admire. His writings and art depict a huge compassion for women worldwide, as he sees them as bearing the cross for much of the world, while they struggles to survive, knowing not who to trust, who to love, or whose children to bear. He believes that womankind is bearing the cross for man's many failings (Figure 1).

Fig 1.

Having worked in International Women's Health for the last decade, and given much thought to what I have seen, I do feel that the journey that women have been on since being on this earth, has generally not been a good one.

The present place of women in society, however, is a relatively new one considering the length of time we have been on earth. There is good evidence that if we go back to pre- history civilisation that Mother Earth, as represented by Shomba the female goddess, was indeed worshipped as a powerful worker of miracles. In the absence of historical literature and records, we must look to art to see how women were represented, and the Venus of Willendorf is a fine example of how women were portrayed and considered. The Venus of Willendorf was found 30 metres above the Danube in Austria, some 30,000 years ago. She is just 12cm tall yet depicts the female goddess as a position of authority, because men realised at that time that you only had to give this Goddess a seed, and she could produce the miracle of a baby. The Goddess Earth Mother was a figure feared and revered in the ancient world, and so society at that time understandably was often matriarchal. As Dan Brown explains in his book, The

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Da Vinci Code, "in pre- religious days women were seen as the essential half of the spiritual enlightenment". The ancient, prehistoric, civilisations of Mesopotamia, Egypt and Anatolia appear also to have been matrilineal, as well as matriarchal. By prehistoric, I mean natural, primitive, uncorrupted and true. The natural state, however, was gradually destroyed as men established the unnatural condition of patriarchy, by subjugating women. My thesis to the reader is, that following tens of thousands of years of paganism and goddess worship, men decided to use religion to change the balance of power. What has followed has been a three thousand year experiment in patriarchy. This patriarchy has not been promoted by the great founders of religions, but it could be contended , has been terribly exploited for their own ends, by many of the men that followed these religions.

Fig 2.

It is generally accepted that the move from matriarchy to patriarchy occurred approximately 3000 to 3500 years ago. Sculpture at that time, such as in Figure 2, reveals a couple at the time of the Pharaohs, showing great equality between the male and female, both sitting and both with appropriate dress code. However, mainstream religions subsequently demoted women to the role of spouse. This move has been accredited to Judean, Hebrew and Greek religious men who divided the one mother goddess into Aphrodite, Athena, Atemis, Henna and Hestia but suggesting that there was one male god concept which is still accepted by most mainstream religions - a classic case of "Divide and Conquer".

The current theory is that male-dominated tribes from the East and North East invaded the Eastern Mediterranean and old Europe, bringing with them the concept of aggressive, male, Gods, who probably had experienced too much of the matriarchal society for their liking.

By historic times, patriarchy was preeminent in much of the world, and the female Pharaoh was now seen as submissive and subservient, standing by her man's side (Figure 3). Art and artists continued to reflect the times and Aphrodite of the Ancient World had women as dutiful wives and housekeepers that were a thing of beauty, as revealed by the artist who used materials such as marble, to reflect the smoothness of their skin. Women were also often depicted as naked, erotic, bathing, and were the "servants of men" (Figure 4).

Fig 3.

Fig 4.

With the establishment mainstream religions, women were increasingly depicted as the mothers of god and artists, now mainly commissioned by the churches, presented them as a frame for the adoration of the baby boy Jesus (Figure 5). The Church, remained, and some would say remains, frightened of the power of women. Dan Brown reminded us that the Heros Gamos, or holy wedding, depicting the act of sexual union

Fig 5.

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between a man and a woman, was required to commune with God. However, in the Dark Ages, holy men feared their sexual urge as the "work of the Devil collaborating with his favourite accomplice, the woman".

Almost all paintings of Eve portray her as naked, mostly showing that while her nakedness is tolerated by men, her thoughts and feeling were irrelevant. Women were untrustworthy, dangerous and were only complete when she became a mother (Figure 6).

Fig 6.

Dan Brown also reminds us of the Malleus Malificarum where, at the end of the Dark Ages between the 10th and the 14th centuries, upwards of one hundred thousand free thinking women were burnt at the stake at the Church's command. Such victims included nature lovers, herb growers and midwives, the latter seen as particularly vile, as they used their theoretical knowledge of medical practice to ease the pain of childbirth, which was at odds with the teachings of Genesis.

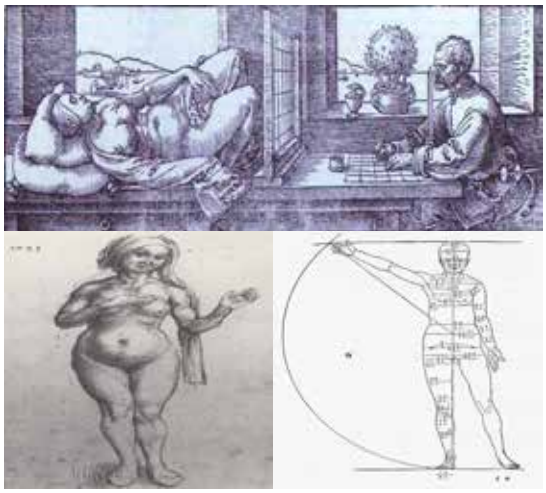

Fig 7.

The 14th century heralded The Renaissance and the flowering of literature, art and science; and the resurgence of learning based on classical sources. The key Renaissance Men were Leonardo Da Vinci and Michael Angelo. Many of their paintings portrayed women as objects of theory and study (Figure 7).

The 16th century marked the beginning of the Baroque period of Reubens and Rembrandt. Ruebens was a Flemish artist and in his early work had an extravagant style that emphasised movement, colour and sensuality. But by the early 17th century, Reuben, whose father had been a Calvinist and his mother Catholic, had become a leading voice of the Catholic Counter Reformation style of painting, to the point where he stated, "my passion comes from the heavens and not from earthly musings". He is well known for his self portraits, and one of his paintings (Figure 8) shows him and his wife, beautiful and clothed, but below him who is deemed to be her master.

Fig 8.

Rembrandt was the true master of the Baroque, and he was commissioned by the Protestant Church to illustrate the ethic of work, prosperity and a stable home. In Figure 9 we see the husband very busy solving scientific and technical problems, while his wife is portrayed as a willing and subservient helper.

Fig 9.

By the 19th century men dominated Europe. Patriarchy was at its height, and women were in their place. One hundred years before Germaine Greer, women were beginning to learn how to use their beauty and then their brains. They were becoming more powerful by making men want them and not just use them. Integral to the great revolution in the 19th century, was their demolition of the hedonist patriarchal society. They were definitely on the comeback trail in the

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developed world at least. Delacroux epitomised this comeback in his 1830 painting "Liberty, Leading the People". (Figure 10) He presents our female leader as working class, Parisian and a revolutionary, albeit with naked breasts and carrying a rifle. This is almost a suggestive French version of our present Deputy First Minister's erstwhile call for battle with a vote in one hand and an armalite in the other.

Fig 10.

The 19th century brought us, among others, Bronte, Austin and Nightingale. Women were to be quiet no longer, and were truly on the comeback trail, at least in the first world.

Changez Sultan believes that two thousand years ago, when Christ was crucified, this was symbolic of the women's place in society being crucified at the same time (Figure 11). He does not blame Christ for this, but rather the 46 "XY" men who have been managing most religions since. Management of religion is generally in men's hands, and frankly, leaves much to be desired. There is little wrong with religion itself, or indeed most of it's founders, but the male followers have often been found wanting.

Fig 11.

Freud asked, "Woman! What does she want?" There is no doubt that having spent thirty five years as an obstetrician in the western world, and for the last ten being very involved in International Women's Health, I personally believe that the first three things women want, or certainly need, are education, education, education, and with that will come a woman's ability to control their own sexuality and fertility.

We spend a lot of time nowadays phaffing around the edges of this problem by trying to offer "CHOICE" of, for example, where and how to deliver. The key questions surely are, however, should women have the choice with whom to make love, with whom to have a baby and when to have it? Women want and should have control over their own fertility and sexuality. Sadly this is not a fact for most women in the world.

Women also want to have equal rights and they want and need Millennium Goal 3 implemented worldwide, immediately. I was privileged to have numerous conversations with Derek Bingham, a well know local intellectual evangelist, prior to his tragic and untimely parting. On one such occasion we talked of the issues in this paper and he reminded me that Jesus had a particular compassion for fallen women, despite the fact that his apostles were all male. Three weeks before the crucifixion He came across an apparent fallen woman being stoned for being a harlot. He walked to the front of the crowd and said, "Let him who is without sin cast the first stone". When the crowd bowed their heads and left, He then went to the woman and said, "I find no fault in thee, go thy way". Just pause and think on those words. Three weeks later Christ was crucified and I am reminded that when Changez said that women's rights were crucified with Christ, he did not mean that it was His intention that this should happen, but sadly, it is what appears to have happened.

Fig 12.

It is perhaps timely to remember that on His final day on earth, before his ascension , Jesus chose a women, Mary Magdalene, the woman of seven devils, to receive the greatest message that was ever to be passed onto mankind (Figure 12). It is a great shame that the men left behind by THE Master, failed to heed the significance of that act. When I say men, I mean most men, but not all men. Not the other Master, Bartholomew Mosse and not, I hope, any male readers of this oration.

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Ulster Med J 2012;**81(3):**143-148

Grand Rounds

The Chest Radiograph

Barry Kelly

Accepted 1 September 2012

INTRODUCTION

The chest radiograph accounts for a very significant proportion of imaging throughout the world. It often represents the first imaging step, not only in diseases that focus on the cardiovascular and respiratory systems, but in systemic illness. For this reason, its ubiquity can be beguiling. There is an inclination to feel that because one grows up with the chest radiograph, there must be an innate and acquired knowledge not always tested by rigorous curriculum or by assessment. The purpose of this Ground Rounds paper is to set out some basic principles which I hope will be helpful for the medical student and postgraduate trainee.

THE NORMAL CHEST RADIOGRAPH

Before reviewing the radiograph itself it is important to confirm that the study associated with the **right patient** and has been performed on the **right date**. As someone once said, it is difficult to make an original mistake, and reviewing a radiograph in its incorrect sequence is not uncommon but can be a very important error in retrospect. It is also important to remember that the most influential radiograph might be the previous study. Therefore, when reviewing any chest radiograph it is vital to ascertain if there are previous studies available, either in celluloid format or on the Picture Archive Communication System (PACS) timeline. For example, the Kerley B lines seen at the costophrenic angles and lateral chest walls are not specific to cardiac failure and, in fact, represent the manifestation of enlargement of the interlobular septa of the secondary pulmonary lobules. In other words, interstitial lung diseases will produce precisely the same appearance. However, it is likely that a patient with interstitial lung disease will have previous studies indicating that the appearances are stable, whereas in cardiac failure, the transient nature of the appearances may be a vital diagnostic clue.

TECHNICAL ASPECTS

The three criteria routinely reviewed to confirm the satisfactory quality of any chest radiograph are: rotation, inspiration and penetration. Penetration, using modern digital techniques is less relevant nowadays, so I will concentrate on the remaining two. A satisfactory chest radiograph should have no rotation. This is confirmed by ensuring that the medial borders of the clavicle are equidistant from the spinous processes of the vertebral bodies.

It is also important to ensure that the patient has made a good inspiratory effort. This is confirmed by ascertaining that there are ten ribs visible posteriorly in the mid clavicular line on the frontal chest radiograph. It is important at this stage to consider why these two technical factors are so important. Effectively, the answer is because in each case, failure to ensure the correct standard can mimic life-threatening pathology.

In the case of rotation, one side of the radiograph becomes darker than the other. This phenomenon is known as *increased transradiancy*. Therefore, one side becomes more transradiant (darker) than the other. The diagnostic error here is that the reviewer may misinterpret this difference in transradiancy as pathology. For example, the darker side may represent a pneumothorax, or pulmonary embolism (the *Westermark* sign). In addition, the lighter side may be misinterpreted as a pleural fluid collection or air space consolidation. This is particularly likely on a supine radiograph.

Poor inspiratory effort is equally important. Essentially, the problem is that with a poor inspiratory effort, the pulmonary vessels become more prominent and an erroneous diagnosis of cardiac failure (probably the single most common diagnostic error made by medical students on any chest radiograph) is all too easy. We will consider the criteria for cardiac failure shortly.

A SYSTEM FOR REVIEWING THE CHEST RADIOGRAPH

Having confirmed that the patient's details are correct and that the radiograph is technically satisfactory one should proceed to reviewing the chest radiograph in a systematic order. There are several such paradigms. This is the one that I use and recommend.

AP or PA Orientation?

The international standard for labelling a chest radiograph is that a PA (posteroanterior) standard film has no annotative marking on it. All other variations: anteroposterior (AP); the decubitus; supine, or semi erect are all so annotated for the reviewer's assistance. By definition the patients in this

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latter category are of increased infirmity and the diagnostic threshold can be challenging.

Radiology trainees are encouraged not to begin a report with reference to 'PA' or 'AP' but to vocalise the following introductory statement: "*This is a frontal chest radiograph of an adult patient*." (I am assuming of course that it is an adult!). Secondly, and if appropriate, one adds a second line, "*Both breast shadows are present*." In any examination context, in particular, this tactic has several advantages. Discussion about the orientation of the chest radiograph is often of limited value diagnostically, but also may represent an uncomfortable detour for a student who does not wish to be interrogated on archaic techniques of radiography. Secondly, there is good evidence to show that most abnormalities are appreciated on a chest radiograph within five to ten seconds. That is not to say that the diagnosis itself is made but the abnormality is recognised as such. By employing both these phrases the examination candidate has time to quickly review the image and look for any obvious abnormalities. In addition, checking that both breast shadows are present is an important exercise and discipline. Failure to recognise a second breast shadow suggests an underlining diagnosis of mastectomy and, therefore, should prompt a systematic review for evidence of breast cancer and its sequelae.

The Heart Size

The maximum transverse diameter of the heart should not exceed 50% of the maximum transverse diameter of the chest on a standard posteroanterior (PA) radiograph. This measurement is known as the *Cardiothoracic Ratio*. On the AP (anteroposterior) portable film there is a magnification factor of approximately 20% and this can present some difficulty in evaluating the cardiac size. However, it is worth stressing that precisely because there is a magnification factor involved, if the heart size is identified as normal on a non PA study, then there can be no cardiomegaly. Gross cardiomegaly should be easily distinguishable from a slightly magnified normal heart. It is, therefore, not correct to infer that the heart size cannot be assessed using an AP study. Difficulties do exist but there are sound principles allowing a logical diagnosis to be made.

Pulmonary Vascularity

When radiologists describe 'pulmonary vascularity' on our reports, we are discussing pulmonary *venous* vascularity. In other words, this is shorthand for the absence or presence of cardiac failure. Enlarged pulmonary arteries, as for example, in a left to right cardiac shunt, is given a specific designation: *Pulmonary Plethora*.

How does the reviewer ascertain that the pulmonary vascularity is normal? There are elementary rules to assist the reviewer:

1. Pulmonary venous vessels should not be discretely visible in the outer third of the lung fields.
2. Approximately 90% of the pulmonary vascular structures are appreciated at the mid and lower zones. This is an effect of gravity.
3. When pulmonary vascularity increases, for example, with heart failure, increased vascular conspicuity is apparent at the apices. This is known as *Equivalence* or *Upper Zone Diversion*. Evaluation of this is qualitative, and requires experience. Consequently, it is often helpful to view the image in a radically different form. If one is not sure whether the vessels are, in fact, more prominent in the upper zones than the lower zones, it is often helpful to flip the image vertically on the PACS system or turn the radiograph upside down. The reviewer's higher cortical and optic pathways will then have to consider the same question, but he or she has been presented with the data in a different way. Try it for yourself. Does the apex now look as you would expect it or not? Often this manoeuvre can be of great diagnostic help.
4. Kerley B lines, please see above.
5. Angel or Bat Wings. These are seen in the most severe form of cardiac failure, pulmonary oedema, and are very rare.

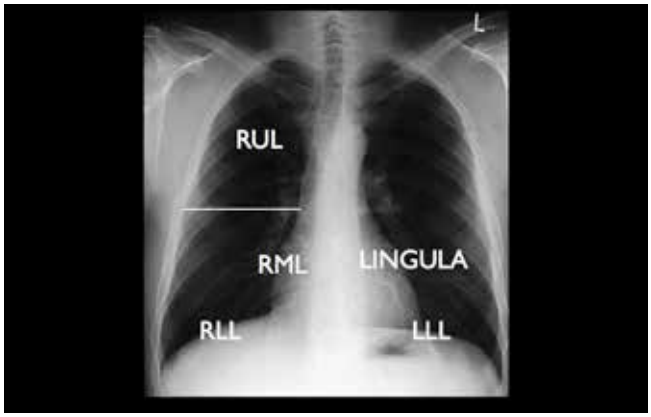

Fig 1. The Silhouette Sign. The diaphragm and heart borders are adjacent to lung lobes.

The Lung Fields

An American Radiologist named Benjamin Felson described *The Silhouette Sign*. He posited out that only three densities are visible on any radiograph. These are bone, air and soft tissue. The reason that we can appreciate one density, for example the heart shadow, is because it abuts a different density, and consequently, we see a silhouette. If that normal silhouette disappears, it implies that the adjoining area has now transmuted into the *same density* as its neighbouring structure, usually indicating lobar consolidation caused by infection. Therefore, all one needs to appreciate the location of the consolidation, is to know which lobe of each lung lies adjacent to the heart and hemidiaphragms. (Please see figure 1)

Review Areas

There are several review areas that a reviewer should consider in every chest radiograph, and it is useful to adopt an order for evaluating these, and then stick to it!

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1. Sub diaphragmatic region

   Pneumoperitoneum, in the absence of recent surgery, often denotes a life-threatening pathology and therefore its confident diagnosis is of crucial importance. On the erect chest radiograph there should be no free gas present under the diaphragm. On the left side, a gastric air bubble is frequently seen. On the right, interposed small or large bowel may occasionally be seen. This is known as *Chilaiditi's Sign* and usually presents little diagnostic difficulty, as the small bowel's valvulae conniventes or colonic haustra are easily distinguishable. Even very small quantities of free gas can be confidently seen under the right hemidiaphragm and this should represent an essential review area (fig 2).

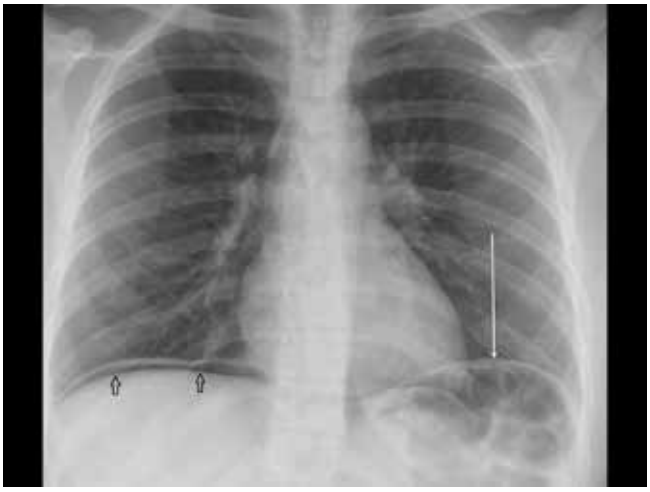

Fig 2. Right-sided pneumoperitoneum and on the left, Chilaiditi's sign.

2. The Lung Apices.

   Evaluating the lung apices can be difficult. This is particularly the case in the older patient where there is asymmetrical calcification of the costochondral junctions. This age-related calcification can mimic a neoplasm. If there is diagnostic uncertainty, or an asymmetry in the apical appearances, the simplest solution is to request a supplementary *apical view (figs 3,4)*. Technically, this allows visualisation of the lung apices without the complication of overlapping bony structures. The apical view is almost always performed to reassure a patient (or his clinician) that the index of suspicion is low, but occasionally it will confirm quite a sizable mass lesion.

3. Trachea

   The trachea is often deviated by pathology within the neck or chest and ascertainment that it is midline is essential. The commonest neck mass to displace the trachea is a thyroid mass, which will displace it to the contralateral side. Within the chest, a tension pneumothorax will displace the trachea to the contralateral side, while collapse or atelectasis of a lobe will draw the trachea towards the side of the abnormality.

4. The Hilum

   The *hilar point* on either side of the heart represent the intersection of the pulmonary arteries and veins. The left hilar point normally lies higher than the right. Aside from this, the hila should always be equal in size and density.

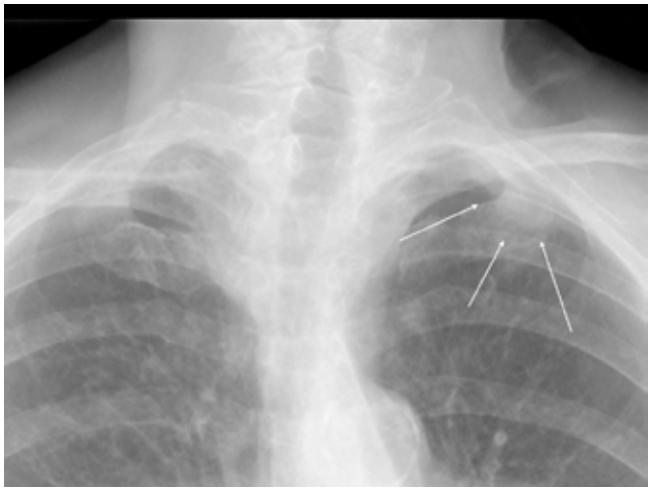

Fig 3. Subtle left apical mass on chest radiograph (arrows).

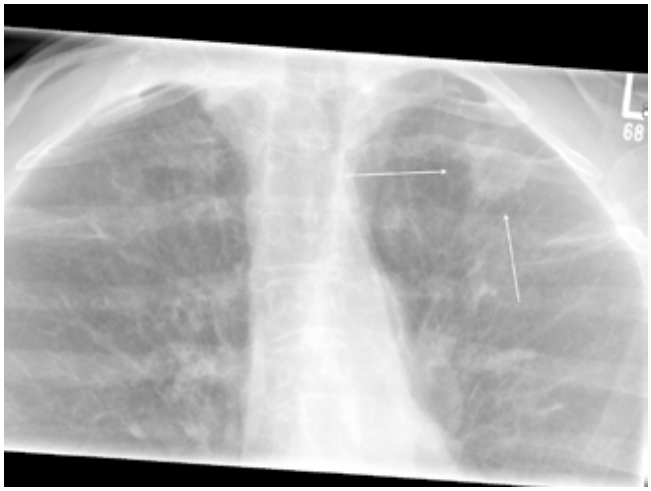

Fig 4. Apical view reveals a distinct neoplasm at the left apex (arrows).

5. The Aorto-pulmonary Window

   As the reviewer follows the left edge of the mediastinum from its superior aspect, the first convexity seen is that of the aortic knuckle. If one traces the edge of the aortic knuckle inferiorly, the next convexity is that of the pulmonary artery. Between the two there is a concavity. There should be nothing within this aorto-pulmonary bay or window. It is very important that review of this window is performed in every chest radiograph. It is well recognised that malignant lymphadenopathy associated with a neoplasm can manifest itself within this window. This may potentially be the only opportunity for the clinician to affect curative therapy. However, it does require the reviewer to understand the fundamental importance, of confirming the emptiness of the normal window.

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6. Bones

   I would suggest that this is the last review area. Contemporary chest radiographs use a technique known as '*high kilovoltage*' (kV). This technique was developed to permit improved evaluation of the chest organs. The cost was that conspicuity of bone decreases. This can be unfortunate, particularly, when looking for rib fractures (which, incidentally, typically occur along the lateral margins of the lower chest). The identification of any rib fracture should prompt the immediate radiological exclusion of pneumothorax.

   Bone review effectively is performed for two reasons:

   a) Trauma: to exclude fractures or dislocations, particularly at shoulder level.

   b) Neoplasia: to exclude infiltration and destruction particularly in metastatic disease and myeloma.

Commenting on bone patterns viewed through the lung parenchyma can be difficult. The highest diagnostic yield is to review bones that are not seen through a haze of lung tissue and pulmonary vessels. Therefore, the shoulder joints, lateral clavicles and lower ribs (that overlie the liver and spleen) provide better diagnostic accuracy for infiltrative bone disease.

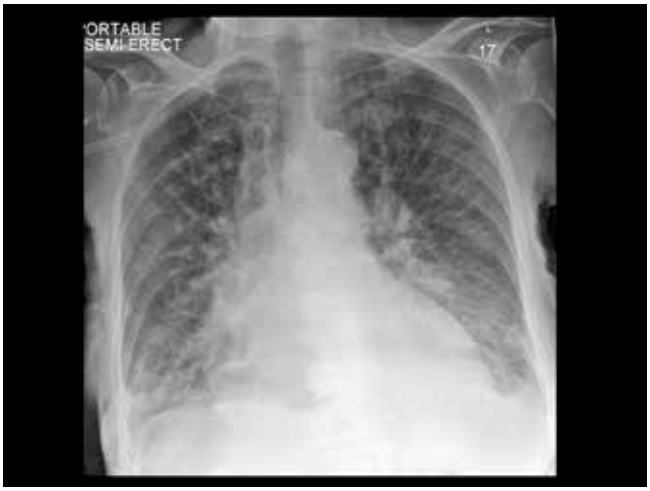

Fig 5. Cardiac Failure.

COMMON PATHOLOGIES

CARDIAC FAILURE

Using our schematic method, the following criteria will help formulate a diagnosis of cardiac failure (Fig 5).

1. Increased cardiothoracic ratio
2. Increased (venous) pulmonary vascularity
3. Kerley B lines
4. Pleural Effusions
5. Bat or Angel Wings

LOBAR CONSOLIDATION

The confident and accurate diagnosis of lobar consolidation rests on an understanding of the silhouette principle as described by Felson. In the annotated chest radiograph (fig 1) all one must do is confirm which silhouette is missing. The appropriate pulmonary lobe can then be identified (fig. 6). These are:

Left lower lobe: Left hemidiaphragm

Right lower lobe: Right hemidiaphragm

Right heart border: Right middle lobe

Left heart border: Lingula.

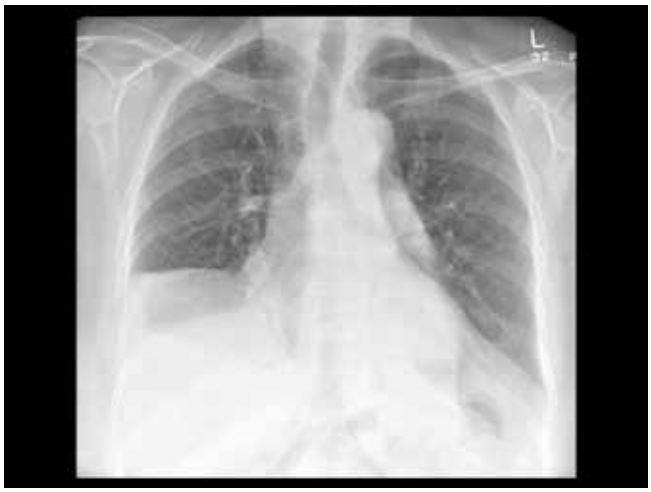

Fig 6. Lobar consolidation involving the right middle lobe, right lower lobe and left lower lobe.

Consolidation in the upper lobes follows the same principle but is slightly different. On the right hand side, the lung is demarcated by the transverse or minor fissure. Consolidation above, and terminating at, the minor fissure indicates right upper lobe consolidation. Consolidation below, and terminating at, the transverse fissure, delineates the right middle lobe. Consolidation of the left upper lobe tends to produce a fuzzy 'veiling' effect with consequent reduced conspicuity of the aortic knuckle's silhouette.

PNEUMOTHORAX

Pneumothorax is divided into the *simple* and *tension* pneumothorax. The tension pneumothorax is diagnosed radiologically when the mediastinum is displaced to the contralateral side and there is inferior displacement of the ipsilateral hemidiaphragm (fig) 7. Accompanying clinical distress is of course also present.

In an otherwise fit and conscious patient, a pneumothorax is seen as the separation of lung edge from the chest wall. This is maximal on expiration because of the relatively increased interpleural pressure, and therefore if there is a clinical suspicion of pneumothorax it is worth requesting an expiratory view.

At this point it is worth discussing an artifact or mimic that

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may occur in both infant chest radiographs and adult non-PA chest studies. This is the *skin fold* and represents the interposition of redundant skin between the patient's back and the X-ray cassette. The appearances can look dramatically like a pneumothorax but careful evaluation will reveal the fact that the pulmonary vessels are seen to cross the 'lung edge' indicating that there is no pneumothorax. Clearly it is also vital to place such a diagnosis within its clinical context.

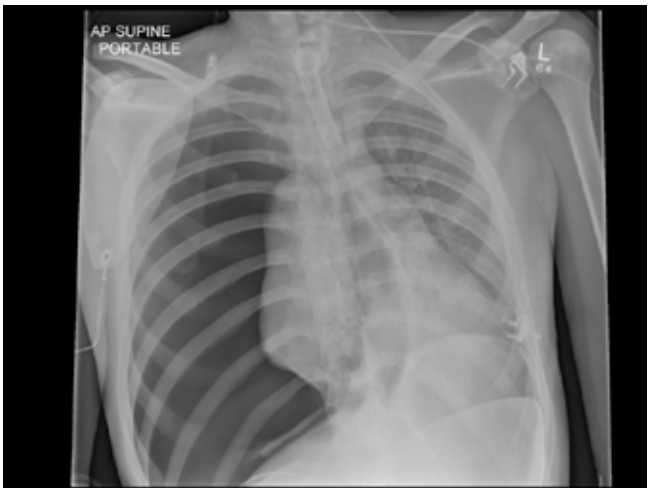

Fig 7. Right-sided tension pneumothorax.

Diagnosis of pneumothorax in the supine patient can be problematic. The lung edge may not be appreciable. However in these patients, the normal costophrenic angle may disappear and be replaced with a 'sausage-shaped' *Deep Sulcus* sign. Identification of this sign (fig 8) in such a patient should raise the possibility of a pneumothorax.

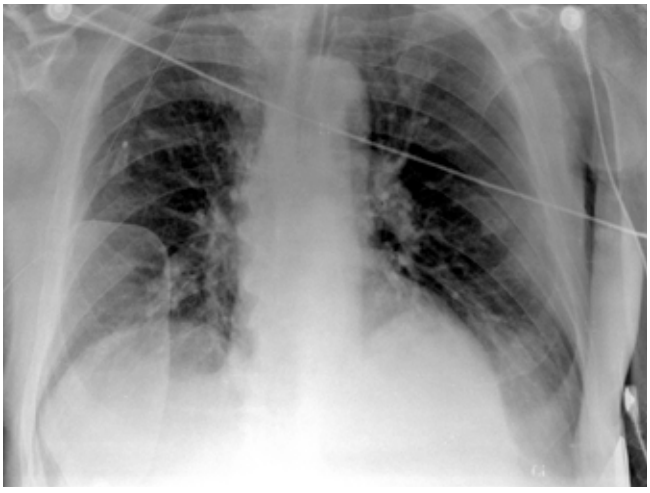

Fig 8. Supine radiograph: Deep Sulcus Sign indicating a left pneumothorax.

PLEURAL EFFUSIONS

Because the chest radiograph is relatively insensitive and can discriminate only air, soft tissue and bone, it is not possible to separate in terms of density, transudates and exudates. The typical appearances of pleural effusion on an erect radiograph are those of an area of increased density with a meniscus rising up the lateral chest wall. This meniscus reflects the negative intrapleural pressure of fluid within the pleural space (fig 9). A horizontal fluid level within the chest, however, suggests a hydropneumothorax with air in the pleural space. Remember also that if the mediastinum is not displaced in the presence of a pleural effusion, this indicates underlying collapse of the ipsilateral lung segment or lobe.

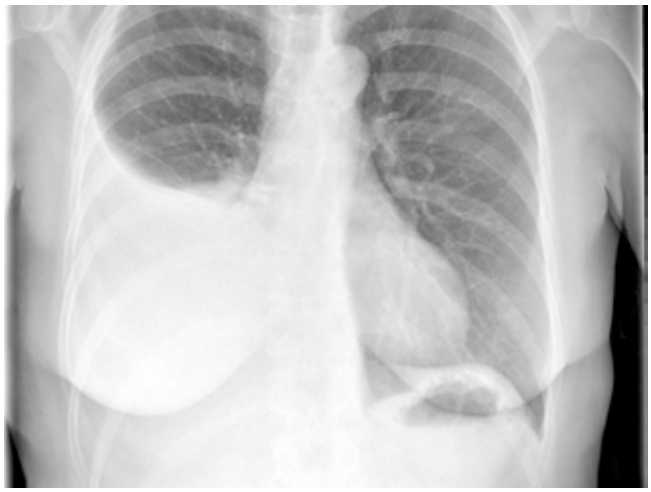

Fig 9. Pleural effusion, right side.

As with the pneumothorax, diagnosis of pleural effusion can be problematic in the supine, unconscious or trauma patient. In these individuals the likely diagnostic sign will be a difference in transradiancy, as previously described. In other words the abnormal lung is lighter than the normal lung. This is because the fluid is now tracking along the posterior pleural space (see figure 10). This emphasises the importance of ensuring that the visualised difference in transradiancy in not the result of a malrotated chest radiograph.

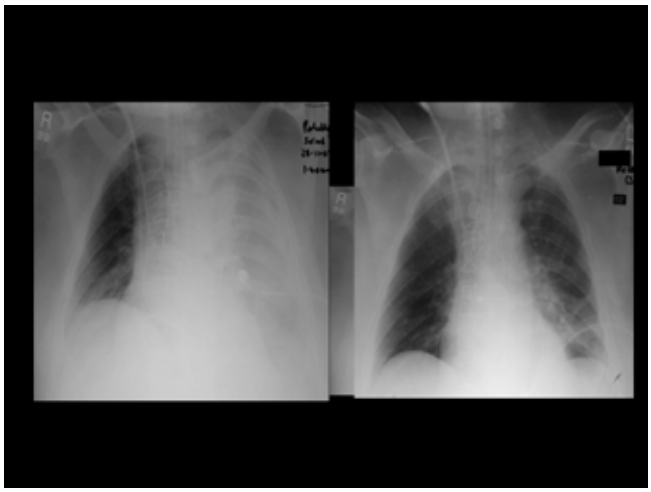

Fig 10. Supine radiograph. Left pleural effusion before and after manipulation of chest drain.

LINES AND TUBES

1. The Nasogastric Tube

   Misplaced nasal gastric tubes are a frequent feature of hospital life. The penalty however for commencing nasogastric feeding when the tube is misplaced within in the bronchus can be very high. The correctly placed

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nasogastric tube should assume a vertical orientation within the chest and pass below the diaphragm. The tube should then be seen projected over the left upper quadrant of the abdomen often crossing the midline to the right, to lie within the gastric atrium. The commonest location for a misplaced nasogastric tube is within the right or left lower lobe bronchus (fig 11).

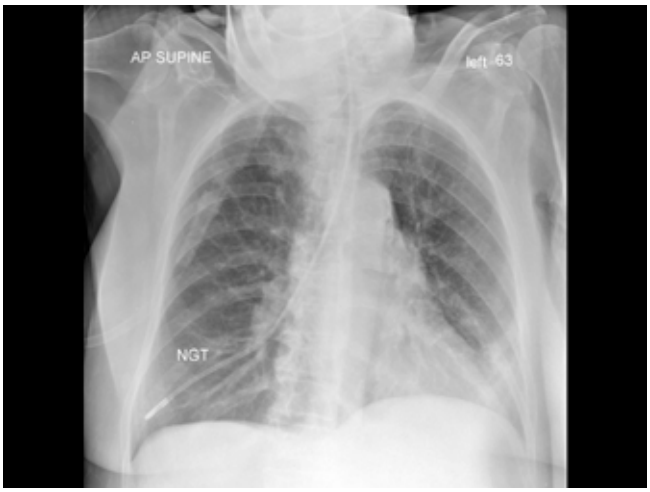

Fig 11. Misplaced nasogastric tube in the right lower lobe bronchus.

2. The Central Venous Line

The tip of the central venous line should lie at the junction of the superior vena cava and the right atrium (fig 12). The reviewer should always ensure there is no associated pneumothorax.

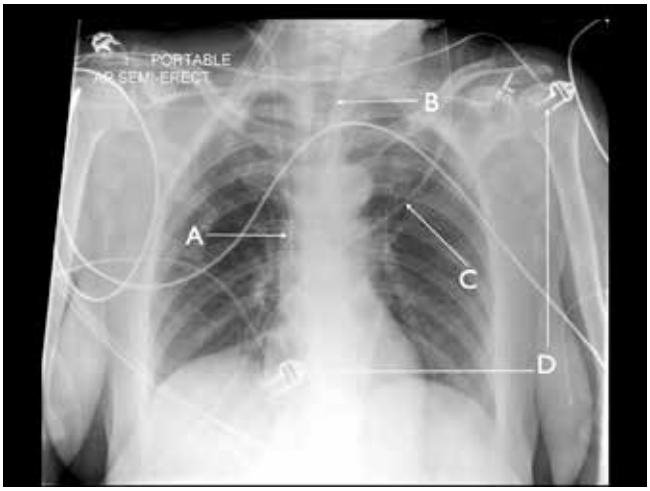

Fig 12. Lines and tubes. (A):central venous line; (B):endotracheal tube; (C): oxygen tubing; (D): ECG electrodes.

3. The Endotracheal Tube

The tip of the endotracheal tube should lie above the level of the tracheal bifurcation or *carina*. Various tests have been suggested; some advocate placement of the tube tip midway between the sternoclavicular joint and the carina, and others use a qualitative measurement of between two to five centimetres above the carina (figure 12). The problem with a chest tube tip at the carina itself is that with respiration it will slide into the right main bronchus obstructing the left and potentially causing left lung collapse.

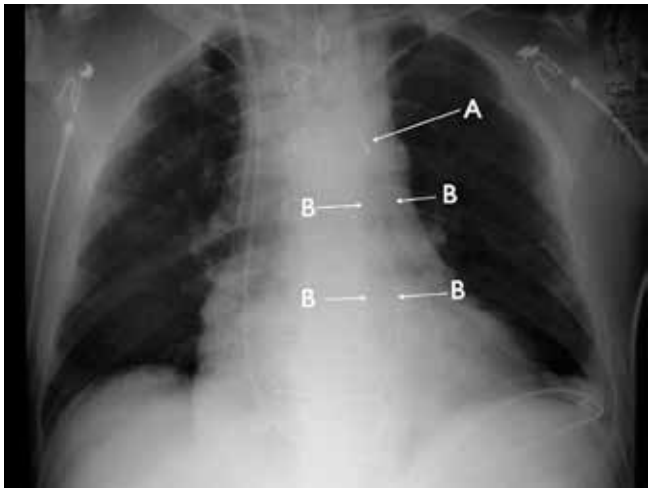

Fig 13. Aortic Balloon Pump: (A): marker indicating cranial end of pump; (B): Inflated balloon.

4. The Aortic Balloon Pump

The aortic balloon pump lies within the descending thoracic aorta. The upper or cranial end of the balloon is marked with a small radio opaque marker (fig 13) . Below this marker there is a 10 cm balloon. The balloon should lie *between* the left subclavian artery and the renal arteries, in order not to obstruct either. The reviewer, therefore, should ascertain that the radio opaque marker is not higher than the aortic knuckle (considering it as a clock face, I use the 'three o'clock position' to mark the ostium of the left subclavian artery). In addition, if the marker is identified at the mid thoracic aortic level, it suggests that the balloon may occlude the renal and splanchnic ostia.

CONCLUSIONS

In this overview, I have attempted to guide the examination candidate with an elementary, structured schematic, for reviewing a chest radiograph. For the junior doctor, the commonest lifesaving diagnoses to make are those of cardiac decompensation, lobar consolidation and the pneumothorax. Although there is no substitute for experience and reporting large numbers of chest radiographs, using these tools, I would hope that the reader has one logical framework for the evaluation of basic pathologies.

My sincere thanks to Ms Lyndsey O'Neill for typing the manuscript.

The author has no conflict of interest

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Ulster Med J 2012;**81(3):**148-152

Medical History

James Alexander Lindsay (1856-1931), and his clinical axioms and aphorisms

Caoimhghin S Breathnach, John B Moynihan

Accepted 28 June 2012

ABSTRACT:

John Alexander Lindsay was born at Fintona, county Tyrone in 1856, and at the age of 23 he graduated in medicine at the Royal University of Ireland. After two years in London and Europe he returned to Belfast to join the staff at the Royal Victoria Hospital and in 1899 he was appointed to the professorship of medicine. He was valued by the students for his clarity and by his colleagues for his many extracurricular contributions to the medical profession in the positions entrusted to him. He published monographs on Diseases of the Lungs, and the Climatic Treatment of Consumption, but his later Medical Axioms show his deep appreciation of studied clinical observation. Although practice was changing in the new century Lindsay displayed an ability to change with the new requirements, as evidenced by his lecture on electrocardiography as president of the section of medicine of the Royal Academy of Medicine in Ireland in 1915. He was impressed by the way the string galvanometer changed attention from stenosis and incompetence of the valves to the cardiac musculature, but rightly suspected that there was more to be told about the state of the myocardium than Einthoven's three leads revealed. His death occurred in Belfast in 1931.

CAREER

The original James Lindsay emigrated from Ayrshire in 1678 and farmed between Derry and St. Johnstone before his family settled on an extensive farm at Lisnacrieve, one Irish mile south-west of Fintona, county Tyrone, in the middle of the eighteenth century. Spinning was at that time a cottage industry, and in July 1822 his descendants, John and David, established the 'Woollen, Linen and Haberdashery Warehouse' in Donegall Place, Belfast. Their business thrived and in October 1858 they opened a retail business at the Ulster Arcade specifically built for the purpose. James Alexander Lindsay, the son of David the successful Belfast textile merchant anxious that his offspring be born at the family homestead, first saw the light at Lisnacrieve House, Fintona, on 20 June 1858. [1] He was educated at the Royal Academical Institution, Methodist College and Queen's College Belfast, graduating BA in 1877, MA in ancient classics in 1878 and MD, MCh in the Royal University of Ireland in 1882. After two years in the clinics of London, Paris and Vienna he returned to Belfast where he was appointed assistant physician at the Royal Victoria Hospital in 1884 and full physician in 1888 until 1921. In 1899 he succeeded James Cuming in the chair of medicine, and held that position until 1923, the year he published his Medical Axioms, Aphorisms, and Clinical Memoranda. He took the membership and was elected a fellow of the Royal College of Physicians of London in 1903 where he delivered the Bradshaw Lectures in 1909 on the evolutionary relationships between structure, disease and race in 'Darwinism and medicine'. [2]

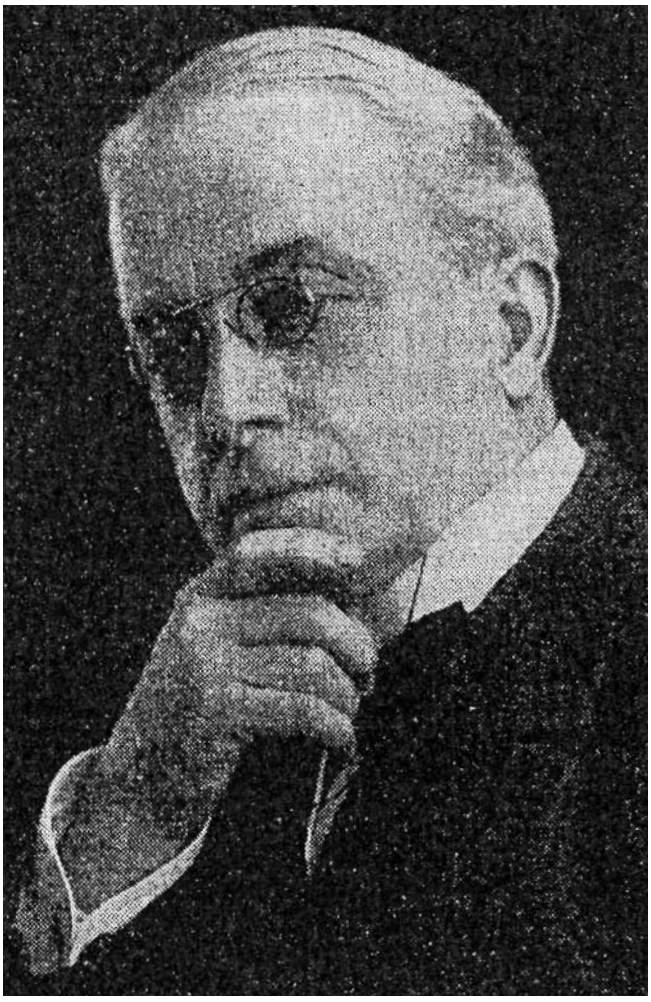

Fig 1. James Alexander Lindsay.

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His duties as a teacher he took seriously, and 'as a clinical teacher he shone with a rare ability; his clearness of vision and crystal clarity of diction rendered his instruction of rare quality and inestimable worth to the student'. Widely travelled he was of broad scholarly distinction for his reading included philosophy, religion and the classics as well as medicine. Many important positions were entrusted to him in the medical organisations he joined; these included the Ulster Medical Society, the Royal Academy of Medicine in Ireland, the Association of Physicians of Great Britain and Ireland and the Aristotelian Society. He served on the central council of the British Medical Association from 1896 to 1899, was president of the Ulster Branch in 1905, and was president of the Section of Medicine at the Annual Meeting in 1909 when the Queen's University celebrated the centenary of the medical school. Even in retirement he had the development of the Belfast medicine at heart: his efforts contributed to the amalgamation of the Royal Maternity Hospital and the Royal Victoria Hospital. For many years he provided editorial assistance to the British Medical Journal and The Lancet. His death occurred on 14 December 1931 in Belfast from cerebral thrombosis. [3, 4]

In his history of the Royal Victoria Hospital, Richard Clarke records that James Lindsay was the first house physician appointed at the Belfast Royal Hospital, where he became Assistant Physician in 1883 and Attending Physician 1888 (Fig 1). He belonged to the school of physicians who concentrated on accurate diagnosis, and that with the aid of his own senses and acumen, but had little interest in medical treatment; he never took up such artificial aids as electrocardiography, although it has to be said in his defence that he learned how to identify the waves defined by Einthoven. This pedantic approach was crystallised in the instruction cards of technique for examination of patients that he published. His lectures also were precise and old-fashioned, delivered at dictation speed throughout, to provide notes for future reference, as was common until good textbooks became more freely available in the 1950s. Lindsay was succeeded in the chair of medicine by William W D Thomson (8.9.1885-26.11.1950) the last of the old-style professors of medicine, who made their mark not by research but by bed-side teaching, and indeed he was the last of the part-time professors of medicine. [4]

ELECTROCARDIOGRAPHY IN BELFAST (1915)

As President of the Section of Medicine of the Royal Academy of Medicine in Ireland he read a paper on 'Some observations upon the electrocardiograph, with notes on cases' on 12 November 1915 in The Royal College of Physicians in Dublin. [7] Einthoven (1860-1927) around 1905 handed over construction of his string galvanometer to the Cambridge Instrument Company whose cardiographs were delivered to physiological laboratories between 1905 and 1907; this company was preferred by the inventor over Edelmann and Sons of Munich who had manufactured the earlier instruments for him.[8]

He began his paper by introducing the history and design of Einthoven's string galvanometer, admitting that his 'own experience with the instrument' was limited to little more than a year. The Dutchman's invention is 'sufficiently delicate to give adequate results … When we examine the photographs of the string movements we observe a series of waves, 'curves' or 'deflections' which are repeated regularly, each series representing the cardiac complex with the intervening pauses'. (Figures 2 and 3). Without identifying them by name

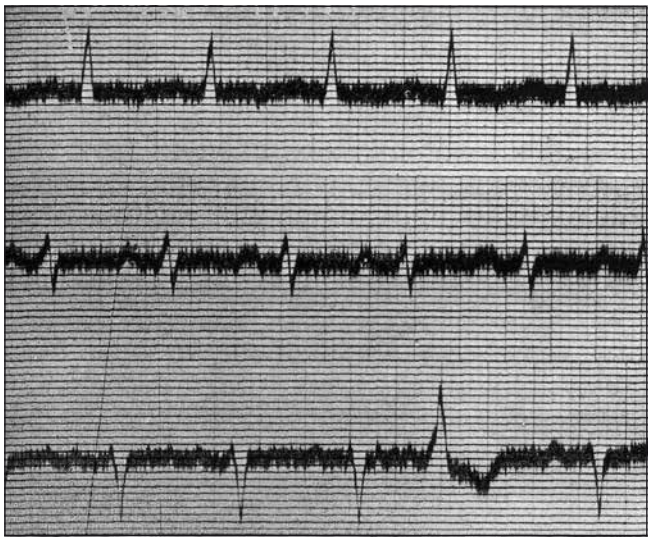

Fig 2. Leads I, II and III recorded by the string galvanometer. Spread of electrical excitation into ventricular muscle generates the QRS complex. Left ventricular preponderance is indicated by high R in Lead 1 and deep S in Lead III.

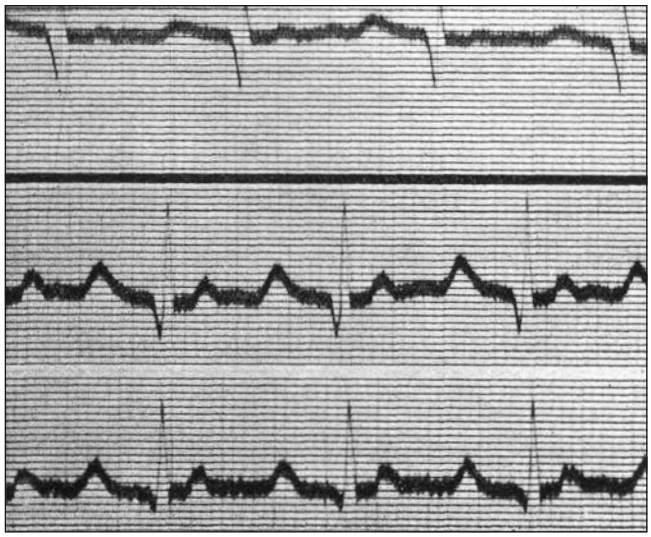

Fig 3. Mitral stenosis eases the load on the left ventricle and increases the work of the right ventricle. A deep S in Lead I and a high R in Lead III typify right ventricular hypertrophy.

Lindsay paid tribute to Mackenzie and Einthoven:

> 'amongst the recent advances in medicine an important place must be assigned to the development of instrumental methods of observation in connection with the heart in health and disease … the polygraph and the electrocardiograph add new important facts … By their instrumentality the heart writes its own message, and the cardiac script can be interpreted … we get the phenomena of disease at first hand: observation is made for us; our task is that of interpretation. … In Belfast we are much indebted to Dr. Ilwaine and Professor Milroy. [7]

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Thomas Hugh Milroy (1869-1950) was appointed professor of physiology in 1902. Dr. Ilwaine was in fact the recently appointed assistant physician John Elder MacIlwaine (1874-1930), an electrocardiographic enthusiast who persuaded James Mackie (1864-1943) of the Albert Foundry to purchase the Einthoven machine; in 1921 he was promoted attending physician and succeeded to the chair of materia medica held by Sir William Whitla (1851-1933). [6]

Further, Lindsay stated openly that he was also much indebted for a large part of his information to the writings of [Thomas] Lewis (1881-1945) [7], who says ' The records from patients are clear messages writ by the hand of disease, permanent and authentic documents, which silence dogma.'. [9] Lindsay concluded his paper

> The electrocardiograph is a marvel of ingenuity … [that] has compelled us to think out old problems from a new angle. It has helped us to fix attention upon the cardiac musculature, rather than on the cardiac valves: But I should be the first to deprecate any exclusive reliance upon instrumental methods in the study of heart disease. The final test of cardiac sufficiency or insufficiency is the appeal to experience. Clinical observation in the broad sense of the term is in the long run more trustworthy than any form of mechanical or instrumental record, but the two should supplement, not supplant, each other. [7]

Professor Thompson (c1860-1918), professor of the institutes of medicine at Dublin University who had been Dunville professor of physiology at Queen's College Belfast from 1893-1902 , inquired whether the large number of tracings shown were the work of the President, who answered adroitly that 'all had been obtained in the Victoria Hospital, Belfast'. He was not a devotee of instrumental methods, but they eliminated 'the personal factor' – a most important quality. [7]

AS AUTHOR

Robert Koch's identification of the causative organism, though a hugely important landmark did not lead immediately to any change in the treatment of consumption, and Lindsay, seeing cases so frequently, tried to assess the value of the highly popular – and expensive, approach in The Climatic Treatment of Consumption (1887) even travelling twice to New Zealand. Of the Home Sanatoria he decided ' Queenstown (now Cobh) and Glengarriff (both in county Cork) are well worth the attention of Irish patients who prefer to remain in their own country. Rostrevor can only be recommended to those living in the neighbourhood who are unwilling to undertake the long journey necessary to reach more desirable sanatoria. [10]. Tuberculosis was still rife in Ireland in 1906 and was given one third of the volume when he prepared the second edition of his Lectures on Diseases of the Lungs. The causes and management of haemoptysis, not surprisingly, were considered in detail. He had to admit that 'most writers affirm the existence of 'vicarious' haemoptysis' but he was doubtful if a true haemoptysis occurs in, for example, patients suffering from amenorrhoea. [11]

In his answer to professor Thompson's loaded question Lindsay admitted that while he knew his Ps and Qs and the R^{e}ST of the trace made with the Einthoven string galvanometer, he was not an electrocardiologist. Of the three categories of physicians recognised by Claude Bernard (1813-1878), Hippocratic, empiric and experimental, he saw himself among the Hippocratists: 'For their part, the Hippocratic physicians are satisfied when they have succeeded in clearly describing a disease in its source, in learning and foreseeing its various favourable or direful endings by exact signs, so as to be able to intervene, if necessary, to help nature and to guide it to a happy ending'. [12] This helps to explain Lindsay's reverence for aphorisms, pithy generalisations embodying clinical wisdom and proverbs, and his practice of distributing aide memoir cards mentioned by Clarke. The experimental enterprise envisaged by Bernard has been so successful that it has led to a flowering of investigative medicine that had so overgrown and outdated clinical aphorisms that it behoves us to recall the wisdom of the ancients that so enthralled Lindsay, (who added his own after making the collection).

LINDSAY'S COLLECTED APHORISMS (1923) [13]

Hippocrates (c470- c400)

Life is short, the Art is long, Occasion sudden, Judgment difficult.

The physician should possess the following qualities: learning, wisdom, humanity, probity.

The nature of the body can only be understood as a whole.

To the love of his profession the physician should add a love of humanity.

Whoever is desirous of pursuing his medical studies on a right plan must pay a good deal of attention to the different seasons of the year and their respective influence.

Neither hunger nor anxiety, nor anything that exceeds the natural bounds, can be good and healthful.

Old men easily endure fasting; those who are middle-aged not so well; young men worse than these; and children worst of all, especially those who are of a more lively spirit.

GREEK MEDICINE IN ROME

Physic is not always good for the sick, but it is always hurtful to the healthy. (Cicero)

Hippocrates said he must needs succeed well in cures that considers and understands such things as are common and proper. (Celsus)

We ought not to be ignorant that the same remedies are not good for all. (Celsus)

Laziness slackens and dulls the body, but labour strengthens and makes it firm. The former hastens old age; the other prolongs youth. (Celsus)

Idleness and luxury first corrupted men's bodies in Greece, and afterwards afflicted them in Rome. (Celsus)

Rest and abstinence are the best of all remedies, and abstinence alone cures without any danger. (Celsus)

Death is intimated when the patient lies back with knees drawn up [together]. (Galen)

It is a distinguishing human trait to supplicate the gods for

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good health. (Galen)

The art of healing depends on local conditions / the physician is nature's assistant. (Galen)

The best physician is also a philosopher. (Galen)

RENAISSANCE

If your doctors fail, let these three be your physician: a cheerful mind, rest, and well regulated diet. (Motto of School of Salerno).

Wisdom is the daughter of experience. (Leonardo)

The sick should be the doctor's books. (Paracelsus).

'Tis a patient and quiet mind (I say it again and again) gives true peace and content. (Cardan)

I dressed him; God cured him. (Paré)

Discuss the coming on of years, and think not to do the same things still; for age will not be denied. (Bacon)

Experience is the mistress of doctors. (Sydenham).

Cleanliness is conducive to elegant health. (Sydenham).

Let me be sick myself if sometimes the malady of my patient be not a disease to me (Sir Thomas Browne).

THE CLINICIANS' CENTURY

The whole art of medicine is in observation. (Louis)

Relief should be the aim of the physician when it is not possible to cure. (Trousseau).

The trouble with most doctors is, not that they don't know enough but that they don't see enough. (Corrigan)

Never look surprised at anything. (Syme).

Never ask the same question twice. (Syme).

The speed of life is not the same for all. (Paget).

Living to old age 'goes in families'; and so does dying before old age. (Paget)

I am sure of this: that as the justly successful members of our profession grow older and probably wiser, they more and more guide themselves by the study of their patient's constitution, learning more of family histories, and detecting constitutional diseases more skilfully in signs which to others seem trivial. (Paget).

Health is that state of mind in which the body is not consciously present to us; the state in which work is easy and duty not too great a trial; the state in which it is a joy to see, to think, to feel to be. (Clark).

A sane mind consists in a good digestion of experience. (Allbutt).

The best physician is the most conscious of the limitations of his art. (Jowett).

The first qualification for a physician is hopefulness. (Little).

Every medical student should remember that his end is not to make a chemist, or a physiologist, or an anatomist, but to learn how to recognise and treat disease, to become a practical physician. (Osler).

I hold that no man is fit to teach medical students unless he himself is a qualified practitioner and maintains his knowledge in a state which would permit him to ply his real vocation. (Keith).

In acute affections we concentrate our attention upon the diseased organ, while in chronic affections we keep the general condition of the patient more in view. (Van Noorden)

LINDSAY THE APHORIST / LINDSAY'S OWN APHORISMS

And having surveyed the sages he distils wisdom from his own experience (p 48 f) [13]:

Medicine is an art, but it is an art which is always trying to become a science.

Attack disease at its beginning – obsta principiis

Few studies are more instructive, more full of warning, or more generally neglected than the study of the history of medicine.

Nature is a good physician but a bad surgeon.

Extreme specialism was one of the causes of the decay of medicine in Ancient Egypt.

Think of common diseases first.

'Queer cases' are usually abnormal types of common conditions.

In searching for the obscure, do not overlook the obvious.

Remember that many symptoms are part of Nature's defensive mechanisms.

In dealing with disease, think of disordered function as much as of damaged structure

It is rarely permissible to base a diagnosis upon a single sign.

For one mistake made for not knowing, ten mistakes are made for not looking.

Weigh your patients, and attach much value to the indications of the weighing machine.

Vulnerability to disease may be local rather than general – i.e. it may be due to some structural defect rather than to general constitutional weakness.

There are few things more difficult than to establish a fact in therapeutics. The post hoc ergo propter hoc fallacy is rampant. The history of medicine is full of the records of fictitious cures.

Tell the elderly not to forget Anno Domini.

For many patients hope is the best medicine.

At the bedside a great deal too much optimism is a venial error compared with a little too much pessimism.

Get a clear answer from every patient to three fundamental

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questions:

a What do you complain of,

b How long have you been ill,

c How did it begin?

In every case of serious illness someone, not necessarily the patient, should know the truth.

When disease takes an unexpected turn, or treatment after due trial proves ineffective, reconsider the diagnosis.

Always ask the question, How is the patient reacting to his malady?

Every disease has a psychological as well as a pathological aspect. The patient's mentality counts for much in his response to treatment.

The doctor 'suggests' even when he makes no conscious effort at suggestion..

A CLOSING WARNING ON AXIOMS

'Gifted with a mind at once scholarly and judicial, Lindsay believed that the teacher's function was to instruct the student how to learn and how to think' [2], and his axioms and aphorisms [13] were intended as clinical memoranda to help the practitioner in making diagnostic decisions in his daily encounters with illness. A man of such gifted clinical acumen cannot have seen them as infallible guides: axioms are subject to the universal law that no rule is free from exceptions, as his younger contemporaries were aware. In a lecture on hyperthyroidism Thomas Gillman Moorhead (1878-1960) reminded his listeners that 'Graves's disease has been defined as one from which no one can recover, and of which no one ever dies', and remarked 'The aphorism is useful, though, like most aphorisms it overstates the facts'.[14] A few years later, in an international review of medical proverbs, aphorisms and epigrams Fielding H Garrison (1890-1935) warned readers: 'Apart from the larger aspirations and ideals of great physicians, aphorisms about medicine are to be approached with extreme caution and are best taken in small doses. Science cannot be reduced to a pocket formula'. And he concludes that there is the wisdom of deep feeling in the monody of the Irish poet:

> The silliest charm gives more comfort to those in sorrow and pain,
>
> Than they will ever get from the knowledge that proves it foolish and vain;
>
> For we know not where we come from and we know not whither we go,
>
> And the best of all our knowledge is how little we can know. [15]

The (unidentified) poet was William Edward Hartpole Lecky (1831-1903) whose Friendship and other poems (1859) was so poorly received that he transferred his allegiance to Clio with spectacular success in Dublin University.

ACKNOWLEDGEMENTS

We are grateful to Robert Mills, Librarian RCPI and Dr. Ted Keelan, cardiologist, Mater Misericordiae Hospital, Dublin.

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Letters

TEACHING RADIOLOGICAL ANATOMY

Editor

Utilising postgraduate trainees to deliver undergraduate teaching is a logical and well established practice. Undergraduate cadaveric anatomy, once the exclusive domain of the surgical demonstrator, has in many institutions dissected itself out of existence. The rationale, if subjected to the same dissection, was in essence too many facts and too costly when software simulation is too sexy to withstand. The consequences, whilst debated in many learned papers are sublimely demonstrated in a BBC documentary "Where's the femur? " (first broadcast Radio 4 Jan 2008), the title referring to a witnessed exchange between two junior doctors. Populism aside, renewed emphasis on basic science is returning to the undergraduate curriculum and fortunately Queens University Belfast has kept it's dissection module intact. Notwithstanding there is laudable enthusiasm for multimodality input and potential for symbiotic learning across the perceived 'MB' divide.

In response an Applied Anatomy class was introduced at the completion of each anatomical module for the academic year of 2011/2012 (first and second year students). Links between clinical radiologists and anatomy departments are well documented, as is the impression of symbiotic mutualism for student and post graduate trainee, which although rational, is difficult to prove. The format over a two hour class involved dividing the students into 7 to 8 groups and rotating them around a matching number of 'stations' at 8 minute intervals. The stations were taught by first year Radiology Registrars preparing for their own FRCR anatomy exam, each addressing different imaging modalities/anatomical regions. On reflection I felt it would be churlish to restrict teaching material to radiological imaging when the students could feast upon the relative technicolor of endoscopy or handle some of the Orthopods expensive hardware – live clinical anatomy. Registrars from Neurosurgery, Cardiology, Respiratory medicine, Orthopaedics and Vascular surgery were thus coerced to attend relevant sessions. Whilst not guaranteeing an additional transfer of anatomical knowledge, at least encountering an endovascular stent, footage of a bronchoscopy, a ventricular shunt or a hip prosthesis etc confirmed relevance of the subject beyond the next exam. Happily the Radiology Registrars all passed their exam and unofficial feedback from the students was favourable, so at worst we have observed commensalism, at best mutualism.

The venue of the anatomy speed dating sessions were in the Dissection Room, which I think is important. The cadavers bear witness to forms of enlightenment which can only be gained via their recent exploration. Ofcourse similar unique perspectives are gained by the contemporary medical imagery surrounding them and many centres are opting for 'simulation only teaching'. I feel the latter is misguided; illuminating difficult concepts from different angles frequently diminishes confusion. Other exclusive benefits of the dissection room are an introduction to the essential clinical paradox of desensitisation and humanity. Anonymous 3D images do not have the physical impact factor or the realisation that this aorta or this hand were used by an individual when they decided to afford the student the present learning experience.

The aim of the current module was to present some relevant clinical 'coat hangers' for the students newly purchased anatomical clothes. At this stage they have an impressive wardrobe, although as all previous generations can testify this diminishes with the wear and tear of time. If in the future all that remains is some well worn underwear and an odd sock at least the Queen's student won't be completely naked.

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TWO CASES OF IMPORTATION OF NEW DELHI METALLO-β-LACTAMASE 1 INTO NORTHERN IRELAND

Editor,

Multi-drug-resistant Gram-negative pathogens are increasingly isolated at hospitals around the world. We report two cases of colonisation and infection with *Enterobacter cloacae* strains producing New Delhi Metallo-β-lactamase 1 (NDM-1), not previously reported in Northern Ireland.

Case 1: A 6 year-old-boy on holiday in India suffered electrical burns to 60% of his body. On day 10 he was airlifted back to the regional paediatric ICU. On day 20 both a swab of burns on his left leg and the tip of a femoral line removed that day, grew multi-resistant *E. cloacae*. Both *E. cloacae* isolates were retested at the Health Protection Agency (HPA) Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) which found carbapenem resistance in the leg isolate (Table 1). This isolate was positive by PCR for $bla_{\text{NDM-1}}$ encoding NDM-1 β-lactamase. The femoral line isolate lacked NDM-1 enzyme, but had an extended-spectrum β-lactamase (ESBL). Pulsed-field gel electrophoresis showed that these *E. cloacae* were distinct strains. Thankfully, the patient did not require antimicrobial treatment for these *E. cloacae* strains, and was discharged on day 91.

Case 2: A 46 year-old man presented with a wound infection a month after external fixation of a fracture of the 4th and 5th metatarsals of the right foot following a road traffic accident in India. Bone samples taken during debridement in theatre on day 7 grew *Pseudomonas aeruginosa* and *E. cloacae*, both multi-resistant. At ARMRL the *P. aeruginosa* was positive by

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PCR for the bla_{VIM} carbapenemase gene whilst the *E. cloacae* was positive for bla_{NDM-1}. On day 50, his antibiotics were changed from colistin and tigecycline to intravenous colistin, aztreonam and fosfomycin on the basis of susceptibility results from ARMRL (Table 1). On day 92, he was discharged following completion of 6 weeks of antibiotic therapy for osteomyelitis and made a full recovery.

NDM-1 is a metallo-β-lactamase (MBL). These have one or more divalent cations, generally zinc, at their active site.[1] Other MBLs include the IMP and VIM types. MBLs hydrolyse carbapenems and all other β-lactams except aztreonam, to which many producers are also resistant for other reasons. They are inhibited by chelators of divalent cations such as ethylenediaminetetraacetic acid (EDTA) but not by clavulanate or tazobactam.[1] MBLs are challenging to detect and molecular methods for identifying individual types of MBLs remain the province of reference laboratories.

TABLE 1:

Final antibiotic susceptibility patterns and additional tests of multi-resistant E. cloacae and P. aeruginosa strains

Antibiotic susceptibility testing	Case 1		Case 2	
	E. cloacae	*E. cloacae*	*P. aeruginosa*	*E. cloacae*
	Tip femoral line	Left leg swab	Bone Sample	Bone Sample
Ciprofloxacin	R	R	R	R
Piperacillin/tazobactam	R	R	R	R
Meropenem	S	R	R	R
Colistin	S	S	S	S
Tigecycline	S	I	R	I
Aztreonam	R	R	S	R
Fosfomycin	I	I	R	S
Imipenem-EDTA Test*	-	+	+	+
ESBL Test	+	-		-
bla_{NDM-1} gene	-	+	-	+
bla_{VIM} gene	-	-	+	-

R Resistant
S Susceptible
I Intermediate, all as graded against European Committee on Antimicrobial Susceptibility Testing and British Society for Antimicrobial Chemotherapy breakpoints
* Screening test for metallo-β-lactamase
+ Positive
- Negative

Referrals to the HPA indicate that the numbers of carbapenemase-producing isolates in the United Kingdom are rising sharply, with NDM-1 often associated with prior medical exposure in India or Pakistan.[2] Most organisms with NDM-1 are resistant to almost all antibiotics except colistin and, less consistently, to tigecycline and fosfomycin, making it important to prevent transmission to other patients.[3]

These cases indicate import of NDM-1 into Northern Ireland and underscore the need for vigilance to the risk of multi-drug-resistant organisms being introduced via transfers of patients who have received medical care abroad. Infection control measures need to be implemented promptly to limit spread of these organisms as there are few, if any therapeutic options available.

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Financial Disclosure: Dr David Livermore has received conference support from and given lectures for numerous pharmaceutical companies, including Merck and AstraZeneca, who make carbapenems. He also holds shares in AstraZeneca, Merck, Pfizer, Dechra and GlaxoSmithKline. The other authors have no conflicts of interest.

ACKNOWLEDGEMENTS

We would like to thank Dr Neil Woodford at ARMRL, clinical and laboratory staff in the Belfast Trust, Northern Ireland.

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CONSENT: TEACHING HOW TO GIVE AND TAKE.

Editor,

Michael Douglas once said "When you don't know what you're doing, it's fatal".

The process of consenting patients is a fundamental part of day to day medical life, so much so that the GMC provide comprehensive guidance on the subject[1]. Teaching begins at undergraduate level however training is variable throughout medical schools in the United Kingdom and regardless of how in-depth or comprehensive the ethics, law and communication

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components of the curriculum are, little clinically applied consent teaching takes place[2]. As a result when junior medical staff hit the ward they are often silently overwhelmed by the task of consenting patients when they have little experience in the proposed procedure. This may cause increased levels of stress for both the patient and junior doctor and may lead to the provision of uninformative or even incorrect answers to patient's questions[3,4].

The purpose of this study was to assess the effect of teaching sessions in improving the validity of consent for tonsillectomy and to develop more efficient and standardised ways to obtain consent.

A retrospective analysis of 70 sets of patient notes was carried out at three ENT centres in Northern Ireland. Consent forms were scrutinised for complications outlined by ENT UK[5]. Several other components of the consent form including the timing of consent and the grade of those taking consent was noted. A teaching session on consent was provided at each centre and a repeat analysis on a further 70 sets of notes performed.

Initial analysis showed 48%, 56% and 66% of consent forms to have been completed to the standards set out by ENT UK at the three centres respectively. Following the teaching session the three centres improved their consent taking standard by an average of 9%. There was considerable variation in the grade of doctor taking consent across the three centres with consent being taken almost exclusively by the SHO grade at one centre. Consent was obtained at the clinic 83% of the time with the remaining consent being taken on the ward prior to the procedure. Consent was not documented in any of the patient notes reviewed.

Consent practices across ENT centres in Northern Ireland are variable often reflecting the constitution of staff in the department. Consent teaching sessions led to improvements across all centres and it would be reasonable to include consent teaching for common procedures as part of an induction program for junior staff. We also recommend the use of prefabricated consent stickers to improve the standardization and efficiency of consenting across all grades, we reiterate both the need for doctors to document consent in both the notes and the consent form and for consent to be taken at the clinic to allow adequate time for patients to weigh up the risks and benefits prior to the procedure.

These recommendations serve not to "dumb down" or allow for outsourcing the process of consenting patients to other healthcare professionals but to create an environment where junior staff can safely be an integral part of the process despite time constraints and legal pitfalls.

The authors have no conflicts of interest.

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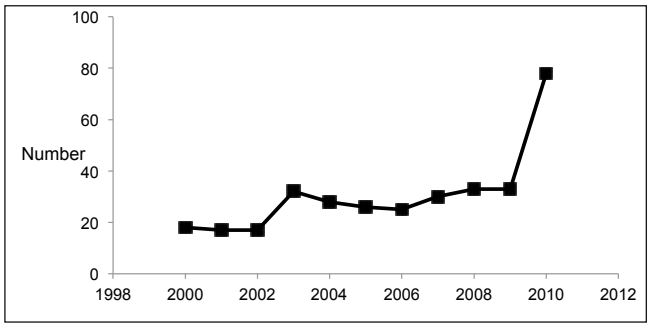
THE EVER INCREASING DEMAND FOR METASTATIC SPINAL SURGERY.

Dear Sir,

Clearly, to allow appropriate resource planning, trends in clinical practice need to be recognised and acted upon.

In the field of spinal surgery, the management of metastatic spinal disease has significantly changed over the years. Surgical techniques have improved and patient survival is increasing. The Patchell paper[1] demonstrated an advantage in clinical outcomes for patients undergoing surgery followed by radiotherapy. NICE guidelines for malignant spinal cord compression (MSCC)[2] promoted spinal surgical input. Improved medical and oncological treatments are leading to increased survival times.



Graph 1. The number of patients with malignant spinal cord compression undergoing surgery

We recently reviewed the fracture outcome research database (FORD) for the last 10 years to assess if our impression of an increasing demand for surgery was real or perceived.

The results are startling.

Of the 3468 patients admitted to the RVH trauma unit in 2000, 351 were spinal admissions of various causes. By 2010, the

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Table 1:

	Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Number	Tumour	18	17	17	32	28	26	25	30	33	33	78
	Fracture	292	352	348	306	279	326	299	326	303	339	357

total number of admissions for general fractures had remained relatively static at 3483, but the number of spinal admissions had increased to 650. 18 patients underwent surgery in 2000 for MSCC, whereas an exponential rise in numbers lead to 78 patients being operated on in 2010 for MSCC (table 1, graph 1). Fractures of the spine undergoing surgery showed no significant increase.

The impact of this increase is twofold. These patients undergo complex surgery taking significant theatre time often displacing other work and the operations these patients undergo require expensive implants. However, the effect of this surgery for the patient is often significant. Whilst survival time may or may not increase, quality of life is significantly improved and the demand for this surgery will not go away in the short term.

This trend will in all probability continue and the impact on time and financial budgets will continue to increase. With advances in medical oncology, the demand will in all likelihood eventually plateau, but as yet we have not reached such a point.

From a managerial perspective, it needs to be clearly understood that this patient group quite rightly will continue to place an increasing financial and time burden on our service. Unlike other conditions, time is of the essence by definition and it will be hard if not impossible to restrict this budget demand.

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Ulster Med J 2012;**81(3):**158-162

Abstracts of Scientific Meetings

2nd Annual Meeting of the Irish Fungal Society
21 & 22 June 2012

Belfast City Hospital

POSTERS

Analysis of sterol regulation in the *Saccharomycotina.*

Sarah Maguire, Cecile Neuveglise, Geraldine Butler.

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Many fungal pathogens grow on superficial and in internal sites in infected hosts, regions that have considerably different oxygen levels. A better understanding of the influence of hypoxia (low oxygen) on virulence and pathogenesis may lead to improved treatments against systemic fungal infections. Hypoxia induces filamentation of *Candida albicans*, which is associated with virulence. However other pathogenic *Candida* species do not grow as filaments, and presumably respond to hypoxia in different ways. In many fungal species (including the *Saccharomyces* and *Candida* clades) the transcription factor Upc2 plays a major role in regulating expression of the sterol pathway, particularly in low oxygen conditions. In other fungi, such as fission yeast *Schizosaccharomyces pombe* and the human pathogens *Aspergillus fumigatus* and *Cryptococcus neoformans*, expression of sterol genes is regulated by SREBP (Sterol Regulatory Element Binding Protein). SREPB is an ancient regulator that is conserved in mammals (including humans). The genome of *Yarrowia lipolytica*, an out-group of Saccharomyces and *Candida* clade species, contains homologues of both Upc2 and SREBP. By carrying out gene deletions in this species, we have shown that the appearance of Upc2 coincides with the acquisition of sterol pathway regulation. Our results also suggest that the remnants of the SREBP proteins regulate morphology and filamentous growth.

Efg1 regulates morphology and biofilm formation in *Candida parapsilosis.*

Leona Connolly, Alessandro Riccombeni, Linda Holland, David Andes, Geraldine Butler.

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The incidence of infection by *Candida parapsilosis* has risen substantially in recent years, possibly because it is easily transmitted to patients from contaminated external sources such as medical devices, catheters, or the hands of health care workers. One of the known virulence factors of *C. parapsilosis* is its ability to form biofilms on indwelling medical devices. In the related species *Candida albicans*, the transcription factor EFG1 is a major regulator of biofilm development and hyphal growth (Ramage et al., 2002). Efg1 is also an important regulator of white-to-opaque switching (Zordan et al., 2007) The role of EFG1 in *Candida parapsilosis* has not yet been studied in detail. Here we show that in contrast to *C. albicans* the Efg1 ortholog in *Candida parapsilosis* is a major regulator of a morphological switch at the colony level, from wrinkled to smooth phenotypes. The rate of switching is greatly increased in an efg1 knockout. The phenotypes of the two colony types are significantly different, suggesting that that there are differences in the cell walls. Smooth cells with an *efg1* deletion are more sensitive to congo red, caspofungin and calcofluor white. In addition, deleting efg1 reduces biofilm formation in in vitro models, particularly for smooth cells. Biofilm reduction is not as significant in in vivo models. Analysis of ChIP-seq and RNA-seq data shows that Efg1 binds to the promoters of several transcription factors and regulates expression of cell wall genes. Results suggest an important role of Efg1 in cell wall regulation and biofilm formation and an ancient role in morphological transition.

Investigating the biological activities of a bacterial metabolite in two model organisms.

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Department of Microbiology, University College Cork.

Naturally occurring antifungal compounds are abundant and very diverse and are mostly considered to be produced to regulate the growth of competing organisms in environments such as the rhizosphere of plants. However, in recent years the concept of antibiotics as signalling molecules has emerged and receives rising attention. In this study we are investigating the effects of the secondary metabolite 2,4-diacetylphloroglucinol (DAPG), which is produced by a few *Pseudomonas* spp. frequently associated to the rhizosphere. This metabolite exhibits a broad spectrum of antimicrobial activity but little is known about its cellular targets or possible fungal resistance mechanisms. We are using two model organisms, *Saccharomyces cerevisiae* and *Neurospora crassa*, to address these questions. DAPG treatment impairs cell growth in both organisms and specifically causes loss of membrane potential in mitochondria suggesting that electron transport is a target. A screen of the yeast deletion library revealed that alterations of several different processes, such as protein biosynthesis and DNA repair, can confer resistance. We also found that in both *S. cervisiae* and *N. crassa*, DAPG induces a transient cytoplasmic Ca2+ signal. The relevance of this signal is part of our current investigations but it may indicate a possible role of DAPG as a signal. The outcomes of this study could facilitate understanding the mode of action of antifungals/antibiotics and their role in inter-and intra-species communication but also help exploitation of this metabolite for agri-biotech and other applications.

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Trichosporon mucoides Fungaemia in a Patient with Solid Organ Tumor.

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Introduction. We report a case of *Trichosporon mucoides* central line associated fungaemia in a 20 year old female with disseminated Ewing's sarcoma. *Trichosporon* species are fungi that commonly inhabit the soil and are known to be present in the normal flora of the skin and gastrointestinal tract of humans. *Trichosporon* spp. more commonly cause superficial infections such as white piedra. However, recently there has been an upsurge of invasive Trichosporinosis in patients with haematological malignancies and recent transplants. Although Candida is by far the most common cause of disseminated yeast infections in humans, *Trichosporon* is making itself known as a less common but still important causative organism in these cases.

Aim. To report a case of central line related fungaemia caused by *Trichosporon* mucoides in a patient with solid organ tumor and its management.

Method: Case report with a review of the literature.

Case Report: Our patient is a 20-year old female with newly diagnosed disseminated Ewing's sarcoma. She presented with ongoing pyrexias and raised inflammatory markers following treatment with broad-spectrum antibiotics for presumed urinary tract infection. Central line related fungaemia was diagnosed following two separate blood cultures obtained four days apart via her PICC line with a good growth of *Trichosporon mucoides*. The line was removed and the patient was treated with liposomal amphotericin B.

Conclusion: This is our first reported case of *Trichosporon mucoides* line related fungemia highlighting an unusual presentation in solid organ tumor. Early detection and appropriate treatment is essential for a good patient outcome.

Epidemiology and Antifungal Susceptibility of *Aspergillus fumigatus* in an Irish Cystic Fibrosis Patient Cohort

Katie Dunne [1,2], Julie Renwick [2], Gerard McElvaney [4], Sanjay Chotirmall [4], Jacques F, Meis [5], Corné Klaassen [5], Philip Murphy [2] and *Thomas Rogers [1.]*

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Aspergillus fumigatus is an opportunistic pathogen known to cause a spectrum of diseases including Allergic Bronchopulmonary Aspergillosis (ABPA) and life-threatening angioinvasive pulmonary disease. *A. fumigatus* is the most common agent causing fungal infections in Chronic Lung Disease such as Cystic Fibrosis (CF), most often presenting as ABPA, whereas *A. fumigatus* commonly presents as Invasive Aspergillosis (IA) in immunocompromised individuals. There are a number of antifungal agents available for the treatment of *A. fumigatus* infections but triazole antifungal resistant *A. fumigatus* strains in CF have been reported [1]. In this study the epidemiology of *A. fumigatus* in an Irish patient population consisting of a CF patient population pre and/or post itraconazole treatment in a major CF Centre (Hospital 1) and a non-CF patient population from a major Teaching Hospital (Hospital 2) was investigated and the anti-fungal susceptibility of all isolates collected was determined.

A. fumigatus isolates from colonized adult CF patients (n=19) and from non-CF patients were collected (n=37). All isolates from the study were confirmed as *A. fumigatus* by PCR and sequencing of the ITS region. Isolates were genotyped using the Short Tandem Repeat assay for *A. fumigatus* (STR*Af* assay) [2]. Minimum Inhibitory Concentrations (MICs) of all *A. fumigatus* isolates to nine anti-fungal drugs were tested using the Sensititre Plate system (TREK Diagnostic Systems, Magellan Biosciences)

Three distinct *A. fumigatus* colonization patterns were observed in the CF cohort, (1) persistent colonization over time with the same genotype (>2 consecutive samples with indistinguishable genotypes), (2) non-persistent colonization with distinguishable genotypes over time and (3) patients sharing an indistinguishable genotype suggesting the possibility of a common source of acquisition. No shared genotypes between the two hospitals were found. These colonization patterns were observed in both CF and non-CF patients. No antifungal drug resistance was observed from any study isolate, even for isolates collected following exposure to itraconazole for 6 weeks. Twelve of 56 *A. fumigatus* isolates had MICs of 2µg/ml for amphotericin B and further investigation is required here.

No *A. fumigatus* genotype was linked with any one underlying disease or colonisation pattern. This suggests the impact of *A. fumigatus* on the patient may be a host trait. Some patients shared indistinguishable genotypes suggesting a common source. No triazole antifungal resistant strains of *A. fumigatus* were detected during this study. Twelve strains had higher than expected amphotericin B MICs which warrants further investigation.

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Investigating potential links between gene composition and protein thermostability in filamentous fungi.

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In Nature, a variety of pathogenic and saprophytic microorganisms play a vital role in the deconstruction and decomposition of plants and plant-derived residues and wastes. While this microbial ecosystem comprises both fungi and bacteria that co-exist and compete in this natural composting process, the filamentous fungi occupy a pivotal role as key players in the biological conversion

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of plants and plant-derived wastes. During the different phases of natural biodegradation, the temperature profile of the composting biomass changes, with the most efficient decomposition taking place during the thermophilic phase. The temperatures in the thermophilic phase generally range from 40-60°C, but can reach up to 70°C. Understanding the phenomenon of plant decomposition and the role of different microorganisms in this process is as central to developing new strategies to combat microbial spoilage of food crops. However, it is also essential for the development of new 'green' and 'white' biotechnology approaches to harness the potential of non-food crops and plant-derived wastes for bioenergy and commodity products.

We have investigated the enzyme machinery and enzyme systems produced by thermophilic, saprophytic fungi. Our work has shown that some of these fungi produce multiple cellulases, hemicellulases and other enzymes that are essential for conversion of plant cell wall biopolymers to simple building blocks. Many of the enzymes are thermostable and act as very effective and efficient biocatalysts. More recently, this work has involved investigating structural and biochemical factors that may enhance the stability of specific biomass-degrading enzymes in comparison with their mesophilic counterparts. Our findings suggest that, although individual covalent and non-covalent interactions may influence enhanced protein stability, no one structural feature is singularly responsible for thermostablity, which also supports reports from other researchers in the field. In this report, we discuss some of the findings to-date and explore whether or not potential clues exist at a genetic level for specific thermostable biomass-degrading enzymes from specific thermophilic fungi, in comparison with the same enzymes from selected mesophilic fungi, and less thermostable enzymes from then same thermophilic fungi.

POSTERS

Analysis of hypoxic regulation in *Candida glabrata* and related species.

Can Wang, Markus Schroeder, Sarah Maguire, Sixiang Sai and Geraldine Butler.

Conway institute, University College Dublin.

Pathogenic *Candida* species colonize hypoxic (low oxygen concentration) environments such as deep in tissue, or in periodontal spaces. We used microarrays to determine the transcriptional response of *Candida glabrata* to low oxygen levels, and to evaluate the role of specific transcription factors. We showed that lowering sterol levels acts as a signal for reduced oxygen, by comparing the transcriptional response of cells treated with ketoconazole (which targets azoles) to those grown in low oxygen conditions. We also determined the transcription profile of *C. glabrata* cells that are deleted for the transcription factor RXL1 (ROX1-like), in hypoxia and normoxia. *C. glabrata* RXL1 is a paralogue but not an orthologue of S. cerevisiae ROX1, a major regulator of the hypoxic response in yeast. C. glabrata has lost the ROX1 orthologue, and *S. cerevisiae* has lost RXL1. We show that in *C. glabrata* RXL1 acts as a repressor of expression of hypoxic genes. The hypoxic response in *C. glabrata* is therefore conserved with other species such as S. cerevisiae but the regulation is different.

We also investigated the regulation of the hypoxic response *in Naumovozyma castellii,* a close relative of *C. glabrata* and *S. cerevisiae*, which contains both ROX1 and RXL1 orthologues. *N. castelli* has a very unusual hypoxic response, with no increased gene expression and very little reduced gene expression. However, we found that *N. castelli* has a similar response to *C. glabrata* to treatment with cobalt chloride ($CoCl_2$), a commonly used hypoxia-mimicking agent. We used microarrays and RNA-seq to show that $CoCl_2$ induces expression of sterol and mitochondrial genes in both *N. castellii* and *C. glabrata*. ROX1 is required for the $CoCl_2$ induction of heme synthesis, sterol synthesis and mitochondrial function. Our results suggest that Rox1 has an ancestral role in regulating the hypoxic response and that Rxl1 has taken over this role in the human fungal pathogen *C. glabrata*.

Biomass to biofuel: Towards the bioengineering of *Saccharomyces* species for cellulose degradation.

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As the world enters the post-fossil fuel era, there is a need to exploit environmentally sustainable energy sources. One such potential energy source is the use of biofuels derived from lignocellulose-based biomass. Cellulose, the main component of lignocellulose, is made up of repeating units of the disaccharide cellobiose, which is comprised of two glucose molecules linked by a Î"-1,4 glycosidic bond. The most characterized microorganism known to ferment simple sugars to ethanol are yeasts belonging to the *Saccharomyces stricto sensu* group, however *Saccharomyces* species do not possess the cellulases required to degrade cellulose. However, the filamentous fungi *Trichoderma reesei* encodes all three major types of cellulases, namely endoglucanases, cellobiohydrolases also and Î"-glucosidases.

The aim of this project was to combine the fermentative capacity of *Saccharomyces* species with the cellulolytic ability of T. reesei to simultaneously saccharify and ferment a cellulose substrate into ethanol. Three cellulolytic genes of *T. reesei* were cloned separately into the bakers yeast *Saccharomyces cerevisiae* and also into a proprietary stress tolerant strain of the industrial yeast S. pastorianus. Each cellulase encoding gene was expressed under the control of a *S. cerevisiae* constitutive promoter. Functional cellulase activity was observed in transformed yeast. The resultant cellulase producing S. cerevisiae and S. pastorianus strains were separately co-cultured with phosphoric acid swollen cellulose (PASC) to produce ethanol. Experiments are being conducted to optimize the activity levels of recombinant cellulases, fermentation conditions and strain selection to increase ethanol production.

The quantification and optimisation of recombinant beta-glucosidase in various *Sacchraomyces* species.

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As our energy requirements and oil prices rise, the need for a more sustainable and environmental friendly fuel source has become a necessity. Biomass has been identified as a possible replacement due to its abundant and renewable nature, with the waste portion namely lignocellulose being of great interest. Lignocellulose is composed of three main components, lignin, hemicellulose and cellulose with the latter two being our main interest. To optimise alcohol production, the use industrial yeast strains, which are conditioned to producing and tolerating high levels of alcohol, is a logical choice, although currently these yeast are unable to naturally ferment both cellulose and hemicellulose.

The overall aim of this project is to reconstitute the lignocellulosic

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degrading machinery from cellulose degrading fungal species within industrial strains, allowing for the effective hydrolysis of lignocellulosic biomass into fermentable sugars and subsequent alcohol production.

Building on previous work, the expression of the lignocellulosic degrading gene beta-glucosidase, which is responsible for the final stage in cellulose degradation has been quantified in various *Saccharomyces* species. Environmental conditions were varied to optimise production and secretion of the enzyme, resulting in increased activity. Using these new strains growth on cellobiose was examined.

Roles of telomere-associated (*TLO*) genes in the pathogenesis of *C. albicans* and *C. dubliniensis.*

John Haran, Hannah Boyle, Tim Yeomans, Derek Sullivan, and Gary Moran.

Dublin Dental University Hospital, Trinity College Dublin.

Candida albicans is widely regarded as the most pathogenic yeast species. Surprisingly the very closely related species *Candida dubliniensis* is far less pathogenic. Comparative genomic analysis of the two species revealed that the genomes are very similar however there is a significant disparity in the copy number of a family of telomere-associated (*TLO*) genes, which encode putative transcriptional regulators. The *C. albicans* genome contains 14 *TLO* genes whereas the far less pathogenic *C. dubliniensis* only encodes two. We hypothesise that this discrepancy in *TLO* copy number may contribute to the differential virulence of these two highly related species.

We have previously shown that the homozygous deletion of both *TLO1* and *TLO2* in *C. dubliniensis* (*tloDD*) significantly reduces its ability to form true hyphae. Subsequent work has also shown that the *tloDD* mutant grows poorly in the presence of alternative carbon sources, such as galactose and succinate, and is more sensitive to oxidative stress induced by H2O2 or menadione. Expression of *CdTLO1* and *CdTLO2* from a doxycycline-inducible promoter in *C. dubliniensis tloDD* restored levels of true hypha formation to 80% and 40% of wild-type respectively. Similarly, expression of selected *C. albicans TLO* genes in the *tloDD* mutant also restored true hypha formation suggesting that the *TLO* families play similar roles in the two species. DNA microarray studies have shown that *C. dubliniensis tloDD* displays altered expression of a number of genes encoding filamentation regulators (*EFG1*, *UME6*), hyphal cell wall proteins (*HWP1,RBT5*), oxidative stress response genes (*SOD1-6*) and genes essential to galactose metabolism (*GAL1,7, 10*).

The presence of a conserved putative Med2-binding domain (associated with RNApol II mediator complex) in the CaTlo and CdTlo proteins suggest that they are a family of transcriptional regulators and we are currently investigating the relationship between the Tlo and Med families.

Whole Genome Sequence Analysis of ten *Candida dubliniensis* isolates.

Brenda McManus, E. Permal, Gary Moran, David Coleman, C. d˙Enfert & Derek Sullivan.

Dublin Dental University Hospital, Trinity College Dublin.

Aim: Previous multilocus sequence typing (MLST) analysis has shown that the population structure of *Candida dubliniensis* is significantly less divergent than that of its closest relative, *Candida albicans*. Furthermore, *C. dubliniensis* has undergone loss in some gene families such as the agglutinin-like sequence (*ALS*) and telomere-associated (*TLO*) families, and pseudogenization of genes proposed to play a role in pathogenesis. The present study undertakes a detailed analysis of genomic content and variation of ten *C. dubliniensis* isolates that represent each of three previously identified MLST clades.

Methods: Ten isolates were sequenced using the Solexa/Illumina technology, and reads were aligned against the reference CD36 sequence using SHORE software v5, allowing determination of normalized coverage scores for all *C. dubliniensis* open reading frames (ORFs) and identification of single nucleotide polymorphisms (SNPs).

Results: Homozygous and heterozygous SNPs were quantified for each of the ten isolates. The majority of SNPs were homozygous in *C. dubliniensis*, in contrast to *C. albicans*, and has been observed previously using MLST. Phylogenetic analysis using homozygous and heterozygous SNP data also identified a population structure that has previously been shown using MLST, consisting of three closely related clades. Normalized coverage scores were obtained for each ORF across the ten isolates. The majority of ORFs that exhibited significant variation or undercoverage amongst the ten isolates encoded transposable elements or hypothetical proteins. In some cases these undercoverage scores may be the result of poor alignment to, or ORF duplication in the reference CD36 sequence. The CaALS DNA sequences were used in separate Basic Local Alignment Search Tool (BLAST) analyses against de novo assemblies of seven isolates, and identified seven *CaALS* homologues in each. No homologues of *CaALS3* or *CaALS5* were identified in any of the assemblies, as previously observed in CD36. The *CaTLO* DNA sequences were used in BLAST searches against the same de novo assemblies and identified two homologues, *CdTLO1* and *CdTLO2*. Interestingly, the genomic region identified upon BLAST search of *CdTLO2* in isolate CD06037 did not align with the reference *CdTLO2* sequence. Further global genomic alignment data and the low coverage score (0.012) for this ORF further suggested that *CdTLO2* is absent in CD06037. Alignment data also identified the movement of *CdTLO2* from chromosome R to chromosome 3 in isolate Wu284.

Conclusions: Our data correlate with previous work that indicates a preference for homozygous SNPs, and a low level of intraspecies divergence in *C. dubliniensis*. No homologues of *CaALS3* or *CaALS5* genes were found, and only the *CdTLO1* or *CdTLO2* genes were identified in the *C. dubliniensis* isolates, suggesting that these gene families are truly reduced in *C. dubliniensis*.

Generation and analysis of putative Tor1 hyperactive mutants of *Candida albicans*.

Peter Flanagan & Gary Moran.

Dublin Dental University Hospital, Trinity College Dublin.

Candida albicans is a commensal inhabitant of the alimentary canal capable of opportunistic infections in a debilitated or compromised host. Responsible for a wide range of superficial to life threatening infections, *Candida* spp. are the fourth most common cause of nosocomial bloodstream infections. The ability to adapt to various nutritive environments presented by the host is essential to its survival as commensal or pathogen. Thus, understanding how cell growth is controlled in response to environmental signals remains an active field of research.

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Target of rapamycin (TOR), a conserved protein kinase, is highly conserved from mammalian to yeast cells. In eukaryotes, TOR is responsible in regulating metabolism and the cell cycle. In *Saccharomyces cerevisiae*, TOR is stimulated by amino acids and an active TOR kinase promotes ribosome biogenesis and glycolysis, as well as repressing genes involved in nitrogen scavenging. Current literature presents several lines of evidence indicating that in *Candida* spp., TOR may play a role in the transition of yeast to hyphae.

The aim of this project is to determine if the TOR1 fungal kinase is a central regulator of virulence. It is hypothesised that an active kinase represses virulence and filament formation. Subsequently, we aim to determine whether strategies to activate this kinase could be valuable in controlling infection. Preliminary work has involved generating a TOR hyperactive mutant using an overexpression strategy with the Enolase 1 promoter (ENOp).

ENOp was placed upstream of VAM6, a protein reported to control TOR complex 1 in S. cerevisiae, in order to promote TOR hyperactivity. Further to this, ENOp was also placed upstream of TOR1 itself and the recently characterized G-protein RHB1.

We will primarily focus on determining the phenotypic differences between mutant and WT strains. Additionally, we will examine whether nutrient depletion or the addition of the drug rapamycin can restore filamentation. Changes in gene expression and the host-cell interactions will be examined.

Chromatin remodelling during stationary phase in *Saccharomyces cerevisiae.*

Conor Young [1], Cory Hillyer [2], Mary Ann Osley [2] and Alastair B. Fleming [1].

[1]Department of Microbiology, Moyne Institute of Preventive Medicine, Trinity College. [2]Department of Molecular Genetics and Microbiology, University of New Mexico School of Medicine.

Eukaryotic genomes are organised as the DNA:protein complex chromatin. The fundamental subunit of chromatin is the nucleosome which comprises 147 base pairs of DNA wrapped around an octamer of histone proteins. This structure is generally repressive to any process, such as transcription, which requires access to the DNA. However, chromatin can undergo changes in its structure which can alter its function.

Histones are the substrate for numerous post-translational modification (PTMs) including acetylation and methylation. Of particular interest is the modification of histone H2B by the addition of ubiquitin (ub), a 76 amino acid protein. In the budding yeast Saccharomyces cerevisiae histone H2B is ubiquitylated at lysine residue 123 in the C-terminal tail. H2B ubiquitylation plays a role in transcription elongation and regulates the downstream methylation of histone H3 at lysine residues 4 (H3K4) and 79 (H3K79).

Recent work has shown that yeast stationary phase (SP) cultures comprise two distinct populations of cells with divergent developmental fates. SP cultures compromise older mother cells that undergo apoptosis and necrosis, and younger daughter cells which become quiescent. The daughter cells retain the ability to re-enter the cell cycles upon nutrient replenishment.

Little is known about the fate of chromatin during SP except that chromosomes become condensed. This event accompanies a general shutdown of transcription. In this project the two SP populations have been separated and the chromatin in each population has been examined. The results have shown that H2B ubiquitylation is lost upon entry into SP, whereas other histone PTMs associated with active transcription are retained during SP. We have also shown that H3K79 di-methylation is specifically depleted in the quiescent population. We are currently investigating the significance of this chromatin remodelling during SP.

Investigating gene repression by the Tup1p-Ssn6p complex in *Saccharomyces cerevisiae.*

Michael Church and Alastair B. Fleming.

Department.of Microbiology, Moyne Institute, Trinity College Dublin.

Transcriptional repression is an important part of gene regulation. In the budding yeast *Saccharomyces cerevisiae* the Tup1p-Ssn6p corepressor complex is recruited to gene promoters to repress transcription in response to nutrient depletion, DNA damage and numerous other signals. The current model for Tup1-Ssn6-mediated repression dictates that Tup1p promotes repression, while Ssn6p acts as an adaptor between Tup1 and the target gene. The aim of this project is to (i) elucidate the contribution of the Tup1p and Ssn6p subunits of the complex to gene repression and (ii), determine if Tup1p and Ssn6p can regulate gene repression independently from each other. The results will help elucidate the precise mechanism of action of gene repression by the evolutionary conserved Tup1p-Ssn6p corepressor complex.

Fungal SMC bioconversion: A potential greener technology.

Finola E. Cliffe[1,2], Manimaran Ayyachamy[1,2], John Collier[1] and Maria G. Tuohy[2].

[1]Monaghan Mushrooms Ltd., Tyholland, Monaghan, Co. Monaghan, Ireland. [2]Molecular Glycobiotechnology Group, Biochemistry, School of Natural Sciences, NUI Galway.

The Irish mushroom industry produces over 400,000 tons of spent mushroom compost (SMC) annually. Currently, this by-product is employed as a soil conditioner; however, the application for SMC is considered very limited due to associated environmental and health impacts. The relatively high carbohydrate content of SMC makes it a suitable alternative feedstock in the biofuel and biorefinery sectors. Biochemical analysis of SMC indicates its potential use as an inexpensive nutrient source for microbial enzyme production. Ligno-cellulolytic enzymes are produced by different fungi. Many of the xylanase- and cellulase-rich commercial enzyme preparations are derived from fungal sources. In this study, we compare the proximate, carbohydrate and metal ion compositions of SMC from different sources and SMC from one of the sources at different annual time points. We also compare the conversion of SMC using the commercial enzyme preparations and an in-house preparation from a thermophilic fungal source. The study shows that the fungal enzymes can be used to generate hydrolysates rich in fermentable sugars for downstream bioenergy production. This process avoids the use of harsh chemical reagents and high operating temperatures which would be beneficial for large scale industrial development and commercialisation.

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Ulster Med J 2012;**81(3):**163-170

Abstracts of Scientific Meetings

15th Meeting of the Irish Society of Human Genetics, Monday 3rd September 2012.

Royal College of Surgeons in Ireland.

PROGRAMME:

10.00 – 10.55	Registration / Tea and Coffee.
10.55 – 11.00	Welcome.
11.00 – 12.00	Oral Presentations. Plenary I: clinical research.
12.00 – 13.00	**Keynote address:** 'Old men and selfish spermatogonia: how much do they contribute to the mutation burden?' Prof. Andrew Wilkie, University of Oxford, UK.
13.00 – 14.00	Lunch and Poster viewing.
13.45 – 14.00	Council Meeting.
14.00 – 15.00	Oral presentations. Plenary II: Basic research.
15.00 – 15.45	Tea and coffee / Poster viewing.
15.45 – 16.00	Business Meeting / AGM.
16.00 – 17.00	**Keynote address**: 'How next generation sequencing changes medicine' Han Brunner, Radboud University Nijmegen, The Netherlands.
17.00 – 18.00	Wine reception / Presentation of Prizes/ Meeting close.
19.00 – 21.00	**Dublin City of Science 2012 Public Event** Your Genes, Your Health, Your Future.

SPOKEN PAPERS:

S01. Exome analysis and cardiomyopathy: The Lazarus story

J Casey[1], P McGettigan[2], N Alkazemi[3], P Maguire[3], B Kennedy[3], D Brosnahan[4], E Treacy[5], K Walsh[4], S Ennis[6,7], SA Lynch[7,8]

[1]National Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin 12. [2]UCD School of Agriculture, Food Science and Veterinary Medicine, College of Life Sciences, University College Dublin, Belfield, Dublin 4. [3]School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin, Dublin 4. [4]Our Lady's Hospital for Sick Children, Crumlin, Dublin 12. [5]National Centre for Inherited Metabolic Disorders, Children's University Hospital, Dublin. [6]School of Medicine and Medical Sciences, University College Dublin, Dublin 4. [7]National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Dublin 12. [8]Genetics Department, Children's University Hospital, Dublin.

We present a study on a non-consanguineous Irish family that includes two siblings (male and female) with dilated cardiomyopathy (DCM) and chorioretinopathy. The children have been extensively investigated by the cardiac, metabolic and genetic teams but the genetic basis of their disorder remains unknown. We aimed to identify the disease mutation by sequencing the exome of the two affected children and their healthy sibling. The data was analysed assuming a recessive model to identify mutations that were uniquely shared by the affected children. One novel heterozygous mutation was identified in the exome data of one patient, but the sequencing coverage was not sufficient to determine the genotype of the second patient. Sanger sequencing was undertaken and showed that both affected children were heterozygous for the maternally-inherited mutation. As a dominant model was unlikely, the entire gene was sequenced and we identified a second paternally-inherited mutation in the patients. Why did the exome analysis fail to identify the compound heterozygous mutation? Retrospective investigations revealed why the candidate mutation was missed in the exome analysis and highlighted potential pitfalls. We have identified a novel candidate gene for this rare phenotype and subsequently investigated defects in Wnt signalling as a possible underlying cause.

S02. Concurrent translocations involving MLL (11q23) and MYC (8q24) in an infant B-cell acute lymphoblastic leukaemia (ALL)

Kelly J[1], Barton L[1], Morris T[1], Smith O[2], Betts DR[1]

[1]National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin. [2]Haematology/Oncology Department, Our Lady's Children's Hospital, Crumlin

Acquired chromosomal translocations frequently provide key oncogenic events and many are specific to particular neoplasms. The MLL gene at 11q23 is frequently disrupted by chromosomal translocations in infant onset ALL and is typically associated with a poor prognosis. In contrast, rearrangements of MYC (8q24) are a feature of aggressive mature B cell lymphomas or leukaemias. We describe an infant of 4 months who presented morphologically with B-ALL. The leukaemia had a complex karyotype with structural aberrations including a translocation involving MLL in 95% of cells, with chromosome 19p13.3 as the partner, and a concurrent MYC translocation with chromosome 22q11 in 30% of cells. Therefore, indicating that the MYC rearrangement has occurred as a secondary event in the leukaemia. To our knowledge there has been only one other case describing co-existing rearrangements involving MLL and MYC in infant or paediatric B-ALL. Given that these events typically occur in very different types of haematological neoplasm the significance of a MYC rearrangement in a subset of leukaemic cells in this case presents a dilemma for the prediction of possible

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clinical outcome and whether the therapy regime requires any modification.

S03. The complexity of counselling families for double heterozygosity in Inherited Cardiac Conditions.

Nicola Harper, Andrew Green

The National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin & The Children's Medical Research Foundation.

Inherited cardiac conditions such as Long QT Syndrome and Hypertrophic Cardiomyopathy can have a major impact on families as the conditions can have a significant risk of sudden death. Clinically, cardiac investigations can identify individuals at an increased risk but due to variable penetrance and expression some individuals at risk may not be identified. Genetic testing can effectively allow identification of family members at risk when a highly likely pathogenic variant is identified. However, these conditions are Heterogeneous and double heterozygosity is reported in 5 to 10% of Hypertrophic Cardiomyopathy and is estimated in 3% of Long QT Syndrome. This leads to added complexity in the Genetic Counselling of families. In this Presentation, we review the Literature regarding Inherited Cardiac conditions and double heterozygosity with particular emphasis on genetic testing and genetic counselling. We present the cases of double heterozygosity seen at the specialist cardiac genetic counselling clinics at the National Centre for Medical Genetics. 9 families have been identified with two variants detected either as double or compound heterozygotes. We discuss the counselling issues that arose regarding segregation analysis, risk assessment and disclosure. This identifies the need for further guidelines on clinical screening for family members and segregation analysis.

S04. NBS Screening for CF in Ireland – First Anniversary Review

Melissa Rogers[1], Karen Meaney[1], Trudi McDevitt[1], Philip Mayne[2], Geraldine Roche[2], David E Barton[1]

[1]National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12; [2] National Newborn Bloodspot Screening Laboratory, Children's University Hospital, Temple Street, Dublin 1

The National Newborn Screening Programme (NBS) for Cystic Fibrosis (CF) began in Ireland on 1st July 2011, employing a two-tier IRT/DNA screening strategy. Blood spot immunoreactive trypsinogen (IRT) is first measured on dried blood spot samples collected between 72 and 120 hours after birth. Babies' samples with IRT in the top 1% are then referred for genetic screening. A total of 628 babies have been genetically screened thus far. They are tested using the xTAG™ Cystic Fibrosis 39 kit v2 for 38 of the most common CF mutations found worldwide. Following analysis, 29 babies with two CF disease causing mutations were identified; 26 had their diagnosis confirmed by means of an elevated sweat chloride result (>60mmol/L), 1 was diagnosed by genetic PND and another diagnosed by the presence of clinical symptoms. The final patient was lost to follow-up. A further 48 babies with 1 CF mutation were identified following screening; 45 of which had a sweat chloride in the normal range, confirming them as carriers only. 1 had a positive sweat chloride and was so diagnosed with CF. This patient subsequently had a second mutation identified following full screening of the *CFTR* gene. Two patients had borderline sweat chlorides, in the range 30-60mmol/L and were referred for full screening of the CFTR gene.

S05. Vascular Ehlers Danlos Syndrome: An obvious diagnosis or not? The Northern Ireland experience and influence of COL3A1 gene testing availability

Donnelly DE[1], Lee B[2], Reid J[2], Kirk S[3], Rea G[1], Stewart FJ[1], McConnell VPM[1]

[1]Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast Health and Social Care Trust. [2]Cardiovascular Surgery Service, Royal Victoria Hospital, Belfast Health and Social Care Trust. [3]Surgery Department, Ulster Hospital, Dundonald, South Eastern Health and Social Care Trust

Vascular Ehlers Danlos Syndrome (EDS IV) is an autosomal dominantly inherited connective tissue disorder (CTD), associated with COL3A1 gene. The combination of any two of the major Villefranche diagnostic criteria of arterial, intestinal and uterine rupture and family history are considered highly specific. The majority of minor criteria whilst being supportive of EDS IV can be regarded as common features of CTDs. Three of the minor diagnostic criteria; characteristic facial appearance, thin translucent skin and extensive bruising are more pathognomic, fulfilling three of the four eligible criteria for COL3A1 gene testing in the United Kingdom. Four of the five COL3A1 families presented after a severe or fatal vascular rupture with variable clinical phenotype and family history. Three of the COL3A1 mutations result in substitution of other amino acids for glycine residues in the triple helical domain; two not previously reported. Another COL3A1 mutation affected the splice site. The remaining mutation involved a complex contiguous genes deletion including COL3A1 and COL5A2 genes supporting the atypical phenotype. Whilst the intra and interfamilial phenotypic variability in our cohort supports the recognised difficulty in ascertaining the EDS IV diagnosis until a severe or fatal clinical event, the advent of genetic testing brings other issues.

S06. Excess of novel nonsense mutations identified in putative susceptibility genes for schizophrenia and autism spectrum disorders.

Sarah Furlong, Elaine M. Kenny, Paul Cormican, Ciara Fahey, Richard Anney, Gary Donohoe, Aiden P. Corvin, Louise Gallagher, Michael Gill, Derek W 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 genetic neurodevelopmental disorders that share certain phenotypes (e.g. cognitive deficits), and may share an underlying pathology due to shared genetic risk variants. This study involves next-generation sequencing of the exonic regions of 215 putative susceptibility genes in an Irish sample of 151 cases of ASD, 274 cases of SZ and 287 controls, to identify rare mutations contributing to one or both disorders. A multiplex target enrichment method combined DNA samples using indexes/barcodes followed by enrichment of exonic regions using Agilent SureSelect and paired-end sequencing on an Illumina GAII. Selected genes were categorised as: 1) NRXN1 and interactors, 2) Post-synaptic Glutamate Receptor Complexes (NMDA, mGluR5 and AMPA), 3) Neural cell adhesion molecules, 4) DISC1 and interactors, and 5) Functional and Positional Candidates. Analysis revealed an excess of rare Loss-of-Function (LoF) variants that are predicted to

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severely disrupt protein-coding sequence in cases versus controls (27 in 421 cases v 9 in 287 controls; p=0.051, odds ratio (OR)=2.12.) Twenty six of these events are singletons, of which there is a more significant excess in the combined case sample versus controls (21 in 421 cases v 3 in 287 controls; p=0.004, OR=4.97) and the effect is similar for both SZ (13 in 273 cases; p=0.008, OR=4.73) and ASD (8 in 148 cases; p=0.009, OR=5.41, 95%CI=1.28,26.14). Two rare LoF variants occurring in the well established candidate genes for neurodevelopmental disorders; *GRIN2B* and *DISC1* were identified as *de novo* in ASD cases. These results supply new supportive data for known risk genes and identify putative new susceptibility genes for both disorders.

S07. Genetic-Epigenetic Association with Parkinson's Disease.

Kerry Moore[1], Francis O'Neill[1], Jill Kilner[1], Owen Ross[2], David Craig[1], Amy Jayne McKnight[1].

[1]School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, N. Ireland; [2]Division of Neurogenetics, Department of Neuroscience, Mayo Clinic, Florida, USA.

Studies have highlighted that Parkinson's Disease (PD) is influenced by differential methylation at several loci. We investigated the DNA methylome by conducting an epigenome-wide association study followed by independent replication and integration with novel genome-wide data. Forty-five individuals with extreme phenotypes were matched for age and gender. Blood-derived DNA was bisulfite treated and hybridised to 450K Infinium methylation beadchips (Illumina Inc, USA). Methylation levels were compared between PD individuals and unaffected controls. Twelve top ranked, significantly associated loci were evaluated in an independent replicate population using Sequenom EpiTyper for 200 PD individuals in a cross-sectional case-control discovery design. Cases and controls were also evaluated using Illumina's Human OmniExpress Exome assay, to explore genetic variation associated with these differential methylation profiles. Genome-wide SNP data was analysed using standard quality control and analysis options. Quantitative methylation values were obtained at single-CpG level for 485,577 features. Logistic regression analysis for individuals with PD compared to controls (adjusting for age and gender) revealed twenty unique genes with a sizable difference in methylation ($P_{adjusted}$<0.05, $\Delta\beta \geq 0.2$) after correction for multiple testing. Genome-wide SNP data was analysed for ~ 700,000 SNPs + ~250,000 SNPs focused in exonic regions; preliminary genetic analysis provides support for seven biologically plausible genes. We have identified differences in methylation profiles both globally, and at individual CpG sites, which are associated with PD and supported by SNP-based data.

S08. Whole exome sequencing in Irish pedigrees identifies novel mutations for epilepsy predisposition

Mark McCormack[1], Gerard D O'Connor[2], Erin L Heinzen[3], Kevin V Shianna[3], Judith Conroy[4], Sean Ennis[4], David B Goldstein[3], Norman Delanty[2], Gianpiero L Cavalleri[1]

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland. [2]Department of Neurology, Beaumont Hospital, Dublin, Ireland. [3]Center for Human Genome Variation, School of Medicine, Duke University, Durham, NC 27708, USA. [4]School of Medicine & Medical Science , Health Sciences Centre, UCD

Through clinics we actively recruit epilepsy pedigrees, providing a valuable resource for identifying mutations that predispose for epilepsy within the Irish population. As part of a collaborative whole exome study, we identified a rare stop-gain mutation exclusive to Irish cases within *CHRNB3*, a member of the nicotinic acetylcholine receptor family. Upon screening our case cohort, we found the mutation in all five affected members of Pedigree 1. Three unaffected members of this pedigree did not carry the mutation whilst it was not present in over 900 population controls. Two sporadic cases also carried the variant, one of whom shares the variant identically-by-descent with Pedigree 1. In family 2, we performed whole exome sequencing on three affected siblings. We limited our analysis to shared variants that were functional and rare (<3% MAF in European-American population). Our top two variants were both novel heterozygous non-synonymous SNPs in *SLC2A1*, encoding the glucose transporter type-1 (GLUT1). Segregation among the extended pedigree reflected a reduced penetrance model. Screening across our case cohort and population controls is currently ongoing. Through multiple genomic approaches we identified rare mutations in two genes from autosomal-dominant pedigrees which may provide further insight into the predisposition to and neurobiology of epilepsy.

S09. The NTD-associated polymorphism *MTHFD1L* rs7646 may increase disease risk by impacting on microRNA regulation.

Minguzzi S[1]*, Selcuklu SD[2]*, Parle-McDermott A[1], Spillane C[2]

[1] Nutritional Genomics Group, School of Biotechnology, Dublin City University, Ireland. [2] Genetics and Biotechnology Lab, Centre for Chromosome Biology, National University of Ireland Galway, Ireland. *These authors contributed equally to this work.

Polymorphisms of the folate related gene *MTHFD1L* have been shown to be associated with the risk of Neural Tube Defects (NTD) in the Irish population. We considered the Single Nucleotide Polymorphism (SNP) rs7646 (A>G), within the 3' UTR (untranslated region) of *MTHFD1L*, as potentially impacting on miRNA regulation. We identified miR-197 which can bind *MTHFD1L* 3'UTR in the position of the SNP rs7646. Allele "G" is predicted to produce an extra matching nucleotide adjacent to the seed sequence of the miR-197. In this study we investigated the binding of miR-197 to the 3'UTR of *MTHFD1L* mRNA and whether the alleles of SNP rs7646 have functional differences in miRNA binding. Results demonstrated that miR-197 specifically binds to the *MTHFD1L* 3'UTR causing a downregulation of the gene in MCF-7 cells. SNPrs7646 significantly changes miR-197 binding affinity, making the repression more efficient for allele "G" than for allele "A". However, the same assays performed in HEK293 and Coriell Lymphoblast cells showed no interaction between miR-197 and MTHFD1L indicating that this effect could be cell, tissue or developmental stage specific. Further experiments are necessary to elucidate the relationship of mir-197 regulation of *MTHFD1L* variants, particularly during early human development and in neural tube defects.

S10. Mutation-specific siRNA therapy for a keratin disorder

Atkinson SD[1], Liao H[2], Szeverenyi I[3], Smith FJ[2], Moore CBT[1], McLean WHI[2].

[1] Biomedical Sciences, University of Ulster, Coleraine, BT52 1SA, UK. [2] Division of Molecular Medicine, University of Dundee, Dundee, DD1 4HN, UK. [3] A*STAR Institute of Medical Biology, Singapore, Singapore

Epidermolysis bullosa simplex (EBS) is one of the major hereditary

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bullous disorders, characterised by blister formation in response to minor mechanical trauma within the basal layer of the epidermis; it is predominantly caused by mutations in genes encoding keratins 5 or 14 (K5 or K14). RNA interference (RNAi) is a complex naturally occurring cellular process where the presence of double-stranded RNA results in the interruption of the cell's translation of its own mRNA. The cellular process of RNAi can be harnessed to exert user-defined gene silencing with potential therapeutic effect in conditions which show a dominant negative inheritance. A luciferase reporter gene system was developed to assay all 19 possible allele-specific siRNA molecules for two K5 mutations over a standardised concentration range. siRNAs were identified that potently inhibited the mutant allele with little effect on wild-type K5. These lead inhibitors were further tested using epitope-tagged K5 expression constructs, where western blot analysis confirmed that they potently and specifically inhibit mutant K5. In addition, the cellular protein aggregation phenotype was reversed in cultured cells treated with mutant-specific siRNA. This work demonstrates the effectiveness of specifically developed siRNAs in inhibiting the expression of an EBS-causing mutation *in vitro*. If used in conjunction with non-invasive delivery systems which are currently in development, these siRNA molecules demonstrate potential for their use in the treatment of EBS and other disorders resulting from keratin mutations.

POSTER PRESENTATIONS:

P01. Sub-Cortical White Matter Abnormalities due to previously undescribed *de novo* 14q12-13 duplication.

Rea G[1], Stallings RL[2], Mullarkey M[3], McKinstry CS[4], McManus D[1], Morrison PJ[1*].

[1]Northern Ireland Regional Genetics Service. [2]Chair of Cancer Genetics, Royal college of Surgeons Ireland. [3]National Centre for Medical Genetics, Ireland. [4]Department of Neuroradiology, Royal Victoria Hospital, Belfast.

Full trisomy 14 has been noted in spontaneous abortions and in live born infants with mosaicism. Partial trisomy of variable segments of 14q has rarely been described. We have identified a previously undescribed *de novo* partial duplication of chromosome 14q in a boy who presented at 14 months of age with neurological abnormalities. This was confirmed by fluorescence in situ hybridization (FISH) and defined by array CGH as dup (14)(q12-q13). Early developmental milestones were delayed. Dysmorphic features include low-set ears, upslanting palpebral fissures with epicanthic folds, a high arched palate and prominent lips. There was general hypotonia and behavioural problems which included self-injurious behaviour. MRI brain showed multiple areas of increased signal intensity in the subcortical white matter of both cerebral hemispheres, most marked frontally and to the vertex. These findings are consistent with hamartomatous lesions, similar to those found to Tuberous Sclerosis (TS). There was no evidence of other features suggestive of TS in this boy and no heterogeneity on TS is suspected as all previously reported cases of TS appear to show linkage to the TSC1 and TSC2 genes on chromosome 9 and 16. The patients clinical features and follow-up over 15 years are described.

P02. Mosaicism and a whole gene deletion in HLRCC.

G Rea[1], S Shanley[2]

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Germline mutations of the fumarate hydratase (FH**,** fumarase) gene are found in the recessive FH deficiency syndrome and in dominantly inherited Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome. We present a pedigree in which the teenage proband presented to dermatology with a painful rash affecting his chest and limbs. Biopsy confirmed multiple skin leiomyomas. There was no family history of note. *FH* sequence analysis failed to detect a mutation but multiplex ligation-dependent probe amplification (MLPA) identified a whole gene deletion. Array Comparative Genomic Hybridisation (CGH) delineated a 668kb deletion in 1q43 which involved *RGS7, KM0, OPN3, CHML, WDR64* and the *FH* gene. Further testing in the family identified that the probands father is mosaic for the deletion, which is present in ~60% of his peripheral blood leucocytes. The father has a large cafe-au-lait pigmented lesion on his left calf and thigh but no recognised features of HLRCC to date. We draw attention to this case to highlight a rarely reported whole gene *FH* deletion and the need to consider mosaicism in apparently unaffected parents. In addition, we review the clinical and molecular aspects of the disease and discuss our recently developed management protocol.

P03. A Retrospective Analysis of the Prevalence of Craniosynostosis on the island of Ireland

Lisa Bradley[1],Tabib Dabir[1] Colm Murphy[2], Dylan Murray[3], Anne McGillivary[3], Sally Ann Lynch[4]

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Craniosynostosis describes the premature fusion of one or more cranial sutures with birth prevalence of 3.5-4.8 per 10,000 live births (LB). Around 15-25% cases are considered to be syndromic. We sought to estimate the prevalence of craniosynostosis within the island of Ireland for cases born within the years 2000-2009. In the Republic of Ireland (RoI), these cases are treated at the Children's University Hospital, Dublin, whilst in Northern Ireland (NI) treatment is at the Royal Belfast Hospital for Sick Children or following onward referral to centres in England. The National Centre for Medical Genetics (NCMG), Dublin and the Northern Ireland Regional Genetics Service (NIRGS), Belfast provide genetic services. We retrospectively reviewed craniofacial/genetic databases, medical/genetic records, X-ray systems and inpatient diagnostic coding data to obtain the relevant information. We identified 208 cases of craniosynostosis in ROI and 99 in Northern Ireland (NI) for the study period. This gave a prevalence of 3.5 per 10,000 LB for the island of Ireland. Syndromic craniosynostosis was noted in 13%. Sagittal craniosynostosis was the most common suture involved in the non syndromic group (37 %) followed by coronal suture (31%). The data was compared with EUROCAT data and published figures, where available. This is the first epidemiological estimate of craniosynostosis in the island of Ireland.

P04. A lesson in the investigation of familial deafness

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A non-consanguineous family consisting of six prelingually, profoundly deaf individuals across two generations presented to our service. The 56 year old father (and his sister) had a clinical diagnosis of Pendred syndrome, a well recognised autosomal recessive condition characterised by congenital profound sensorineural hearing loss (SNHL), vestibular dysfunction, temporal bone abnormalities and development of euthyroid goitre in late childhood to early adulthood and known to have considerable phenotypic variability even within families. The 49 year old mother's profound deafness had been attributed to infantile measles. The couple's four daughters (aged 12, 15, 17 and 19 years) were all profoundly deaf with otherwise normal clinical examinations. Various modes of inheritance were considered including: maternal autosomal dominant inheritance with incomplete penetrance (both maternal grandparents had normal hearing); alternative autosomal recessive deafness genes in the maternal family with paternal carriage; and maternal carriage of Pendred. The stepwise investigation of this family is presented with interesting results leading to diagnosis in the daughters and mother.

P05. Identifying the genetic basis of Landau-Kleffner Syndrome

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Landau-Kleffner syndrome (LKS) is an extremely rare form of epilepsy, accompanied by abnormal EEGs and a loss of language in a previously normal child. This results in "word deafness" or auditory verbal agnosia. Additional features may include seizures, behavioural disturbances and cognitive regression. The aetiology of LKS remains unclear. This study was undertaken in two phases. Phase 1 involved genotyping and methylation profiling in two discordant twin pairs and 3 isolated LKS cases. No common disease-causing CNVs or differentially methylated genes were identified. Exome sequencing of the discordant twin pairs and 2 of the 3 isolated cases was performed using the Agilent SureSelect 38Mb enrichment system. Initial data analysis identified no common LKS disease-causing gene. This does not rule out a genetic role in the development of LKS. It is possible that (1) mutations in >1 gene can cause LKS, 2) the exomic region containing the mutations may not have been on the Agilent 38Mb kit and (3) mutations are intronic or intragenic. In order to address these possibilities exome sequencing was performed on an additional 5 LKS isolated patients using the 44Mb Nimblegen enrichment system (Phase 2). Data analysis is currently underway and will be presented at this meeting.

P06. Making matches- linking large Irish Traveller pedigrees as a way of helping gene identification

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Irish Travellers marry young and traditionally have large families. Pedigree structure is complex. Many individuals have common first and surnames and linking families is difficult. Our research work, on two Traveller families with non-specific microcephaly, illustrates this. Microcephaly is relatively common and proving it is due to a common homozygous mutation is difficult phenotypically. As both families share similar names, we hypothesised that they were distantly related and shared the same disease mutation. Homozygosity mapping in the first family identified high levels of homozygosity (25.3%), with 27 candidate loci containing 1,152 genes. Subsequently, a second family with microcephaly was referred consisting of 5 affected individuals. Comparing the homozygous segments shared by the affected individuals from both families would increase the likelihood of disease gene identification if a common gene was the cause. Four generation pedigree analysis of both families revealed >200 individuals in each pedigree with only 6 surnames in total. This explains the high (25.3%) level of homozygosity found. All 6 surnames are common to both pedigrees. The index case and father from pedigree one share their full name with 6 individuals from pedigree 2. Despite this we have not established a link. We are proceeding to analyse pedigree 2 independently but will also determine if there is any overlap in candidate loci between the two families.

P07. An Interesting Case of Vascular Ehlers Danlos Syndrome due to an Interstitial Deletion of Chromosome 2.

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Our patient presented at 15 years of age with acute dissection of the abdominal aorta at the level of the visceral vessels. Emergency surgery was promptly carried out but, unfortunately, bilateral, through knee, amputation of the lower limbs was required. Twelve days later, further dissection of the mid-thoracic aorta occurred which was managed with an endovascular repair. There is no family history of note. Pathology of the aorta showed marked calcification and intimal wall thickening. Multiplex ligation-dependant amplification (MLPA) revealed a heterozygous deletion of the entire *COL3A1* gene. Subsequent microarray analysis showed an interstitial deletion of the long arm of chromosome 2, with breakpoints at q32.1 and q32.3. This deletion is approximately 8.4Mb in size and contains 27 HGNC genes, including the *COL5A2* gene which is associated with Classical Ehlers Danlos Syndrome. Similar deletions have been reported; common clinical features include mental retardation, behavioural problems, thin, transparent skin, mild facial dysmorphism and cleft palate. Our patient is of above average intelligence and is non-dysmorphic. Extended testing of family members shows that this deletion appears to have arisen de novo.

P08. Classical Galactosaemia- a modifiable Glycosylation Disorder?

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Background: Classical Galactosaemia (Gal) is a rare genetic disorder of carbohydrate metabolism. Treatment, restriction of dietary galactose is life-saving in the neonate. However, long-term complications persist including cognitive impairment, speech and language abnormalities and infertility in females. Gross N-glycan assembly defects in the untreated neonate largely correct on treatment but processing defects persist in adulthood (Coss *et al,* 2012).

Aim: IgG N-glycan profiling to monitor galactose liberalisation and variations in glycosylation in treated adults in parallel with analysis of T-lymphocyte gene expression.

Materials and Methods: NP-HPLC of IgG N-glycans in 27 treated and 5 Gal patients on galactose liberalisation. T-cell RNA gene expression (AffymetrixU133a plus2.0) in 12 adult patients with KEGG analysis to identify dysregulated pathways. Results: Galactose incorporation in IgG was studied with G0/G1 and (G0/G1)/G2 ratios. This identified ongoing N-glycan processing defects in treated Gal patients with significant variability and galactose tolerance amongst patients. Gene expression analysis identified dysregulation of 36 glycan biosynthesis genes by at least 2-fold. Abnormal expression of a number of these genes of physiological relevance including galactosyltransferase B4GALT1 and oligomeric golgi complex member COG1 was validated with qPCR.

Conclusions: Our study suggests Gal is a systemic, modifiable glycosylation defect providing possible new treatment targets.

P09. Optimisation of Modified Methylation Specific Digital Karyotyping (MSDK)-Seq for genome wide DNA methylation analysis

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The methylation the 5'carbon of cytosine in DNA plays an important role in the control of gene expression and repression. This enigmatic enzymatic process has many ties with cell differentiation, human disease, and cancer development. Many methods and techniques have been described to analyse DNA methylation patterns and profiles on both a locus-specific and genome-wide scale. Here we describe an example of the latter. Modified methylation-specific digital karyotyping (MMSDK) results in the generation of a library of short sequence tags to be amplified and sequenced by direct, massively parallel sequencing. This method allows for high-throughput and low-cost genome-wide DNA methylation mapping, and is well suited for the search of new genomic regions that vary their methylation patterns in response to physiological or environmental stimuli. The multi-step nature of this method involves many alternating DNA ligation and restriction digestion steps. Here we focus on troubleshooting these steps, and assessing the coverage that MMSDK-seq provides throughout the genome.

P10. Pharmacogenomics of Valproate induced weight gain

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Sodium valproate (VPA) is one of the most commonly used anti-epileptic medications (AEDs) in the treatment of seizure disorders. Weight gain is one of its known side effects. Up to 70% of people exposed to VPA experience some weight gain while about 10% have significant weight gain necessitating discontinuation of therapy. However, the exact mechanism of VPA-induced weight gain is not fully understood. The aim of the study is to apply the latest generation of genetic mapping techniques to identify genetic and environmental risk factors predicting weight gain induced by this commonly used AED. Blood/ saliva samples for genetic analysis will be collected from 250 children (age 2 – 18 years old) attending the three paediatric hospitals in Dublin who have been diagnosed with epilepsy and are on treatment with VPA for at least six months. Clinical phenotype of weight gain during the treatment period will inform the interpretation of genetic studies (Single Nucleotide Polymorphism (SNPs) and/or Genome Wide Assay Studies (GWAS)). To date 187 patients have been recruited. Phenotype analysis in the first 125 patients is nearly completed. Recruitment to this study is progressing as planned and will be completed by December 2012.

P11. High density imputation of the ASD-associated MACROD2 gene region identifies eQTL for plausible ASD-related genes

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Background: In a recent GWA, the Autism Genome Project (AGP) identified a strong association within the gene MACROD2 and autism (Anney *et al,* 2010). We sought to identify whether additional genotype information could better describe the ASD association signal, and examined whether the ASD associated region was also associated with gene expression in the human brain. Methods: Imputation was performed using BEAGLE in approximately 2900 probands and 2900 pseudo-controls from the AGP ASD sample (Anney et al, 2010) and 193 samples from a human cortical gene expression eQTL dataset (Myers *et al*, 2007).

Results: This association study confirmed the association identified in the 2010 AGP study, and following imputation additional supporting markers were identified. One of the significant trans-eQTL associations supporting the ASD-related MACROD2 association signal locus is between rs439451 and CNTN1, a gene previously implicated in ASD. Discussion: The imputation of the MACROD2 locus in this study demonstrates that imputation can enrich the original association signal and provide additional supporting associated markers. The observation of a trans-eQTL between MACROD2-AS1 and CNTN1 may indicate that molecular follow-up studies should consider exploring the role of these intragenic genes. The authors acknowledge grant support from the HRB and the Autism Genome Project.

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. Myers AJ *et al*, A survey of genetic human cortical gene expression. *Nat Genet* 2007; **39(12):** 1494-9.

P12. Risk factors affecting mitochondrial function are associated with diabetic kidney disease

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Small-scale studies suggest that DNA variants in the mitochondrial genome influence kidneyfunction. We sought to explore genetic variants that affect the mitochondria for association with diabetic kidney disease. Common SNPs in the mitochondrial genome were genotyped using Sequenom and Ion Torrent technologies. Additionally, tag and pfSNPs (n=26,766, 113 genes) were analysed for autosomal variation that may influence mitochondrial function. A case-control study was conducted (n_{max}=2,100) where all White individuals had long duration of type 1 diabetes. Case had consistent proteinuria versus unaffected controls. Logistic regression was adjusted for age, duration of diabetes, gender and multiple testing. Replication was conducted in a total of 5886individuals from Denmark, Finland and the USA. Meta-analysis was performed using RevMan software from Cochrane Reviews. mtDNASNP 3243A> was significantly associated with diabetic kidney disease, and a larger effect was observed for end stage renal disease (Padjusted=0.003). 142 unique SNPs were identified with nominal significance in the discovery dataset.An intronic SNP located in the *COX10* gene revealed significant association (P=0.0002) in the meta-analysis where all groups showed effects in the same direction. Additional replication is on-going using independent European cohorts. We have indentified significant SNPs represent important risk factors for diabetic kidney disease.

P13. Association of functional DNMT3B polymorphisms and increased global methylation levels with suicide attempters.

Therese M Murphy[1], Niamh Mullins[1], Tom Foster[2] , Chris Kelly[3], Roy McClelland[3], John O'Grady[3], Eleanor Corcoran[4], John Brady[4], Michael Reilly[5], Anne Jeffers[6], Katherine Brown[7], Anne Maher[7], Noreen Bannan[8], Alison Casement[2], Dermot Lynch[2], Sharon Bolger[1], Avril Buckley[9], Leah Quinlivan[1], Leslie Daly[10,11], Cecily Kelleher[12], Kevin M Malone[1]

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INTRODUCTION: Recently, a significant epigenetic component in the pathology of suicide has been realised. We investigated candidate functional SNPs in epigenetic-regulatory genes, DNMT1 and DNMT3B, for association with Suicide Attempt (SA) among patients with co-existing psychiatric illness. In addition, global DNA methylation levels between SA and psychiatric controls were examined.

METHODS: DNA was obtained from blood of 79 suicide attempters and 80 non-attempters, assessed for DSM-IV Axis I disorders. Functional SNPs were selected for each gene (DNMT1; N=7, DNMT3B; N=10), and genotyped. Allelic and genotypic tests of association between genetic variants and SA were conducted using Chi squared test of association. Global DNA methylation levels in a subset of patient DNA samples were quantified using the Methylflash Methylated DNA Quantification Kit (Epigentek, USA).

RESULTS: We identified a SNP in the 3'UTR of the DNMT3B gene, which showed evidence of association with SA compared to a non-attempter control group (P=0.004; Bonferroni adjusted P value=0.02). Moreover, haplotype analysis identified a DNMT3B haplotype (TTTAT) which differed significantly between cases and controls (P=0.01). Global methylation analysis revealed that psychiatric patients with a history of SA had significantly higher levels of global DNA methylation compared to controls (P≤0.001, Mann-Whitney test).

CONCLUSION: Our findings support the hypothesis that aberrant DNA methylation profiles play a significant role in the pathogenesis of suicidal acts.

P14. Analysis of the hexonucleotide repeat expansion at C90RF72 in an Irish psychosis case-control sample.

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A hexonucleotide repeat expansion 'GGGGCC' in an intronic region of the C9ORF72 (chromosome 9 open reading frame 72) gene has been found to account for up to 60% of familial amyotrophic lateral sclerosis (ALS) and up to 10% of sporadic ALS. The repeat expansion is located between exon 1a and exon1b of this gene and although function is unknown, it is thought to impact on gene expression. One in seven ALS patients develops frontotemporal dementia (FTD). Analysis of an Irish population-based cohort of ALS identified a higher rate of FTD in ALS patients carrying the repeat compared to those that do not carry the repeat (PubMed ID (PMID): 22305801). Study of an independent FTD sample showed a strong association between C9ORF72 mutations and psychotic symptoms: delusions, hallucinations, paranoid ideation and disordered thinking (PMID: 22300873). Therefore, we sought to screen a large Irish psychosis case-control sample for evidence of association between the repeat expansion and psychosis. Our sample included 742 schizophrenia, 261 bipolar disorder, 162 schizoaffective disorder cases and 1,283 control samples. We used a reverse primed PCR method to amplify the hexonucleotide repeat expansion. Analysis of PCR products was

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carried out using a 3130xl Genetic Analyzer and GeneMapper 3.0 software (Applied Biosystems).The pathogenic range of the variant is >30 repeats and the expansion can extend up to 700-1600copies in ALS/FTD sufferers. All samples were genotyped in 96-well plate format and each plate contained two positive control samples that had both previously been confirmed to contain 34+ repeats. Overall the distribution of repeat numbers was very similar for cases and controls. We identified four samples that carried a repeat number approaching the pathogenic range. There were two controls samples (23 and 24 repeats respectively) and two schizophrenia cases (both 26 repeats). Initial reports on this repeat expansion indicated that the normal range of repeats does not usually exceed 23 copies of the hexanucleotide. A small number of apparently normal individuals have an intermediate number of repeats between 24 and 29, the significance of which is unclear. The repeat length in two cases with schizophrenia lies within this intermediate range, raising the possibility of an association between C9ORF72 repeat expansions and psychosis. As expansions may be tissue specific, further studies using Sothern blotting may be warranted to test the hypothesis that some forms of psychosis are linked to C9ORF72 repeat expansions.

P15. Inheritance of chronic kidney disease in men: association with Y chromosome.

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Men have an increased risk of chronic kidney disease (CKD) and end-stage renal disease. Genetic and epigenetic factors on the Y chromosome were explored for association with end stage renal disease. Haplogroup I of the Y chromosome was more commonly observed among 1,361 white European men who developed CKD (20% in cases versus 15% in unaffected controls, p=0.03). Age-adjusted analysis confirms that haplogroup I is significantly associated with an increased risk of CKD (OR=1.36, 1.02-1.83, p=0.03). Association with cardiovascular disease within this CKD cohort was also observed (p=0.008). 238 probes on the Y chromosome were evaluated for differential DNA methylation status in 225 males (151 cases with CKD, 74 age-matched controls with no evidence of kidney disease). Three loci (*DDX3Y*, *NLGN4Y*, and *TTTY14* genes) demonstrated significant association with CKD ($P<10^{-6}$). Two sites flank the SNP defining haplogroup I on the Y chromosome in Europeans, while *TTTY14* is a validated non-coding RNA expressed in the kidney. Male gender is associated with shorter life expectancy for individuals with CKD and with increased cardiovascular mortality in particular. These results suggest that the Y chromosome should be further studied employing large renal disease genetic consortia to explore gender differences associated with risk of CKD.

P16. Rare Copy Number Variation in Neuropsychiatric Disorders: Exploring the Phenotype

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There is emerging evidence that copy number variants (CNVs) provide a new vista on understanding unique and pleiotropic susceptibility to neuropsychiatric disorders such as Autism Spectrum Disorders (ASD) and schizophrenia. Rare CNV and detailed phenotype data were derived from the Autism Genome Project and Irish schizophrenia cases. Patients were classified by whether a rare CNV impacted any genes previously implicated in ASD or Intellectual Disability (ID) or not (0/1), or any genes that are differentially brain expressed (BE) or not (0/1), and association with candidate neurodevelopmental phenotypes were examined. Random forests and mixture models were used to explore whether phenomic features identify CNV-associated sub-groups. No statistically significant univariate associations between CNVs and selected phenotypes were identified for either ASD or schizophrenia. Exploratory analyses suggest sub-phenotypes that might provide good targets for association analyses in future studies, and indicate that distinguishing deletions and duplications is important. Inconsistency of measurements by site in large collaborative studies is a major impediment to assessment of genotype-phenotype associations. Sophisticated modelling suggests that CNV-associated subgroups may exist, however the clinical applicability of these remain to be demonstrated.

P17. Allele specific siRNA as a potential therapy for corneal dystrophy

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The corneal dystrophies are incurable diseases affecting the transparency of the eye. They are predominantly caused by heterozygous, dominant negative mutations in the cytosketetal keratins K3/K12, which provide structural support to the cells; and the TGFBI gene, which is important for corneal development and healing. Here, a siRNA sequence walk and a dual luciferase reporter gene assay was used to determine the best mutation specific siRNAs for the K12 mutation Leu132Pro. Further screening of these siRNAs by standard and dual-tag infra-red western blots as well as pyrosequencing confirmed mutant allele specificity at protein and mRNA levels. 5'Race confirmed a RISC-mediated mode of mutant mRNA knockdown. Cytoskeletal filament aggregation was reduced by mutation specific siRNA treatment in a cultured cell model and no off target effects were observed against closely related keratins in another model epithelial cell line. No immunological response to siRNA via TLR3 upregulation was observed using semiquantitative RT-PCR. Overall this allele specific siRNA approach yields promise for a potential personalised treatment of these disorders via specialised eyedrop formulations.

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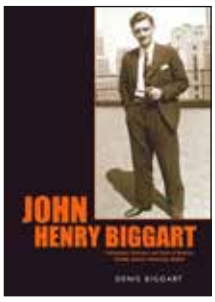
Book Reviews

JOHN HENRY BIGGART



By Denis Biggart, Ulster Historical Foundation, Published 2012, Pages 194, Price £9.99

This is a delightful book written by John Henry Biggart's son, Denis.

Those of us who were interviewed by him as applicants to study Medicine at Queen's University, remember well a man who controlled our futures – beginning the interview – do you play rugby? Do you play for the First XV and what position do you play?

This book is a beautiful commentary on a man who was the 'star' of Ulster Medicine for over 40 years.

The book begins with John Henry Biggart's memories from his personal papers, meticulously dissected by his son, Denis (himself a Consultant Pathologist and academic in Queen's University). For those interested in social history there are titbits of the times in which he lived from his birth in Belfast in 1905, to his school days, University days (with the remarkable pranks of yesteryear) to the multiple anecdotes of the 'man himself', his mentors and teachers. As an aside there are wonderful stories of 'icons' of the day – such as Dr Richard Hunter (Dicky) – author, actor, artist, anatomist and circus ringmaster. In the one year John Henry won the Symington Medal in Anatomy and the University Billiard championship!

The book traces John Henry's career as a young doctor in the Royal Victoria Hospital, his two years in John Hopkins in Baltimore and in 1937 his appointment, at age 31, as Professor of Pathology at Queen's University – the remarkable 27 years as Dean of the Faculty of Medicine, Knighthood in 1967 and Pro-Chancellor in 1972, his GMC role and his sudden death on the way to a GMC meeting in London on 21st May 1979.

A doyen of Ulster Medicine with a local, national and international reputation and yet with a quiet 'soft' side – which those of us as students never saw (the poet – appendix 4).

This little book will be of interest to those of us who were his students and to his many colleagues, as well as students of medical and social history. I would particularly encourage our new students of medicine, trainees and younger colleagues to purchase this little book – not only to realise the legacy left by this giant of Ulster Medicine but to learn about times and personalities gone by –maybe we can still learn from the past!

Well done Denis! – with the encouragement of Sir Peter Froggart you have done a great service in producing this book.

Professor RAJ Spence

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So you want to be a **Dermatologist**

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Dermatology is a medical specialty involving the management of skin conditions. It is one of the most diverse specialties treating patients from all age groups with inflammatory, inherited, environmental, occupational and malignant skin diseases.

Dermatology is predominantly outpatient based within the hospital. However, patients with acute systemic upset or severe inflammatory or blistering skin disorders frequently require specialist care within a day-care or dermatology inpatient facility.

Dermatologists link closely with other specialities and we are frequently asked to provide consults on hospital inpatients.

Skin cancer comprises a large and ever increasing volume of a Dermatologist's workload and skin surgery is integral to the service. Complex skin cancer cases are discussed weekly at the Skin Cancer Multidisciplinary meeting. We work closely with our colleagues from Pathology, Plastic surgery, Ophthalmology, ENT & Oncology.

Dermatology training includes subspecialty experience in areas such as Paediatric dermatology, phototherapy/ photobiology, dermatopathology, allergic disorders and dermatological surgery. The field of medical dermatology has really taken off, with many dermatologists running specific chronic disease clinics for the patients on immunosuppressive therapy. The development and licensing of the biological therapies for conditions such as psoriasis have helped transform patient's lives. With new drugs continuing to evolve it is an exciting time for both patients and clinicians.

Most consultant dermatologists develop a subspecialty interest and are encouraged to spend time in specialised centres elsewhere in the UK or further afield. Participation in research and medical education is also encouraged.

Medical students unfortunately gain limited exposure to Dermatology, usually within the third year of studies, but the length of placement varies around the UK from none at all to 2 weeks. This is too short a time to secure a firm knowledge of the speciality, particularly when you consider that up to 20% of GP consultations relate to skin conditions.

Dermatology is a competitive speciality so career planning is crucial. It is important to demonstrate interest in the speciality and it is most valuable to gain clinical experience before pursuing higher specialist training. As an undergraduate there are Special Study Modules which are helpful at providing an insight to the life of a Dermatologist. Taster modules can also be arranged for foundation year doctors.

To further a career in Dermatology junior doctors are encouraged to apply for a core medical training post at either CT 1 or CT 2 level to gain experience in the speciality. ST3 posts are always competitive and full MRCP is required prior to taking up a training post. An alternative career path is as a specialty doctor in dermatology.

Dermatology specialist training is 4 years. During this time trainees are encouraged to attend a number of core specialty courses and meetings.

Training can be extended by 2 or 3 years if time is taken out to complete an academic degree to MD or PhD level. Recently the Specialty Certificate Examination (SCE) was introduced and this is now sat in year 2 of training.

So what is your week like.....Consultants will do 5 outpatient clinics, 2 ward rounds, attend the Skin Cancer MDM and carry out regular liaison ward work. Teaching of the medical students and junior doctors is built into the weekly timetable. Most UK units have a core teaching session, which all doctors attend, and this involves clinical cases, audit, journal club and guest lectures. On call varies around the UK, with many units having lost their on call service. Dermatology units who are still able to provide out of hours cover are on call from home.

So do you want to be a Dermatologist? It is a highly varied and rewarding specialty. You are very busy during daytime hours seeing a great mix of clinical cases and life is never dull..... I thoroughly recommend it!!

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THE ULSTER MEDICAL JOURNAL

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Volume 81 No. 3 **September 2012**
ISSN 0041-6193

Cover legend: nasogastric tube coiled within the oesophagus.