ISSN 0041-6193

THE ULSTER MEDICAL JOURNAL

Volume 82 (2) May 2013

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)

Statement: The Ulster Medical Journal is an international general medical journal with contributions on all areas of medical and surgical specialties relevant to a general medical readership. It retains a focus on material relevant to the health of the Northern Ireland population.

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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.

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

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Editorial

Benediction

In this edition, I am delighted to inform you that we are publishing articles not only from these islands but also from the United States, Austria and Germany. Two articles consider those who decide to undertake medical undergraduate training in Europe. The first, our Review Paper by Professor John Mayberry, details the data on students from Ireland and the UK who did precisely that between 1990-2005. The second, written by Dr Rhiannon Killingbeck, tells us what it's like to enroll abroad in a foreign English language medical degree course and specifically, what it is like to study, live, work and play there. As Rhiannon observes, some of these venerable European academic institutions have been in existence for over 600 years and have an impressive medical and scientific pedigree. The distance, culture shifts and language barriers are not inconsiderable, and as she also wryly comments, 'there won't be anyone there to hold your hand.'

People from these Islands have, of course, been travelling to Europe for centuries, often leaving their mark, sometimes literally. In the ninth century, an Irish Benedictine monk was hard at work in his cell in Reichenau Abbey, which is located on an Island in Lake Constance on the borders between Germany, Austria and Switzerland. He was working on a manuscript now known as *The Reichenau Primer*. This was written using a medieval script system called 'Insular Script', a cartographic technique that had its genesis in Ireland and travelled eastward with the Irish missionaries who founded many of the European monasteries. This technique is also associated with Insular Art and such illuminated manuscripts as the *The Book of Kells*.

The monk's only companion in that lonely cell was his cat, Pangur Bán. In the manuscript's margin, he wrote a poem, comparing Pangur's feline activities to his own scholarly pursuits. The original text is in medieval Gaelic but the first lines (from a translation by Robin Flower) begin:

I and Pangur Bán my cat,
'Tis a like task we are at:
Hunting mice is his delight,
Hunting words I sit all night.

The primer, now housed at Saint Paul's Abbey library in Lavanttal, Carinthia may be viewed on line (http://en.wikipedia.org/wiki/File:Reichenauer_Schulheft_1v_2r_kl1.jpg), Extraordinarily, the poem *Pangur Bán* is still easily recognisable in the lower left hand side of the page.

The patron saint of Europe, Saint Benedict of Nursia (480 -547 AD) is that long forgotten monk's patron. Benedict, incidentally, is also the patron saint of students and of renal disease. Now honoured by the Catholic, Eastern Orthodox, Lutheran and Anglican Churches, Benedict began life as a wealthy Roman but converted to Christianity, adopting a frugal and austere hermitic existence. Invited to become Abbot of a neighbouring monastery, his regime quickly proved too strict and the monks attempted to kill him (by poisoning his kidneys -hence his association with renal disease!), but following a series of miraculous divine interventions he escaped to resume his hermit's life.

Benedict eventually founded twelve monasteries including the great Benedictine monastery at Monte Cassino. His opus magnum, *The Rule of St. Benedict*, was distributed by Charlemagne throughout Europe. Considered balanced, reasonable and moderate, it served as a template not just for Europe's religious but also in the secular milieu as it embodied the ideas of a written constitution and emphasised the centrality of the rule of law.

CURIOSITAS AND BOOK CASE

I am pleased to announce two new sections to the Journal. The first, snappily entitled 'Curiositas' will be a cornucopia of brief medical vignettes, and we hope that both undergraduates and postgraduate readers will submit topics to it. The section editor is Dr Gerry Gormley (curiositas @ums.ac.uk). The printed version of Curiositas is, forgive the luddite term, merely a shop window into a larger on line resource. The idea here is that the interested reader can explore the Curiositas topics in more depth, and as the project grows, eventually interact with the subject matter -CME being a desirable first step.

The second is Book Case. Although we already have an excellent Book Reviews section under the expert stewardship of Professor Roy Spence, I thought it might be interesting to invite experts and luminaries to suggest favourite books that could be of general interest to this journal's wide and discerning readership. No experts or luminaries being to hand at short notice, I have complied the first list myself, so forgive me inflicting my literary tastes on you all. Mea maxima culpa.

So from these islands, centuries ago, missionaries and educators travelled into every corner of the world. One medieval monk and his cat left a mark for generations to enjoy. Others from these Islands continue to travel into the centre of St. Benedict's Europe to educate and to be educated. So, we conclude with *Pangur Bán* and the poetry of his Benedictine cellmate, whose writings, from the heart of Europe, still speak to students of all ages, across the ages.

Practice every day has made
Pangur perfect in his trade;
I get wisdom day and night
Turning darkness into light.

Please do keep sending me your good papers.

Barry Kelly
Honorary Editor

Recognising Fabry Disease

A rare, X-linked, progressive genetic lysosomal storage disease

The wide ranging symptoms mean that patients can present to many different specialities before a diagnosis is made

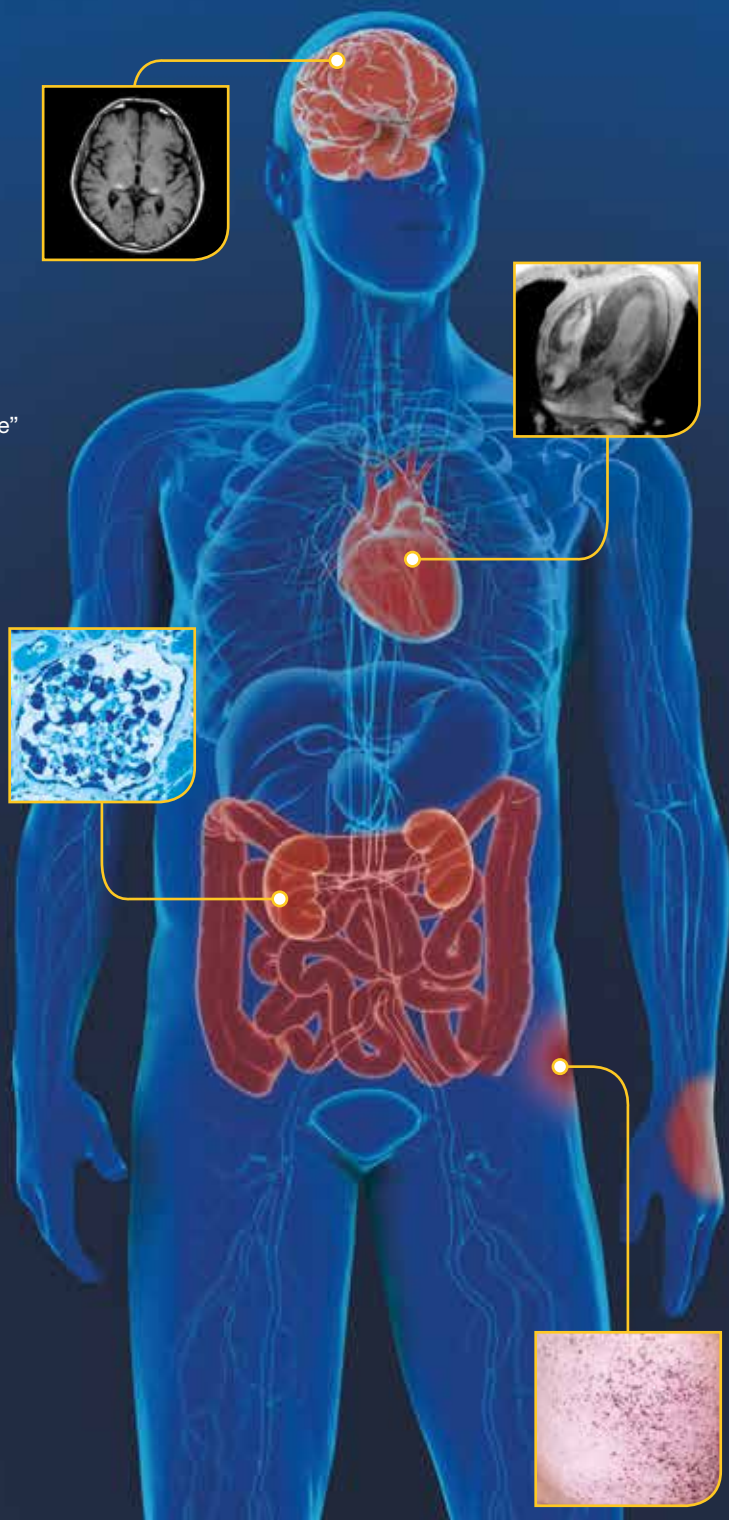
Patients may present with one or more of the following signs and symptoms:

Early Onset

- Neuropathic pain, particularly at the extremities
- Sweating abnormalities
- IBS-type symptoms
- Lethargy and fatigue
- Progressive hearing loss
- Ocular changes
- Angiokeratoma
- Proteinuria

Later Onset

- Renal failure
- Heart abnormalities (LVH)
- History of T.I.A. or “mini stroke”
- Early stroke



Does your patient…

- Have multiple unexplained symptoms?
- Have a family history of early onset renal or cardiac disease or early stroke?
- Take regular powerful painkillers?
- Have any family members who have died before the age of 60 from kidney failure, heart attack or stroke?

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Date of preparation: April 2013
IRE/HG/REP/13/0002a

Ulster Med J 2013;**82(2):**71-74

Review

The Registration of Medical Graduates from Eastern European Union Countries with the General Medical Council (GMC) and the Medical Council, Ireland

John F. Mayberry

Accepted 2 April 2013

ABSTRACT:

The purpose of this study was to identify the number of medical graduates registered with the General Medical Council (GMC) between 1990 and 2005, whose initial training was in Eastern Europe and who came from universities which have subsequently developed an "English Parallel" course and are now within the European Union (EU). A similar exercise was undertaken with graduates registered with the Medical Council, Ireland.

Between 1990 and 2005 one thousand six hundred and fourteen (1614) doctors, who had trained in the selected universities from Eastern Europe, registered with the General Medical Council (GMC) in the United Kingdom (Table 1). The Register of Medical Practitioners for Ireland as at 1st July 2005 was also scanned manually to identify graduates from these countries who were registered in Ireland. Sixty four such graduates were identified of whom 6 qualified before 1990 and 5 were in their internship year. The study suggests that since 2000 younger graduates who sought training in Central and Eastern Europe are returning to the UK shortly after graduation to register and start clinical training.

INTRODUCTION:

During the last twenty years there has been a significant growth in the training of overseas students especially within the European Union. As part of its drive to create a European identity, the European Union (EU) has long been committed to the principles of mobility between member countries and common recognition and equivalence of qualifications. This study will concentrate on English Parallel courses, which embody many of these principles. The recent emergence of comparable schools at Pavia and Milan in Italy and Groningen in the Netherlands gives some urgency to the need to understand the magnitude of these training programs as well as the needs of students studying outside their home country. It also raises questions about the need to develop integration programs for such graduates when they return to their home communities to practice.

The purpose of this study was to identify the number of medical graduates registered with the General Medical Council (GMC) between 1990 and 2005, whose initial training was in Eastern Europe and who came from universities which have subsequently developed an "English Parallel" course and are now within the European Union (EU). A similar exercise was undertaken with graduates registered with the Medical Council, Ireland. At present we have limited understanding of the magnitude of the training of British citizens in the European Union and so of its potential impact on job opportunities within the UK.

METHOD:

The General Medical Council of the UK and the Medical Council of Ireland were asked to provide a list of the names of graduates together with their year of registration from:

Czech Republic:	Charles University, Prague
	Palacky University Olomouc
	Masaryk University Brno
Slovakia	Pavol Jozef Safarik University, Kosice
	Comenius University, Bratislava
Poland	Uniwersytet Medyczny, Lodz
	Bialystok Akademia Medyczna
	Akademia Medyczna im. Karola
	Marcinkowskiego W. Poznan
	Jagiellonian University Krakow
	Academia Medyczna w Gdansku
	Medical University of Silesia, Katowice
Hungary	University of Pecs Medical School
	University of Szeged
	Debreceni Orvostudomanyi Egyetem
Estonia	Tartusskogo Universiteta

These data were made available as a computer print-out. Similar data were extracted from the Register of the Medical Council of Ireland, which was available as a compact disk. [1]

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Data were analysed by country, date of graduation and date of registration. Statistical comparisons across time periods and between British and Irish registrants were performed using Arcus Quickstat software.[2] The comparison of rates and proportions used by this software depended upon tests developed by Fleiss.[3]

RESULTS:

Data were collected from two sources – the General Medical Register of the United Kingdom and the Medical Register of Ireland. This allowed a comparison of registration of Eastern European graduates in two separate English speaking jurisdictions.

Between 1990 and 2005 one thousand six hundred and fourteen (1614) doctors, who had trained in the selected universities from Eastern Europe, registered with the General Medical Council (GMC) in the United Kingdom (Table 1). Most English parallel courses started after 1994. The courses are generally 6 years in duration, although some are 5 years. The impact of such courses can, therefore, be seen from 1999 or 2000. In 2004 these countries became members of the EU and registration with the GMC no longer required applicants to have taken the Professional and Linguistics Assessments Board (PLAB) examination.

Table 1:

Graduates from Selected Eastern European Countries who qualified between 1990 and 2005 and were registered with the General Medical Council or the Medical Council in 2005.

Country	University	Number of Graduates	
		UK	Ireland
Czech	Prague	385	16
	Olomouc	86	3
	Brno	48	2
Slovakia	Kosice	72	3
	Bratislava	176	13
Poland	Lodz	104	3
	Bialystok	51	2
	Poznan	45	2
	Krakow	77	7
	Gdansk	133	2
	Katowice	115	3
Hungary	Pecs	175	4
	Szeged	58	0
	Debreceni	95	1
Estonia	Tartu	27	1

The Register of Medical Practitioners for Ireland as at 1st July 2005 was also scanned manually to identify graduates from these countries who were registered in Ireland.[1] Sixty four such graduates were identified of whom 6 qualified before 1990 and 5 were in their internship year. Of the 58 physicians who qualified after 1990, 28 registered with the Medical Council, Ireland in 2004 and 30 in 2005. Of these doctors 3 had typical British or Irish surnames. Two qualified from Charles University in Prague in 2002 and 2004. Both registered in 2005 and 2004 respectively. The third qualified from Palacky University, Olomouc, Czech Republic in 2003 and registered in 2005.

Charles University has one of the longest running English parallel courses amongst this group of universities. Its first graduates from these courses were in 2000 with 31 people registering with the GMC. Since that date, on average, about 40 people have registered each year. During a comparable period, from 2000 to 2005, there have been only 6 registrants from the University of Tartu in Estonia. Its English parallel course was only initiated in 2006 and so these registrants will have received their training in the medium of Estonian.

In an attempt to discover which graduates were on English parallel courses those with English sounding surnames and first names were identified and those qualified between 1994 and 1999 compared with those qualified in the six year period from 2000 to 2005 (Table 2). In the earlier period there were 18 such graduates compared with 27 in the latter period. Of these 27 data were available for 26, the other doctor working under supervision. The median duration from qualification to registration with the GMC was 7 years for those who qualified between 1994 and 1999. For those qualified after 2000 the median interval was 1 year. A Mann Witney comparison showed that this difference was highly significant with $p < 0.0001$ adjusted for ties. This corresponds with the significant increase in registrations which followed the entry of the selected countries into the European Union in 2004. Of the 18 graduates from before 2000, nine were on a specialist register compared with one from 2000 onwards. These proportions are significantly different ($z = 3.5$, two sided $p < 0.0004$).

Table 2:

Doctors registered with the GMC during the periods 1994 – 1999 and 2000 – 2005 with an English sounding name and who were graduates of selected universities from the Eastern part of the European Union

This table excludes British citizens with Asian surnames, who were students in Eastern Europe. Citizens of other countries with Asian surnames cannot be distinguished from this publicly available data.

Specialty	Qualified before 2000	Qualified after 2000
General Practice	5	0
Cardiology	1	0
Neurology	1	0
Obstetrics & Gynaecology	1	0
Trauma & Orthopaedics	1	0
Anaesthesia	0	1

They suggest that since 2000 younger graduates who sought training in Central and Eastern Europe are returning to the UK shortly after graduation to register and start clinical training. For the earlier graduates general practice was the most frequently chosen specialty.

TABLE 3:

Entries on Specialist Register of Doctors with British Style Surnames who qualified in Eastern Europe

Country	University	Number of Graduates	
		1994 – 99	2000 - 05
Czech	Prague	5	14
	Olomouc	0	7
	Brno	1	0
Slovakia	Kosice	3	0
	Bratislava	3	1
Poland	Lodz	0	0
	Bialystok	0	0
	Poznan	0	2
	Krakow	0	0
	Gdansk	4	0
	Katowice	1	0
Hungary	Pecs	1	1
	Szeged	0	1
	Debreceni	0	1
Estonia	Tartu	0	0
Total		18	27

Forty eight per cent of registrants with the General Medical Council had qualified in either the Czech Republic or Slovakia. Fifty eight per cent of registrants with the Medical Council, Ireland had originally qualified in one of these two countries ($z = -1.6$ n.s.). Of the 1614 Eastern European graduates who registered with the General Medical Council 45 had an English/Irish style surname. Of the 64 graduates who registered with the Medical Council, Ireland 3 had English/Irish style surnames. A comparison of these proportions, using a z test, showed no significant difference ($z = - 0.89$ n.s) If graduates from Charles University, Prague are examined then of 385 registrants with the GMC 19 had an English/Irish style surname, compared with 2 of 14 in Ireland. Again comparison between these two proportions showed no significant difference ($2 = - 1.5$, n.s). The level of specialist practice was similar amongst those with English/Irish surnames in both the United Kingdom and in Ireland ($z = 0.9$, n.s.).

The British and Irish Registers were examined for graduates of Central and Eastern European Universities with English Parallel courses as documented above. In order to ensure accuracy of data collection the exercise was carried out on two separate occasions. In addition to identifying all graduates from these universities the data were scrutinised for registrants with English, Welsh, Scottish and Irish surnames, including those of South Asian origin. When doubt existed about the origins of a surname it was checked against "British Isles Surnames".[4] Although a number of British citizens have Asian studies these were excluded from the final stages of analysis as the data available did not allow a decision as to the nationality of the graduate. This weakened the results and means that the figures underestimate the true number of British citizens who have either trained or are training on English Parallel courses.

DISCUSSION:

Between 1990 and 2005, one thousand six hundred and fourteen doctors, who had trained at a university with an English Parallel course, registered in the UK. Of these, at least 45 were British citizens, 19 of whom trained at Charles University, Prague. In 2004, there was a surge in the number of registrations, but the increased level appears to continue at a higher rate with the inclusion of Central European countries in the EU. In addition, there was a significant reduction in the time between graduation and registration – falling to one year or less. The findings from Ireland confirm this dramatic growth in registrations after 2004 with all Irish citizens registering after that date.

This study of registration data confirms that with the entry of countries from Central and Eastern Europe into the EU the number of people training on English Parallel courses who have registered in Britain or Ireland has dramatically increased and these numbers are likely to continue. At the time of this survey the majority of students trained in Prague. However, during the last decade the number of English Parallel courses has increased and the output from these schools is likely to contribute to the number of doctors registering and working in the UK and Ireland.

The main sources of unreliability in this study are the source of the data and the identification of graduates as of British or Irish origin. The data were only available from the two registration authorities and there are no independent ways of confirming these data. The Medical Annual is an independent list of doctors working in the UK but inclusion in it is voluntary. Lists of graduates from English Parallel courses would not provide evidence of registration. In contrast all practitioners must be registered with the national licensing body and so these lists are likely to be comprehensive.

Prior to 2004 students from English Parallel courses were required to take the PLAB route to registration. As part of this requirement prospective registrants were exposed to a range of training programs which introduced them to UK practice. At present these graduates can move directly into clinical practice without any preparatory introduction to British or Irish medicine. In the past most graduates from English Parallel courses went into general practice and if this trend continues such introductory training would be particularly useful.

One reason students chose to train on English Parallel courses is because they failed to achieve the requisite grades for

admission to a British or Irish medical school. There is some irony in this situation when one considers that Ireland actively recruits rejects from Canadian medical schools.[5] In addition, the UK recruits a significant number of fee-paying overseas students, with British citizens training in Europe only to enter practice in the UK.

Clearly the rationale behind European medical training has to be reviewed. The EU wishes to promote and support professional mobility and this can be seen , to some degree, with the movement of French general practitioners to the London area.[6] Perhaps formal links should be developed between medical schools in the East and West and the North and South of Europe. During their training program medial students would be expected to spend two semesters away from their home school, one would be in the East West pairing and the other in the North South pairing. Such an approach would encourage linguistic skills, demonstrate a range of approaches to clinical care and the provision of health services as well as engendering an European identity

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Paper

The mediastinal staging accuracy of 18F-Fluorodeoxyglycose Positron Emission Tomography / Computed Tomography in non-small cell lung cancer with variable time intervals to surgery.

Karen Booth[1], Gerard G Hanna[2,3], Niall McGonigle[4], Kieran G McManus[1], James McGuigan[1], Joe O'Sullivan[2,3], Tom Lynch[3,5], Jonathan McAleese[2]

Accepted 13 March 2013

ABSTRACT:

Background: PET/CT scanning can determine suitability for curative therapy and inform decision making when considering radical therapy in patients with non-small cell lung cancer (NSCLC). Metastases to central mediastinal lymph nodes (N2) may alter such management decisions. We report a 2 year retrospective series assessing N2 lymph node staging accuracy with PET/CT compared to pathological analysis at surgery.

Methods: Patients with NSCLC attending our centre (excluding those who had induction chemotherapy) who had staging PET/CT scans and pathological nodal sampling between June 2006 and June 2008 were analysed. For each lymph node assessed pathologically, the corresponding PET/CT status was determined. 64 patients with 200 N2 lymph nodes were analysed.

Results: Sensitivity of PET/CT scans for indentifying involved N2 lymph nodes was 39%, specificity 96% and overall accuracy 90%. For individual lymph node analysis, logistic regression demonstrated a significant linear association between PET/CT sensitivity and time from scanning to surgery (p=0.031) but not for specificity and accuracy. Those scanned <9 weeks before pathological sampling were significantly more sensitive (64% <9 weeks, 0% ≥9 weeks, p=0.013) and more accurate (94% <9 weeks, 81% ≥9 weeks, p=0.007). Differences in specificity were not seen (97% <9 weeks, 91% ≥9 weeks, p=0.228). No significant difference in specificity was found at any time point.

Conclusions: We recommend that if a PET/CT scan is older than 9 weeks, and management would be altered by the presence of N2 nodes, re-staging of the mediastinum should be undertaken.

INTRODUCTION

Lung Cancer is a leading cause of cancer death and non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers[1]. Of the many prognostic factors that determine outcome in NSCLC, tumour stage grouping is the most important[2]. 18-F Fluorodeoxyglucose (FDG) Positron emission tomography (PET) has improved staging in NSCLC as compared to computerised tomography (CT) scanning alone by detecting otherwise occult metastases[2].

Several meta-analyses have reported a high accuracy rate for FDG-PET staging of regional lymph nodes, with sensitivities of 79-85% and specificities of 89-92% compared to CT with sensitivities and specificities of 57-61% and 77-82% respectively, the results from these studies are summarized in table 1[4,5,6,7]. Furthermore FDG-PET correlated with CT has been demonstrated to be being superior to its individual components and integrated FDG-PET/CT scanning better that PET and CT visually correlated[8-10]. Two recent studies randomising patients to conventional staging without PET and conventional staging with PET/CT have shown a beneficial effect of the addition of PET/CT to conventional staging in appropriately selecting patients for curative therapy[11,12].

The impact of PET in routine clinical practice

FDG PET is now used routinely as a baseline staging tool in NSCLC. Most international guidelines now endorse the

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Table 1:

Mediastinal staging performance of CT as compared to PET in four meta-analytical series

	CT mediastinal staging performance		PET mediastinal staging performance	
Meta-analysis	Sensitivity	Specificity	Sensitivity	Specificity
Dwamena et al (1999)[4]	60 (58-62)*	77 (75-79)*	79 (76-82)*	91 (89-93)*
Gould et al (2003)[5]	61 (50-71)†	79 (69-98)†	85 (67-91)†	90 (82-96)†
Toloza et al (2003)[6]	57 (49-66)*	82 (77-86)*	84 (78-89)*	89 (83-93)*
Birim et al (2005)[7]	59 (50-67)*	78 (70-84)*	83 (77-87)*	92 (89-95)*

Key to table: * = sensitivity and specificity measurement in means and range in brackets defined by 95% Confidence intervals. † = sensitivity and specificity defined by median values and range in brackets defined by inter-quartile range.

routine use of PET in selecting patients for radical therapy[13,14]. In our institution, pre-operative patients with FDG-PET negative mediastinal nodes as assessed by a PET radiologist are not routinely considered for biopsy of the Mediastinal nodes by mediastinoscopy. If considered for radical therapy, such patients proceed directly to surgery or radiotherapy to the primary lesion only. Patients who are considered for radical therapy and who have FDG-PET positive lymph nodes in the mediastinum will have confirmation of the pathological status of the involved lymph nodes with surgical sampling of positive lymph nodes. However, in patients with positive lymph nodes, where the pattern of disease, the activity on PET and the lymph node size are highly suggestive of nodal metastases the PET findings are presumed to be correct and no surgical sampling is undertaken. In addition to the role of FDG-PET for baseline staging in NSCLC, FDG-PET is now used for target definition in the treatment planning process for radical radiation therapy. A large number of radiotherapy planning studies have indicated that there is a significant benefit of using FDG-PET both for selection of patients and as target volume delineation tool[3,15,16,17].

Aim of Current Study

This study retrospectively compares the diagnostic accuracy of PET/CT scans in routine clinical practice at our institution in assessing the involvement of N2 disease. In this study we compare varying time frames from PET/CT to surgery with the accuracy of the PET/CT analysis and suggest an optimal timing of the using of PET/CT information or a "best before" time interval.

MATERIALS AND METHODS

Patient identification and data collection

In an institutionally approved retrospective study, we examined the records of all patients at our centre who had a staging FDG PET/CT scan followed by central Mediastinal lymph node (N2) staging, either at the time of radical surgery (lobectomy or pneumonectomy) or at mediastinoscopy, between June 2006 and June 2008. For all patients, at least 4 mediastinal (both N1 and N2) nodes were sampled. Pathological sampling from endoscopic or endobronchial ultrasound was not used. Patients were identified from the Belfast Lung Multidisciplinary Meeting database, which has

Table 2:

Study Population Baseline Characteristics

Gender (Male; Female)		35:29
Median Age (range)		65 years (42 to 82)
Median time from Scan to Sampling (Mean, Range)		8 weeks (8.5, 1 to 22)
Median SUVmax of Primary (Range)		11.8 (2.2 to 31.5)
Median SUVmax of Nodes (Range)		4 (2.1 to 11.4)
Surgery Type n (%)	Mediastinal Sampling	4 (6.2%)
	Lobectomy	38 (59.4%)
	Pnuemonectomy	22 (34.4%)
Pathological Subtype n (%)	Squamous	36 (56%)
	Adenocarcinoma	25 (39%)
	Adenosquamous	1 (2%)
	Poorly Differentiated	2 (3%)
Pathological Stage (AJCC*) n (%)	I	27 (42%)
	II	23 (36%)
	III	13 (20%)
	IV (2 lobes involved)	1 (2%)
Tumour Stage (T) n (%)	1	8 (13%)
	2	46 (72%)
	3	7 (11%)
	4	3 (5%)
Nodal Stage (N) n (%)	0	36 (56%)
	1	18 (28%)
	2	8 (13%)
	3	2 (3%)

Key to table: SUVmax = Maximum Value of Standardised uptake value within tumour.
* = 6th Edition of American Joint Committee on Cancer staging

TABLE 3:

Sensitivity, specificity and accuracy of PET/CT staging of individual N2 lymph node analysis and timing from scanning to surgical sampling.

Time between PET/CT and Surgery	Patients (n)	TP	FP	TN	FN	Sensitivity* (%)	Specificity* (%)	Accuracy* (%)
≤ 6 Weeks	21	4	1	61	2	67 (22-96)	98 (91-100)	96 (88-99)
6-8 Weeks	17	3	3	65	2	60 (95-15)	96 (88-99)	93 (85-98)
9-12 Weeks	19	0	3	35	6	0 (0-46)	92 (79-88)	80 (65-90)
>12 Weeks	7	0	1	13	1	0 (0-98)	93 (66-99)	87 (60-98)
All Patients	64	7	8	174	11	39 (17-64)	96 (92-98)	91 (86-94)

Key to Table: TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative
* = 95% Confidence Intervals of result shown in brackets

been prospectively collecting full clinical information on all patients diagnosed with lung cancer in the Belfast area of Northern Ireland since 2006. Patients who had received interval treatment, such as induction chemotherapy, between PET/CT scanning and surgery were excluded from analysis. All patients were scanned using a GE Discovery LS fusion PET/CT scanner using a standardised imaging protocol. Patients were scanned after injection of FDG 375 MBq followed by a 45-min uptake period and CT scan acquisition. A standard diagnostic imaging protocol was used and no special breathing instructions were given during the CT acquisition. Image acquisition was from the vertex of the skull to the mid-thigh region. The PET/CT and pathology data were acquired for each patient. Four patients with nodal-sampling longer than 35 weeks after the staging PET/CT scan were excluded, given the very long time interval for these patients. For each lymph node assessed pathologically and with complete anatomical location descriptors from the surgical procedure, the corresponding radiological status on PET/CT for that given lymph node position was determined. Pathological subtype, size of the primary tumour on PET/CT scan and maximum standardized uptake value (SUV_{MAX}) of the primary and lymph nodes on PET for each patient were recorded. Metastatic involvement of a lymph node on PET/CT was deemed positive or negative by assessment by a consultant PET radiologist, blinded to the pathology report.

Analysis and Statistics

The lymph node status at pathology was considered as the gold standard for comparison purposes. Sensitivity was calculated as true positive/ (true positive + false negative) x 100, specificity as true negative / (true negative + false positive) x 100 and accuracy as (true positive + true negative)/ total number x 100. The students t-test was used to compare the means of normally distributed data and the Fisher's exact test were used for analysis of the categorical data, given the small numerators in many of the categories analysed. Logistic regression was undertaken to assess the presence of any correlation between the accuracy of the PET/CT scanning and the time between the PET/CT scan and the surgical procedure. In the logistical regression analysis of the individual lymph node data with time, given that several nodes were taken from the same patient and scan and that these results may not be independent, analysis with robust standard errors was also performed to adjust for any over-estimation of power[18]. All calculations were performed using Stata version 9.2 (StataCorp LC, College Station, Texas, USA). Descriptive statistics were used where appropriate.

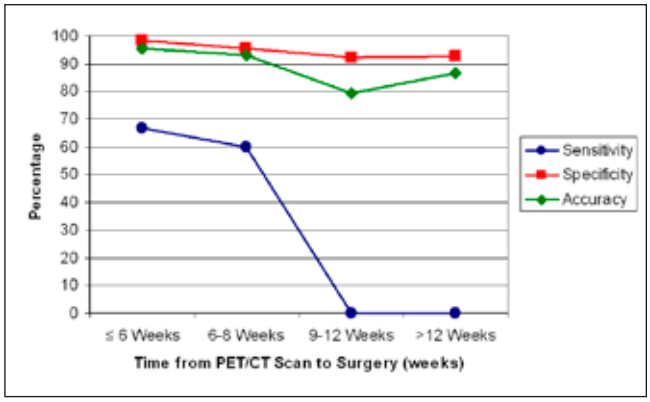

Fig 1. Sensitivity, Specificity and Accuracy of PET/CT staging of individual N2 lymph nodes at various time intervals between scanning and surgery.

RESULTS

Patient and tumour characteristics

From June 2006 to June 2008, sixty-four patients with NSCLC were identified who had been staged with PET/CT scanning and who had undergone subsequent pathological nodal sampling of N2 nodal stations. A total of two-hundred mediastinal (N2) individual lymph nodes were identified. The patient's baseline characteristics are shown in table 2.

The median time between staging PET/CT scan and lymph node sampling was eight weeks, reflecting an often complex assessment and treatment pathway for radical patients. The overall male to female ratio was 1.21 to 1 and the ratio for squamous carcinoma to adenocarcinoma was 1.44 to 1. Of note, adenocarcinomas had a significantly lower primary tumour SUV_{MAX} than tumours with squamous cell carcinoma pathology (mean 10.5 for adenocarcinoma versus 14.5 for squamous carcinoma, student's t-test p=0.005), had a non-significantly lower nodal SUV_{MAX} (mean 3.7 for adenocarcinoma versus 5.8 for squamous carcinoma, student's t-test p=0.052), and were of smaller size on staging PET/ CT (median primary tumour size 3.6cm for adenocarcinoma versus 4.7cm for squamous carcinoma, student's t-test p=0.042).

Staging performance and the effect of time on staging accuracy for individual lymph node analysis

Analysis of the staging accuracy for individual lymph nodes revealed relatively poor overall correlation between PET/CT staging and pathological staging of mediastinal lymph nodes with a low sensitivity. The results obtained for all lymph nodes were closer to those expected from CT staging alone with an overall sensitivity 38%, specificity 96% and accuracy 91%. These results are summarised in table 3 and illustrated in figure 1. Using logistic regression, the association between sensitivity, specificity and accuracy with the time interval between PET/CT scanning and surgery was estimated. There was no association between specificity and time (p=0.249) and analysis of accuracy and time also failed to reach significance (p=0.061). However, logistic regression, demonstrated a significant reduction in sensitivity with time (p=0.031) and this remained significant after adjustment for any lack of independence of nodes by using robust standard errors (p=0.007). Three different time intervals between PET/CT scanning and surgical sampling (less or equal to 6 weeks as compared to greater than 6 weeks, less than 9 weeks as compared to 9 weeks or greater and less than 12 weeks compared to greater than 12 weeks) were examined to see if at any given point in time was there a significant reduction in sensitivity, specificity or accuracy. At the cut-point of less than 9 weeks as compared to greater than or equal to 9 weeks from PET/CT scanning to surgery there was a statistically significant difference in the sensitivity and overall accuracy of N2 nodal detection (Fisher's exact test 2-sided significance, p=0.013 and p=0.007 respectively), with superiority in sensitivity and accuracy for those lymph nodes whose PET/CT scan was within 9 weeks of surgery (sensitivity 64% for less than 9 weeks as compared to 0% for greater than or equal to 9 weeks and accuracy 94% for less than 9 weeks compared to 81% for greater than or equal to 9 weeks). No significant difference for specificity was observed at any of the time intervals.

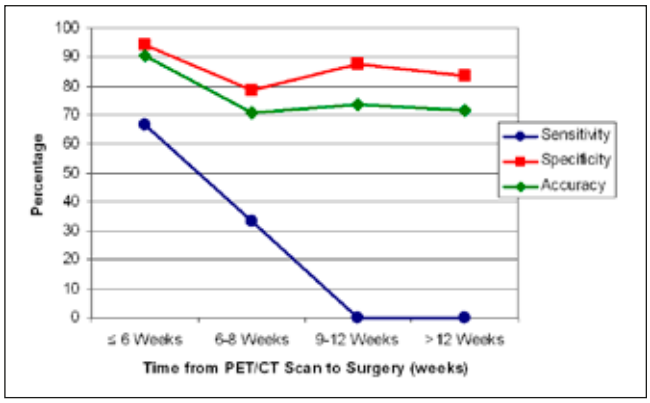

Fig 2. Sensitivity, Specificity and Accuracy of PET/CT staging of N2 lymph node status, for each patient at various time intervals between scanning and surgery.

Staging performance and the effect of time on staging accuracy for individual scan analysis

TABLE 4:

Sensitivity, specificity and accuracy of PET/CT staging of N2 lymph nodes, analysed for individual patient scans with various time intervals from scanning to surgical sampling.

Time between PET/CT and surgery	Patients (n)	TP	FP	TN	FN	Sensitivity* (%)	Specificity* (%)	Accuracy* (%)
≤ 6 Weeks	21	2	1	17	1	67 (9-99)	94 (73-100)	90 (70-99)
6-8 Weeks	17	1	3	11	2	33 (8-91)	79 (49-95)	71 (44-90)
9-12 Weeks	19	0	2	14	3	0 (0-71)	88 (62-98)	74 (49-91)
>12 Weeks	7	0	1	5	1	0 (0-98)	83 (36-100)	71 (29-96)
All Patients	64	3	7	47	7	30 (7-65)	87 (77-96)	78 (66-88)

Key to Table: TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative

* = 95% Confidence Intervals of result shown in brackets

Analysing the staging accuracy based on the performance of each scan for staging N2 disease, similar results were found (see table 4 and figure 2). For all 64 patients, the sensitivity was 30%, specificity was 87%, and accuracy was 78%. In the comparison of sensitivity, specificity and accuracy with the time interval between PET/CT scanning and surgery, no association was found using logistic regression analysis (sensitivity p=0.112, specificity p=0.448, accuracy p=0.205). When the three various time intervals described above were compared, although early scans had greater staging accuracy, no significance difference in sensitivity, specificity and accuracy was observed between the various time intervals.

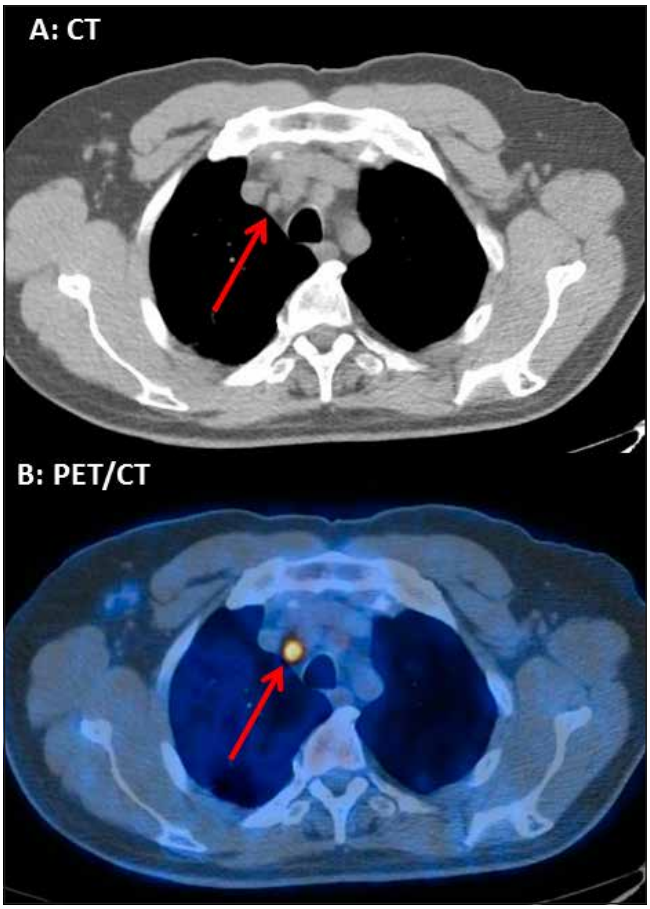

Fig 3. An axial slice on A: CT and on B: fused PET/CT of a patient with true positive upper right paratracheal lymph node at surgery. The red arrows denote the position of the node which is of borderline significance on CT size criteria alone but is clearly FDG avid positive on PET/CT.

Differences in patient and tumour baseline characteristics with time.

To ensure that the time between PET/CT scanning and baseline surgery was not influenced by other patient or tumour characteristics, we compared a number of clinicopathological factors. In comparing stage, SUV_{MAX} and surgery type in those with a time to surgery of less than 9 weeks to those patients who had surgery greater than or equal to 9 weeks from PET/CT, no significant difference in either direction was seen: stage grouping (p=0.373); SUV_{MAX} (p=0.406); surgery type (lobectomy, pneumonectomy or sampling) (p=0.371). Using logistic regression, no association between these variables and time to surgery was noted (stage grouping p=0.363, SUV_{MAX} p=0.588 surgery type p=0.840).

DISCUSSION

As stated earlier, PET and PET/CT data are becoming increasingly integrated into both surgical and radiation oncology management strategies for NSCLC[3-7,15-17,19,20]. The four systematic reviews listed in table 1 clearly define a benefit of PET over CT in terms of accuracy for staging of the mediastinum[4-7]. Further to this, a number of studies demonstrate higher accuracy rates and clinical utility for fused in-line PET/CT scans compared to PET alone or PET co-registered with CT[8-12]. This retrospective study highlights that, despite the superior staging accuracy PET/CT over CT there remains potential uncertainty of PET/CT for detecting metastatic mediastinal lymphadenopathy. In assessment of the PET/CT scan central mediastinal lymph nodes (N2) were deemed negative by assessment by a PET radiologist. Whilst the radiologist will consider both the lymph node size (<1.0cm in the short axis) and the SUV_{MAX} (SUV_{MAX} <2.0), the final determination of N2 positivity on PET/CT is made by a clinical assessment by the radiologist. Figure 3 illustrates an example of N2 lymph node which is <1.0cm in its short axis but is highly FDG avid on PET and was positive at surgery.

The false negative rate was 10.9% with 7 out of 64 patients being incorrectly identified as having no N2 disease on the PET/CT. This may represent micrometastic disease present in small lymph nodes, whose small size are unlikely to be detected by PET/CT which has in our study are a resolution of 5mm slices. Central tumours with occult nodes on PET or could be related to lymph node size. In this study Pathological sampling commented on the presence of metastatic disease only and did not measure the size of the positive node to enable comparison to size on the pre-op PET scan. Furthermore, the reporting radiologist did not report the SUV_{MAX} for those N2 nodes deemed negative on PET/CT. Hence it is not possible to assess the impact of nodal size and SUV_{MAX} thresholds on the staging accuracy of PET/CT for N2 nodal stations. Positive N1 nodes on the basis of size or SUV_{MAX} criteria did not affect the decision to proceed with radical surgery for these patients and therefore had no bearing on the staging accuracy or the likelihood to surgically sample N2 lymph nodes. Clearly a false negative rate is to be expected with the known potential of micro metastatic disease, particularly in adenocarcinoma. Figure 4 illustrates an example a false negative pre-tracheal lymph node which was positive at surgery.

PET scanning accuracy and Radiotherapy Planning Implications

Elective nodal irradiation is no longer routinely used in the treatment of NSCLC with radiotherapy[21]. Delivering radiotherapy to involved nodal volumes based on CT data alone does not result in a high rate of nodal failure[22]. PET

based elective nodal irradiation has also been shown to have a low rate of isolated nodal failure[19,20]. In our study, those patients with scans less than 9 weeks old had a negative predictive value of 90% (95% Confidence Intervals 74-98%). This would suggest that, if the PET scans were used within 6 weeks, only 10% of scans would fail to delineate involved tissue for the purposes of radiotherapy planning. This is comparable to the results obtained by De Ruysscher et al and Klopp et al[19,20].

"Best before date" of PET/CT scanning and optimal timing of scan acquisition

A short time interval between PET/CT scanning and radical therapy with either surgery or radiotherapy is clearly desirable. Even with the most efficient organisation, patients with lung cancer, because of comorbidity, may experience non-elective delays owing to inter-current illness. In our study, the median time interval between staging scan and surgery was 8 weeks with a percentage increase in patients operated on in 6 weeks from 26% in 2007 to 44% in 2008. This suggests an improvement in the local patient pathway. At what time point should the findings of baseline staging be questioned? In our study we found that, if mediastinal sampling was undertaken within 9 weeks of the PET/CT scan, mediastinal staging was of high accuracy and was comparable to the literature standards[4-7]. However, scans older than 9 weeks had a reduced sensitivity and increased false negative rate. This is likely to reflect the progression of the cancer over time and the detection of previously occult metastases. This raises the question, should pre-operative staging with PET/CT occur after determination of fitness for radical treatment? For centres with complex referral patterns and in patients with high prevalence of co-morbid illness, it may be desirable to time the PET/CT in close proximity to a planned intervention. This would ensure a higher accuracy of PET/CT. In our centre, dedicated tracking clerical staff who are attached to our multi-disciplinary team follow the clinical course of each patient suspected or newly diagnosed lung cancer in an attempt to reduce unnecessary delays to definitive treatment.

Study Limitations

This investigation has a number of limitations, of which the greatest is the small sample size. The numbers in the categories of true positive, false positive and false negative are particularly small. Hence a significant effect on specificity may have been missed or conversely, the association between sensitivity and accuracy with time may have been overestimated. Although, with the small numbers in this study, the sensitivity falls to 0 after 9 weeks owing to the lack of true negative N2 nodes. If a larger cohort was available for analysis, then sensitivity is likely to be higher. This uncertainty is illustrated by the wide 95% confidence intervals seen for the sensitivity results seen in tables 3 and 4. Furthermore, analysing several nodes from the same patient's PET/CT scan, may lead to an inherent bias dependent on the characteristics of that patient or their scan. Patient or tumour based 'factors' that cannot be standardized with use of our scanning protocol, that may lead to a repeated measurement effect and thus bias in a given direction include: the pathological subtype; the SUV_{MAX} of the tumour; patient blood glucose level; body mass composition; tumour stage; extent of surgery. We have examined the relationship of stage, SUV_{MAX} and type of surgery with time and have found no significant relationship. However, there remains the potential for such bias. Finally, the retrospective nature of this study is a potential limitation of this study. However, performing a prospective study with elective delays to surgery would not be ethical to undertake, hence any further information suggesting an optimal time-frame to surgery will be retrospective in nature.

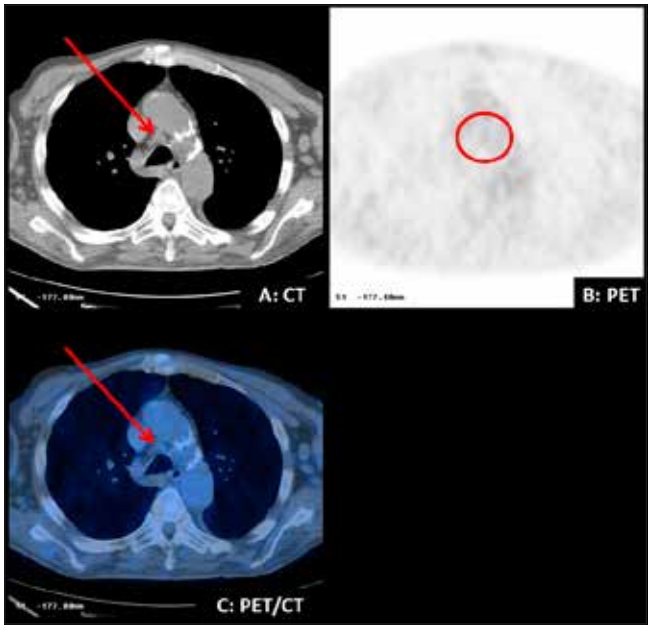

Fig 4. An axial slice on A: CT, on B: attenuated corrected PET and on C: Fused PET/CT on a patient with a false negative pre-tracheal lymph node on PET. Although the CT image suggests nodal positivity by size criteria, the PET (region of interest denoted by red circle) does not demonstrate any significant uptake in this region. The enlarged node was positive at surgery.

CONCLUSION

This study provides some suggestive evidence, but with significant limitations, of an association between time from PET/CT scanning to surgery and the specificity and accuracy of PET/CT scanning in assessing central mediastinal (N2) nodal status. We suggest that in order to improve the outcomes of patients with NSCLC, PET/CT scan data older than 9 weeks, should be regarded as potentially inaccurate for the purposes of central mediastinal (N2) nodal staging.

The authors have no conflict of interest

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Ulster Med J 2013;**82(2):**82-84

Paper

Cataract Surgery Planning in Amblyopic Patients – Which eye first?
Awareness of the Potential for Post-operative Diplopia amongst Consultant Ophthalmic Surgeons in Wales

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Accepted 27 February 2013

ABSTRACT

Aim: To explore the views of consultant ophthalmic surgeons in Wales in the context of planning cataract surgery in patients with amblyopia. To compare prevailing views and preferences with recommendations in published literature.

Method: A cross-sectional survey was conducted in which all consultant ophthalmologists working in Wales were invited to complete an online survey designed using the Survey Monkey tool (http://www.surveymonkey.com). The survey included a clinical scenario involving an amblyopic patient with bilateral cataracts with questions designed to elicit responders' preferences with regard to which eye they would operate on first as well as the reasoning behind their clinical decision making.

Results: 32 out of 42 consultants responded to the survey (a response rate of >75%). With regards to the chronological order of surgery 18 (56.26%) indicated that they would perform cataract surgery first on the non-amblyopic eye, 11 (34.4%) would surgically address the amblyopic eye first and three (9.4%) indicated that patient preference would dictate the choice regarding the laterality of the eye to be operated on first. While 24 responders (75.0%) had encountered amblyopic patients who had developed problems after cataract surgery only 10 (31.3%) opined that formal guidance from the Royal College of Ophthalmologists was warranted.

Conclusion: These results indicate that awareness of post-cataract surgery diplopia, and in particular fixation switch diplopia, is not widespread amongst consultant ophthalmic surgeons in Wales.

INTRODUCTION

Meticulous planning prior to cataract surgery with intraocular lens implantation is vital in order to achieve an optimum post-operative outcome. A potentially problematic situation surrounds the planning of adult cataract surgery in patients with a history of amblyopia, a condition known to affect around 3.6% of the population of the United Kingdom[1]. Fixation switch diplopia is an acquired form of diplopia which can affect patients with a history of childhood strabismus and/or amblyopia in which relatively impaired vision in the dominant eye encourages fixation with the non-dominant eye[2]. Post cataract surgery diplopia can affect up to 3% of patients[3] and published literature recommends the exercise of caution when deciding to perform cataract surgery on an amblyopic eye prior to that on the stronger eye in order to avoid such fixation switch diplopia[4]. Once this occurs, the treatment of this problem can be difficult, with significant resultant morbidity[5]. In view of this, and the large numbers of cataract extractions performed annually in the United Kingdom[4], we set out to investigate current practices in planning cataract extractions in such patients amongst consultant ophthalmic surgeons in Wales.

METHODS

A cross sectional survey was designed in which an email was sent to every consultant in Wales inviting them to take part in an anonymous online survey, the link for which was included. The online Survey Monkey tool (http://www.surveymonkey.com) was used to construct the survey and analyse the results. The following scenario was described:

"A 56year old gentleman in good general health presents with symptomatic visual impairment. Best corrected spatial acuity measures 6/18 in the right eye and 6/60 in the left. Ocular examination is unremarkable apart from nuclear cataracts of similar density in both eyes and a barely noticeable and

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cosmetically excellent concomitant left esotropia of 10Δ.

Past ophthalmic history includes left amblyopia (previous documented best-corrected acuities are 6/4 right eye and 6/9 left eye). He is eager to continue his occupation as an accountant and also to drive a motor vehicle – and is keen on surgical intervention."

Respondents were asked which eye they would operate on first and why. In addition, respondents were asked if they were familiar with amblyopic patients who had developed problems following cataract surgery and also whether they thought any formal guidance from the Royal College of Ophthalmologists was warranted. A total of six weeks was allowed for replies to be collected. A second wave of email invitations were then sent in order to give those that had not completed the survey the first time an opportunity to do so.

RESULTS

Thirty two out of forty two polled consultants responded to the survey, a response rate of >75%. Of the 32 responders to the survey 18 (56.26%) opted to perform right (dominant) eye surgery first, 11 (34.4%) opted to perform surgery on the left (amblyopic) eye first and three (9.4%) opted to give the patient the choice. Of those who would operate on the right eye first, 13 (72.2%) stated 'better visual potential' as a reason while two (11.1%) responders mentioned post-operative diplopia as a risk were the non-dominant eye to be operated on first. In those opting to perform surgery on the amblyopic eye first the commonest reason stated was the worse acuity (seven responders – 63.6%) in that eye. A further two (18.2%) stated that an operative complication would be less of a problem in an amblyopic eye. In all, while 24 responders (75.0%) had witnessed amblyopic patients develop problems after cataract surgery only 10 (31.3%) thought that formal guidance from the college was warranted.

DISCUSSION

The results of this online cross sectional study suggest that awareness of post cataract surgery diplopia, and in particular fixation switch diplopia, is not widespread amongst consultant ophthalmic surgeons in Wales.

Implicit to the clinical problem is the fact that, subject to the procedure being uneventful, the post-operative best corrected spatial acuity in the left (non-dominant) eye would be 6/9, whilst the acuity of the right (dominant) eye would remain at 6/18 – a minimum angle of resolution of double the magnitude - arguably conditions that would be ideal for the development of FSD.

It is interesting that 34.4% of responders would operate on the amblyopic eye first. Not only would this run the risk of fixation switch diplopia, it would also leave unaddressed the principal complaint of the patient - i.e. subjective visual impairment, a symptom related to the dominant eye. Also the majority (63.3%) of those who opted to operate initially on the amblyopic eye selected 'eye with the worse visual acuity' as their reason for doing so. In itself this belies a fundamental misunderstanding of the nature of amblyopia. It is also of concern that 18.2% indicated that they would perform surgery on the amblyopic eye first on the grounds that any complications would be less significant than were they to occur in the better eye. This leaves unaddressed the fact that the better eye would still need to undergo cataract surgery in order to resolve the visual symptoms and arguably, operating initially on the amblyopic eye merely delays this risk. Also of note is that whilst 75% of responders had personally encountered amblyopic patients with problems following cataract surgery, only 31.3% felt that formal guidance from the college was warranted. It would appear reasonable to infer that these clinicians felt that cataract surgery planning in such patients was already well understood by the current generation of cataract surgeons working in Wales; whereas the results of this study would suggest otherwise. At the very least in the drafting of such guidelines priority might perhaps be leant to pre-cataract visual acuity function in each eye, a factor not routinely taken account during planning of surgery.

Whilst the incidence of diplopia following cataract surgery can affect up to 3% of patients[3], the reasons for this are varied and include poor suppression, central fusion disruption and concurrent onset of systemic disease; as well as the potential for fixation switch diplopia discussed in this study. It is a possibility that the type of amblyopia; deprivational, strabismic and refractive, might also play a role in generating post operative diplopia; although no studies have explored this to date. Only a few of these factors are included in standard pre-operative cataract checks and it might be helpful for orthoptists to have a role in cataract surgery planning, although the provision of this new service could of course cause quite considerable strain to eye department service organisation.

Some might argue that treatment of post-operative diplopia produced in this fashion can be treated easily by performing surgery on the fellow eye or by fitting prisms to the patient's glasses or even by performing muscle balance surgery to align the eyes. Whilst this is true it should not substitute for a well thought out cataract surgery planning process and a proper informed consent of all the potential risks, including diplopia in all it's forms following cataract surgery.

The response rate was gratifyingly high for a questionnaire based study, with more than 75% of all ophthalmic consultants in Wales responding. This being said, it is also relevant that Wales as a region is small and whilst this response rate is indeed impressive it nevertheless amounts to only 32 individual ophthalmic consultants. It would have been pleasing to achieve a 100% response rate but unfortunately the constraints of the questionnaire system used meant we were unable to identify who had and who had not responded in order to target specifically the non-responders, although reminder emails were sent out to the entire cohort. Whilst a small study, we submit that the findings are relevant in the contexts of the large number of cataract surgeries performed in the United Kingdom each year (>300,000)[4]

and the estimated prevalence of amblyopia of around 3.6%[1]. We therefore suggest that a nationwide survey with a view to generating increased awareness of this issue would be most relevant, whilst also establishing the case as to whether formal guidance from the Royal College of Ophthalmologists is warranted in the context of cataract planning in amblyopia. In addition to this a prospective analysis of amblyopic patients undergoing cataract surgery that subsequently develop diplopia would also be very useful as a means of attempting to discern which additional factors might need to be taken into account and thus be controlled for in the drafting of such new guidelines.

The authors have no conflict of interest

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Ulster Med J 2013;**82(2):**85-88

Paper

Outcome of ^{131}I therapy in hyperthyroidism using a 550MBq fixed dose regimen

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Accepted 30 January 2013

Summary

Background: Radioiodine is the treatment of choice for relapsed hyperthyroidism although the optimum protocol is uncertain. Fixed dose radioiodine is increasingly popular but responses may vary.

Aim: To assess the outcome of 131I therapy in hyperthyroidism using a standard dose regimen in a regional referral centre and to explore factors influencing outcome.

Methods: We studied 449 patients (M:F 82:367; age range 13-89y, median 42y) with hyperthyroidism treated between 2003 and 2007 with a standard dose of 550MBq 131I. Patients were classified as either Graves' disease, toxic multinodular goitre or indeterminate aetiology. Antithyroid drugs were routinely stopped at least 1 week before radioiodine.

Results: One year after radioiodine 334 (74%) were hypothyroid, 85 (19%) were euthyroid and 30 (7%) had required a further dose of 131I. Patients with Graves' disease were more likely to become hypothyroid than those with toxic multinodular goitre (78% v 37%, p<0.001) and less likely to become euthyroid (11% v 55%, p<0.001). Free T4 >80pmol/L (normal range 9.0 – 19.0 pmol/L) at presentation was associated with an increased failure rate (17% compared with 5% and 3% for 40-79pmol/L and <40pmol/L respectively; p=0.01). Patients with either a small or no goitre were more likely to be successfully treated by a single dose (96%) than those with a medium/large goitre (85%, p<0.001). Anti-thyroid medication was taken by 345 (77%) (carbimazole n=319) patients up to 1 week prior to 131I and was associated with an increased failure rate (8% v 2%, p=0.027) compared to those who had not had antithyroid medication. Logistic regression showed free T4 at presentation to be the only independent risk factor for failure of the first dose of radioiodine (OR 2.5; 95% CI, 1.2-5.1, p=0.012).

Conclusion: A single standard dose of 550MBq 131I is highly effective in treating hyperthyroidism. The aetiology, severity of hyperthyroidism at diagnosis, goitre size and prior antithyroid medication all had a significant effect on outcome.

Keywords: Radioiodine, hyperthyroidism,

INTRODUCTION

Hyperthyroidism is a common condition which may be associated with significant morbidity.[1] Cardiovascular morbidity secondary to hyperthyroidism is more common in the elderly and includes atrial fibrillation and congestive heart failure.[2-5] Hyperthyroidism may also contribute to increased all cause and circulatory mortality.[6,7] It is therefore important that hyperthyroidism is treated promptly and effectively to minimise adverse outcomes.

Radioiodine is a safe and effective management option in hyperthyroidism although there is no clear consensus regarding its use. In the United States ^{131}I is often recommended first line whereas in Europe it is the treatment of choice for relapsed hyperthyroidism.[8] There is also variation in ^{131}I dosages used between centres. Studies investigating the role of variable dose ^{131}I administration through initial assessment and dose calculation with ultrasound and radioiodine uptake have been performed but have shown no clear advantage of dose adjustment over fixed dose regimens with regard to final outcome of radioiodine treatment.[9,10] Various fixed dose regimens have been employed with higher doses of radioiodine being associated with improved outcomes and lower failure rates.[11-13] These fixed dose regimens are less expensive as estimation of gland size by ultrasound or radioiodine uptake scan prior to treatment is not required.[9,14]

The aim of ^{131}I treatment varies between centres although many now target hypothyroidism as opposed to euthyroidism as this reduces the risk of late onset hypothyroidism.[14] There is some evidence that following radioiodine, euthyroid patients not requiring levothyroxine and hypothyroid patients

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not on replacement therapy have an increased mortality risk compared to those on adequate replacement.[5]

In the present study we assessed the effects of a 550MBq standard dose regimen for the treatment of hyperthyroidism. We also explored clinical factors previously suggested to influence outcomes such as age, gender, goitre size and severity of hyperthyroidism.[11,12,15]

METHODS

We performed a case note study of 449 consecutive patients treated with ^{131}I for hyperthyroidism between 2003 and 2007at the Royal Victoria Hospital. Patients had either been referred by their general practitioner with relapsed hyperthyroidism or had already been attending our centre for treatment of their initial episode of hyperthyroidism. Data was retrieved by a single investigator (ASL).

Age and thyroid function at initial presentation were defined as the patient's age and thyroid function when abnormal thyroid function was documented for the first time. Graves' disease was classified as biochemical hyperthyroidism accompanied by 2 of the following 3 criteria: a diffuse goitre, a significant anti-TPO antibody titre and dysthyroid eye disease. Toxic multinodular goitre was diagnosed either by clinical examination or if a multinodular goitre was confirmed by ultrasound scanning; ultrasound scanning was not performed routinely. Aetiology was classified as indeterminate if either of these criteria were not met. Presence of goitre was assessed clinically by one of six endocrinologists (ABA, PMB, CHC, DRM, KM, SJH) and documented as either none, small, medium or large. Eye signs were defined according to the NOSPECS[16] classification and recorded as either present or absent at the time of radioiodine dose. The use of steroid cover for ^{131}I in those with documented dysthyroid eye disease was also recorded. Our policy was not to use radioiodine unless the dysthyroid eye disease had been established to be stable. The use of antithyroid medication prior to radioiodine was defined as antithyroid medication (carbimazole or propylthiouracil) started following relapse of hyperthyroidism. All antithyroid medication was stopped at least 1 week before radioiodine administration. Patients on combination therapy with antithyroid drugs and thyroxine had their thyroxine stopped 4 weeks before radioiodine.

A fixed dose of 550 MBq was administered and patients subsequently attended standardised follow-up at the endocrine specialist nurse led clinic at 6 and 12 weeks and then as required before attendance with an endocrinologist at 6 months. Thyroid function, recorded during each of these visits, was retrieved and yearly data were obtained from the patient chart, the hospital laboratory results computer system or the general practitioner records. Outcome of therapy was recorded as: 1) hypothyroid defined as low free T_4 and high TSH requiring thyroxine replacement, 2) euthyroid defined as normal thyroid function off all thyroid medication at 1 year post radioiodine, or 3) required further radioiodine defined as a relapsing high free T_4 and suppressed TSH.

Statistical analysis was performed using SPSS version 15.0. The χ^2 test was used to test for associations between categorical variables and independent samples t test was used for relationship between continuous variables. Logistic regression was used to determine which factors contributed to the prediction of outcome of treatment.

RESULTS

The demographic and clinical details of the patients at presentation are in table 1. One hundred and one patients (22.5%) were classified as having Graves' disease, 75 (16.7%) had toxic multinodular goitre and the remaining 273 patients (60.8%) were classified as indeterminate aetiology. Patients with Graves' disease were younger (40.0 v 57.2y, $p<0.001$) and had higher free T_4 at presentation than the patients with toxic multinodular goitre. All patients had eye status documented and 39 patients (8.7%) had dysthyroid eye disease at the time of ^{131}I. Of these patients 87.2% had steroid therapy across ^{131}I treatment. The remainder had burnt out disease. Prior use of antithyroid medication occurred in 345 patients (76.8%). There was no significant difference noted in T_4 levels or goitre size in those who were on prior antithyroid medication and those who were not.

One year after radioiodine, 334 patients (74.4%) were hypothyroid, 85 (18.9%) were euthyroid and 30 (6.7%) had required a further dose of radioiodine (table 2). Hypothyroidism was more likely to occur in Graves' disease patients than in those with multinodular goitre (78.2% v 37.3%, $p<0.001$) and euthyroidism was less likely (10.9% v 54.7%, $p<0.001$)(table2). There was no significant difference in the numbers requiring a further dose of radioiodine. Patients with indeterminate aetiology had similar outcomes to the Graves' disease patients with 83.2% hypothyroid, 12.1% euthyroid and a slightly lower figure of 4.8% requiring a further dose of radioiodine.

A high free T_4 at presentation was associated with an increased failure rate of radioiodine. Those presenting with an initial free T_4 >80pmol/L were found to have an increased failure rate compared to those presenting with an initial free T_4 of 40-79pmol/L or <40pmol/L respectively (16.7% v 5.0% v 2.9%, $p=0.003$). More of those presenting with a medium or large goitre required a further dose of radioiodine than those with a small or no goitre (14.7% v 4.3%, $p<0.001$). More of the patients who were on antithyroid medication required a second dose of radioiodine than those who were not (8.1% v 1.9%, $p=0.027$).

Gender did not influence the outcome nor was there any gender association with initial free T_4 or aetiology of hyperthyroidism. Females were however more likely to have a positive family history of thyroid dysfunction (52.5% v 37.3%, $p=0.025$) although this did not influence outcome. There was no association between cigarette smoking and outcome of radioiodine therapy.

Logistic regression analysis was performed with the inclusion of free T_4, goitre size and prior antithyroid medication. It showed initial free T_4 at presentation to be the only independent risk factor for failure of the first dose of radioiodine (OR 2.5; 95% CI, 1.2-5.1, p=0.012). The influence of goitre size was not significant in the logistic regression model with the inclusion of free T_4 at presentation. Prior antithyroid drug use also lost significance in the logistic regression model (OR 5.5; 95% CI, 0.7-43.1, p=0.10). Further analysis suggested the reason for this may be the reduced number of patients with free T_4 levels available (n=257) rather than an interaction between free T_4 and prior antithyroid drug use.

DISCUSSION

The use of radioiodine for hyperthyroidism has increased[17] with recognition of the low likelihood of success with antithyroid drugs. Initially the focus of ^{131}I therapy was to achieve euthyroidism utilising low/adjusted dose regimens[18-20] however it is now recognised that the development of hypothyroidism is progressive, with an annual incidence of 2-3% many years after therapy.[21] Many clinicians now prefer to give a large ablative dose of ^{131}I which results in early hypothyroidism and prompt stabilization with longterm thyroid hormone replacement. Various clinical factors may influence the outcome of ^{131}I therapy and knowledge of these can help inform patients prior to treatment and can aid follow-up planning. In this study 93.3% were treated effectively by a single dose of radioiodine with 74.4% rendered hypothyroid and 18.9% euthyroid at one year. These levels compare favourably with similar fixed dose regimens which described cure rates of up to 84.5% with comparable radioiodine doses.[11,12]

Graves' disease patients were more likely to be rendered hypothyroid than those with toxic multinodular goitre and those with toxic multinodular goitre were more likely to be rendered euthyroid. This concurs with other published data which have shown a similar relationship even years after initial radioiodine administration.[11,22-25] One explanation for this could be that suppressed extranodular thyroid tissue exhibits less uptake of radioiodine and continues to function normally after ablation of the nodal tissue.[14] A recent study showed that in toxic nodular goitre TSH levels at the time of radioiodine dose influenced outcome of radioiodine therapy; higher levels were associated with increased rates of hypothyroidism. This was thought to be due to the suppression by antithyroid medication of the autonomous nodules to a near euthyroid state allowing the remainder of the gland being able to take up radioiodine and therefore subsequently leading to an increased risk of hypothyroidism.[22]

Previous studies have shown both goitre size and severity of hyperthyroidism to be independent indicators of response to radioiodine therapy[11,12] but this study found severity of hyperthyroidism to be the only independent factor with goitre size losing significance indicating a relationship between the two. Increased failure rate of radioiodine was associated with free T_4 >80pmol/L at presentation (16.7%). It was also seen with medium or large goitres but this was not statistically significant in the logistic regression model. It should be acknowledged that goitre size was determined clinically by one of 6 consultant endocrinologists rather than by an objective measurement. Some inter-observer variability would be expected in this setting and should be acknowledged.

Prior use of antithyroid medication was initially found to be associated with an increased failure rate of radioiodine in univariate analysis but this was no longer significant in the logistic regression model. This may be a result of reduced numbers of free T_4 levels available for analysis rather than any interaction between the two variables. Antithyroid medication is used to diminish symptoms while awaiting radioiodine and to reduce the risk of acute hyperthyroidism, including thyroid storm, following radioiodine therapy.[26] By treating hyperthyroidism with medication, uptake of radioiodine in the thyroid can be reduced with loss of potential effect. Previous studies found increased failure rates with prior antithyroid medication and also increased frequency of hypothyroidism in those who were successfully treated,[26] a finding confirmed by the current data. These studies contrast with that of Allahabadia et al who found that antithyroid medication taken within two weeks of radioiodine did not significantly affect outcome when doses of 370MBq or more were used.[11] We have no explanation for this discrepancy.

Our study did not take into account the recognised phenomenon of transient hypothyroidism.[27] A retrospective study from Japan studied 260 patients with Graves' disease treated with radioiodine in the preceding 1-15 years. It identified 39 patients (15%) with transient hypothyroidism, 33 (84.6%) of whom were euthyroid at one year and the other 6 (15.4%) were hyperthyroid.[28] Rates of transient hypothyroidism range from 9-17%.[29,30] Given that our patients with radioiodine induced hypothyroidism were not given a trial period off thyroxine it is possible that a proportion were wrongly labelled as hypothyroid. We would not, however, expect this to alter the failure rate of radioiodine as patients relapsing, even from an initial hypothyroid state, would be expected to do so within a year of treatment. A study at 1 year of brief withdrawal of thyroxine to ensure the presence of hypothyroidism would answer this question and be a valuable addition to the literature.

In conclusion we have demonstrated that a fixed dose of ^{131}I 550MBq is highly effective in the treatment of hyperthyroidism. A standard fixed dose is a simple and relatively inexpensive method of radioiodine administration[31] which avoids the need for thyroid ultrasound or iodine uptake scans and reduces the need for repeated doses of ^{131}I. In addition it achieves rapid resolution of hyperthyroidism and simplifies follow-up. In our case we have used a structured specialist nurse led clinic in the early months and this has proved invaluable. Knowledge of the presenting freeT_4, which we were not always able to obtain, has shown that a

level >80pmol/L is the most important prognostic indicator of relapse and can be used to inform clinicians of the likely requirement of repeated doses of radioiodine or alternatively, and in our view preferably, the use of a higher initial dose in these patients.

The authors have no conflict of interest

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Ulster Med J 2013;**82(2):**89-93

Paper

Recombinant PTH: A Study of the Outcome of Teriparatide Therapy for 138 Patients with Osteoporosis

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Accepted 24 January 2013

ABSTRACT

Introduction: Osteoporosis results in significant morbidity and mortality for a large number of patients within Northern Ireland. Recombinant PTH (Teriparatide) is one of a growing number of treatment options for the disease.

Methods: A retrospective analysis was carried out for all patients who had been commenced on Teriparatide since it was first used in the Belfast Health and Social Care Trust (BHSCT) in 2007. Patient demographics, clinical history and prior treatment were recorded prior to an eighteen month treatment protocol. Outcome measures including bone densitometry, bone turnover markers and health status were assessed on commencement and completion.

Results: 138 patients have commenced teriparatide therapy since 2007 (9 male, 129 female). At the time of analysis 60 patients had completed treatment, 53 patients were receiving ongoing treatment and 25 patients did not complete the 18 month course. On completion vertebral bone mineral density (BMD) had increased by 8.3% while femoral neck BMD had increased by 3.5%. Bone turnover markers demonstrated a significant increase of bone formation and resorption at 4 months, with a smaller increase at 18 months. Health outcome measures (EuroQoL-5 and patient visual analogue scale) indicated improvement in the quality of life of patients of those who completed the treatment course.

Conclusions: Experience in the BHSCT with teriparatide since 2007 demonstrates improvement in BMD comparable to published data, changes in bone turnover markers consistent with increased bone remodeling and better health outcomes for patients.

Keywords: Osteoporosis, Teriparatide, Bone Density, Bone Turnover Markers, Outcome

INTRODUCTION

Osteoporosis has been estimated to affect over 2 million people in the UK.[1] Mistaken as a silent disease it has significant consequences in terms of morbidity and mortality to those afflicted. Calculation of Disability Adjusted Life Years indicates that osteoporosis has a greater impact than most types of cancer.[2] Hip fractures alone are calculated to cost the National Health Service £2 billion per year.[3]

Osteoporosis has been defined as a bone mineral density (BMD) of more than 2.5 standard deviations below the average value.[4] Post-menopausal women are most at risk as falling oestrogen levels cause an increase in bone turnover at the expense of bone microarchitecture and subsequent bone strength.[5]

Teriparatide, recombinant human PTH (1-34), is an anabolic agent indicated in the treatment of osteoporosis. By stimulating osteoblast activity it causes increased bone formation with resultant improved bone strength and mass[6,7].

Administration is by a once daily subcutaneous injection. Phase III data by Neer et al[8] showed an increase of 9% in BMD at the lumbar spine with a more modest 3% increase at the neck of femur after 18 months treatment. There was a corresponding reduction in vertebral fractures from 14% on placebo to 5% with active treatment. Initially licensed for a duration of 18 months, extension trials showed further benefit up to 24 months[(9)] and the licence has changed accordingly.

The National Institute for Health and Clinical Excellence (NICE) issued guidance in 2008 limiting teriparatide use to post-menopausal women who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.[1]

To date, NICE has not issued guidance for male patients. However trial data demonstrates teriparatide has similar benefits in male patients with significant increases in BMD and reduction in fracture risk.[10]

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Within the Belfast Health and Social Care Trust (BHSCT) teriparatide has been in use since 2007. The aim of this study is to review the clinical experience with Teriparatide so far, assessing compliance with NICE guidance and the clinical outcomes following treatment.

METHODS

As of January 2011, 138 patients (129 female, 9 male) had been commenced on teriparatide in the BHSCT. Each patient had been under regular review by the regional osteoporosis service. They were put forward for teriparatide after consultant review deemed it necessary.

Baseline data was collected as part of the initial assessment and subsequent review, then entered into a database used to monitor patients progress while taking the drug. Patient consent for storage of personal information was sought at the time of starting teriparatide. Ethical approval was not sought for this study as the analysis relates to a retrospective review of teriparatide administration.

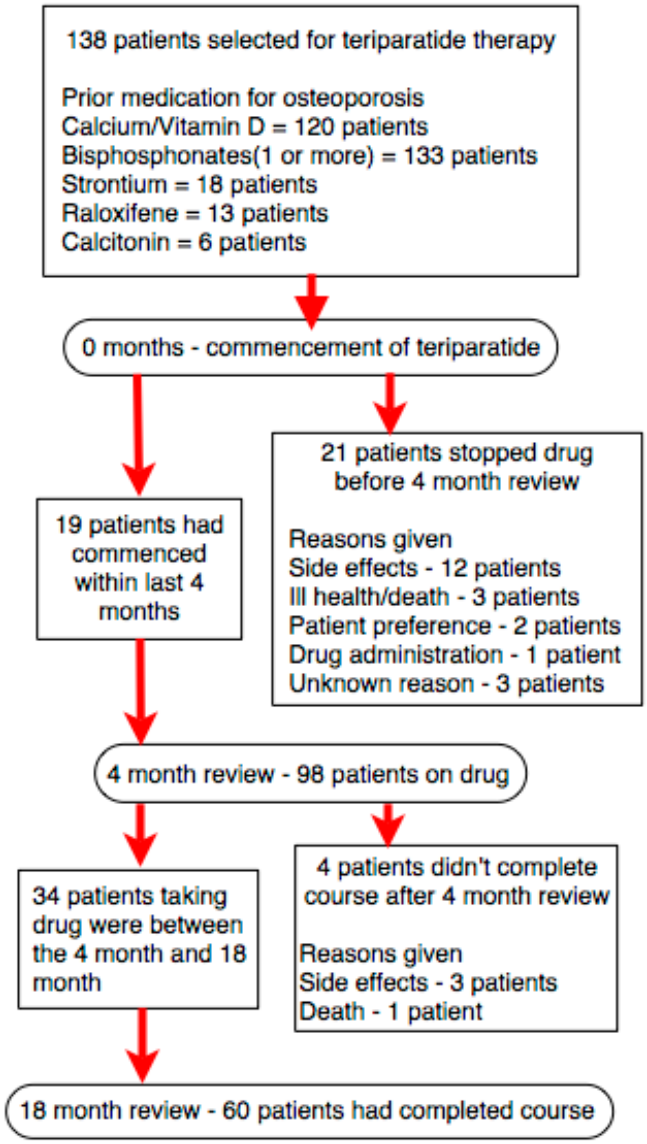

Fig 1. Progressive of patients through treatment course

At the time of analysis a total of 60 patients had completed a full 18 month treatment course, while 25 patients had stopped taking the drug prior to completing the treatment course and 53 patients were still in the process of completing their treatment regime. (Fig 1)

Bone mineral density at the lumbar spine and femoral neck was assessed using dual-energy x-ray absorptiometry at baseline and completion of treatment. The reference population for hip measurements included NHANES gender and ethnically matched populations[11], with the manufacturer Hologic and Lunar reference populations for spinal measurements[12,13]. Measurements are given in g/cm^2 and also in terms of standard deviation (SD) to the reference populations above.

Bone turnover was assessed using two markers measured at baseline, 4 months and on completion of treatment. P1NP (Procollagen type 1 N-terminal Propeptide) is a measure of bone formation (normal range 20.3 - 76.3 ng/mL) while CTX (C-terminal Telopeptide Collagen breakdown product) is a measure of bone resorption (normal range: female <1.008 pg/mL, male <0.854 pg/mL). These were measured in the Royal Victoria Hospital by immunoassay[14]

Two different patient-reported measures of health status were performed at commencement and completion of the treatment course. EuroQoL-5 is a validated measure of patient quality of life involving five items of patient health, specifically: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[15]. Each item is coded using 3-levels (1 = no problems; 2 = some problems; 3 = severe problems). Calculation of the EuroQoL-5 gives a range of results varying from -0.549 to 1 (-0.549 represents worse possible health state, 0 equates with death and 1 correlates with perfect health).

Secondly, a visual analog scale (VAS) of current health state, ranging from 0 (worst imaginable) to 100 (best imaginable), was used. It has been validated as a tool to measure global rating of current health[(16)].

An online Wilcoxon rank sum test was used to assess change in BMD and health outcome measures[17]. The test was carried out two tailed and considered significant if $p<0.05$. Standard error of the mean was used to interpret change in bone turnover markers.

RESULTS

Prior to commencement of teriparatide the mean number of vertebral fractures was 4.3/pt and non-vertebral fractures was 1.4/pt. The prior medication use for osteoporosis is noted in fig 1. Of the 129 female patients commenced on teriparatide, 59.6% of them met the criteria suggested by NICE for when patients should receive the drug[(1)].

The mean age of patients at commencement was 74.0 years (Standard error (SE) - 0.72 yrs) with a range from 46 to 90. (fig 2)

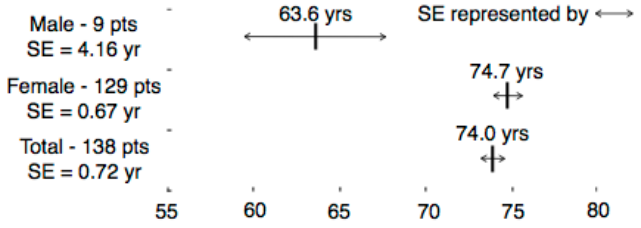

Fig 2. Age at commencement of teriparatide

VERTEBRAL BMD

At commencement, mean vertebral BMD was 0.715 g/cm^2 with a mean T score of -3.52 SD(total 118 patients). Following 18 months treatment the mean vertebral BMD was 0.772 g/cm^2 with a mean T score of -3.09 SD (total 53 patients).

A complete data set was available for 49 patients of vertebral BMD at commencement and completion. For this subgroup, initial mean spinal BMD was 0.707 g/cm^2 (T-score -3.67 SD) and on completion mean vertebral BMD was 0.766 g/cm^2 (T-score -3.16 SD). There was a 8.3% increase in vertebral BMD following 18 months of teriparatide treatment (p=0.031).

FEMORAL NECK BMD

At commencement, mean femoral neck BMD was 0.574 g/cm^2 with a mean T score of -2.88 SD (total 127 pts). Following 18 months treatment the mean femoral neck BMD was 0.592 g/cm^2 with a mean T score of -2.80 SD.

A complete data set was available for 52 patients of femoral neck BMD at commencement and completion. For this subgroup, initial mean femoral neck BMD was 0.576 g/cm^2 (T-score -2.83 SD) and on completion mean femoral neck BMD was 0.596 g/cm^2 (T-score -2.78 SD). There was a 3.5% increase in femoral neck BMD following 18 months of teriparatide treatment (p=0.455).

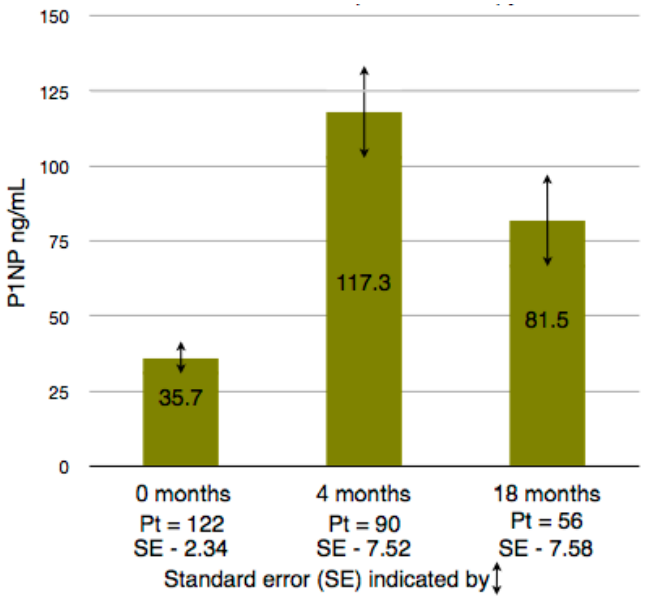

Fig 3. Change in mea P1NP level over the duration of Teriparatide therapy

BONE TURNOVER MARKERS

P1NP (normal range 20.3 - 76.3 ng/mL)

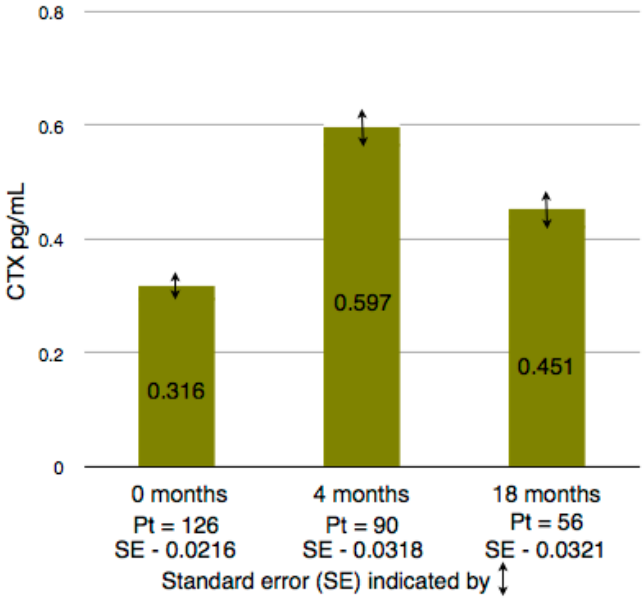

Fig 4. Change in mean CTX level over the duration of Teriparatide

At commencement the mean P1NP level for 122 patients was 35.7 ng/mL (SE - 2.34). At 4 months of treatment the mean P1NP was 117.3 ng/mL (SE - 7.52) for a total of 90 patients. On completion of the 18 month course the mean P1NP value was 81.5 ng/mL (SE - 7.58) for a total of 56 patients. (fig 3)

CTX (normal range: female <1.008 pg/mL, male <0.854 pg/mL)

At commencement the mean CTX level for 126 patients was 0.316 pg/mL (SE - 0.0216). At 4 months of treatment the mean CTX was 0.597 pg/mL (SE - 0.0318) for a total of 90 patients. On completion of the 18 month course the mean CTX value was 0.451 pg/mL (SE - 0.0321) for a total of 56 patients. (fig 4)

HEALTH OUTCOME MEASURES

29 patients contributed sufficient information to fulfill a complete data set of health outcome measures. On starting mean EuroQoL-5 was 0.450 (SE - 0.306) improving to a value of 0.611 (SE - 0.256) after 18 months (p=0.008).

Mean patient-reported VAS on commencement was 53.2 (SE - 11.9) with an increase to 64.3 (SE - 18.6) on completion (p=0.003). However these two results have to be approached with caution as 31 of the 60 patients who completed the treatment schedule didn't supply any health outcome data.

DISCUSSION

In the treatment of osteoporosis, teriparatide represents a viable second line treatment option after standard therapy has proved unhelpful. The use of teriparatide in daily practice has been restricted based on the guidance by NICE which advocates it's use after key clinical criteria have been met.

Our study demonstrates the experience in daily clinical practice of teriparatide therapy when utilized in the outpatient setting.

In the original phase III trials for teriparatide the mean vertebral BMD was approximately 0.820 g/cm^2 and at femoral neck was 0.640g/cm^2[8]. Only 15% of patients had been on previous osteoporotic therapy and the history of vertebral fractures averaged 2.3±1.8[8]. This represents a considerable variation from the typical patient in this study. Our reported fracture incidence is considerably higher while all patients had been on some form of osteoporotic therapy prior to teriparatide. Initial BMD values in our cohort showed a value of 0.722 g/cm^2 (T-score -3.52 SD) at the spine and a value of 0.570 g/cm^2 (T-score -2.91 SD) at the femoral neck.

Therefore patients commenced on teriparatide in the BHSCT represent osteoporosis patients with much lower BMD values, implying that their disease was more advanced and that they had accumulated more damage from fractures related to their disease. The guidance by NICE for selection of patients suitable for teriparatide will identify those patients with more advanced disease and this is reported in our study population.

However only 59.6% of our study population started on teriparatide have met NICE guidance for commencement of the drug. There are a number of considerations when assessing this figure. With more advanced osteoporosis there will naturally be more accumulation of osteoporotic damage. This will have an effect on BMD assessment by DEXA scanning where the presence of an osteoporotic fracture will give an artificially higher BMD reading at that vertebral level, resulting in a higher average BMD reading across the spine despite the presence of significant vertebral osteoporosis.

Another potential confounding factor is that the group of patients put forward for teriparatide in the BHSCT will also include patients who have been intolerant or have had complications with prior osteoporotic medication. Where there is ongoing need for osteoporotic treatment and all other treatment options have failed, teriparatide may have been used as the only alternative treatment despite patients not fully meeting NICE guidance.

In our study, we report improvement of vertebral BMD of 8.3%, which was statistically significant, and femoral BMD of 3.5% over the treatment course. The percentage changes in BMD is comparable with the data reported in the initial trials where there was a reported improvement in vertebral BMD of 9% and femoral neck BMD of 3%[8]. Both these changes were significant as the studied population was much larger than in our case.

Measurement of P1NP and CTX in our population suggests correlation with the known increase in bone formation and bone turnover that occurs with teriparatide therapy. Within the limits of our measurements it appears bone turnover reaches a peak after commencement. At the completion of the treatment course both markers remain elevated but at a lower level than when measured at four months.

Studies have shown that P1NP levels correlate with the formation of new bone and have been demonstrated to rise on initiation of treatment, remaining elevated for over a year[18]. There is also the suggestion that monitoring of P1NP levels shortly after starting the drug may be a useful means of identifying patients who will respond to teriparatide therapy[19]. CTX levels have been shown to drop in the first 2-3 weeks of teriparatide therapy before there is evidence of increased bone turnover.[20] It has not been possible to demonstrate this in our population due to the timing of CTX measurement.

The measurement of health outcome using EuroQoL-5 and patient reported VAS may indicate an improvement on quality of life following teriparatide treatment. However there are significant deficiencies in data to draw any meaningful conclusions from this. With 31 patients who completed treatment not supplying responses for health outcome and 25 patients not completing the treatment course the true picture is not clear.

As teriparatide was being given over an 18 month duration it is inevitable that there will be a number of patients who are unable to complete the course. Other co-morbidities will develop which take precedence over the treatment of osteoporosis while changes in health status will alter a patient's ability to self inject. Side effects secondary to the medication itself will also have a bearing, as highlighted in our case by the 14 patients out of 25 who cited it as a reason for stopping the drug.

A total of 25 patients not completing the 18 month treatment course may seem to be a significant proportion, however compliance with other osteoporotic medication is considerably worse. Patients persisting with bisphosphonate therapy after 1 year of commencing has been reported to be anywhere between 18% and 78%[21].

As our study is based in daily clinical practice the non-completion of the treatment course by 25 patients would be comparable with the percentages highlighted above. However this number of patients not finishing the course will limit the degree to which the final results can be extrapolated to other populations.

CONCLUSION

This study demonstrates the efficacy of teriparatide therapy for patients in clinical practice with severe osteoporosis, with significant gains in bone mineral density at both the spine and hip comparable to outcome data reported in phase III trials. The adherence to treatment in clinical practice was good with few reported side effects.

The authors have no conflict of interest. We gratefully acknowledge the assistance of Dr Hugh Taggart and Dr Pooler Archbold in obtaining information from subjects treated at Belfast City Hospital.

The authors have no conflict of interest

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Ulster Med J 2013;**82(2):**94-96

Case Report

Tracheal bronchus associated with recurrent pneumonia

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Accepted 30th January 2013

ABSTRACT

Abnormalities of the major airways are uncommon congenital conditions which occur in approximately 2% of the adult population. Usually aberrant bronchi are asymptomatic and are only found by coincidence. We present the rare case of a 49-years-old woman with a tracheal bronchus associated with recurrent pneumonia of the right upper lobe.

INTRODUCTION

Congenital abnormalities are only infrequently encountered during bronchoscopy or bronchography[1]. In adults these conditions are occasionally associated with pulmonary infections and recurrent pneumonia[2]. In the daily clinical routine delayed diagnosis is quite frequent because anatomical variants of the airways are not routinely included in the differential diagnosis of persistent or recurrent pulmonary infections.

CASE HISTORY

A 49-year-old woman with a history of recurrent right upper lobe pneumonia was admitted to our department of thoracic surgery. For more than 10 years she has repeatedly sustained pulmonary infections and has been in hospital on several occasions. During the last episode of pneumonia bronchoscopy had been performed for the first time. An accessory bronchus originating from the proximal right main bronchus was found [Fig 2]. The regular right upper lobe bronchus was not displaced but consisted of only two segmental bronchi. Computed tomography of the chest confirmed the diagnosis of an aberrant apical segmental bronchus of the right upper lobe [Fig 1], a so called tracheal bronchus. Furthermore, the images showed acute as well as chronic inflammatory lesions and calcifications within the apical segment of the right upper lobe [Fig 1c]. The parenchymal changes were limited to this segment and formed tumorlike nodules. Preoperative FDG-PET-CT was not obtained.

She underwent segmentectomy of the apical upper lobe segment. Upon operation we encountered the tracheal bronchus which led into the apical segment. The anatomy of the pulmonary artery as well as the venous drainage was normal. There were dense inflammatory adhesions between the tip of the right lung and the parietal pleura as an expression of the recurrent infections. The apical segment showed numerous nodules and calcifications. Frozen section was obtained to rule out pulmonary carcinoma.

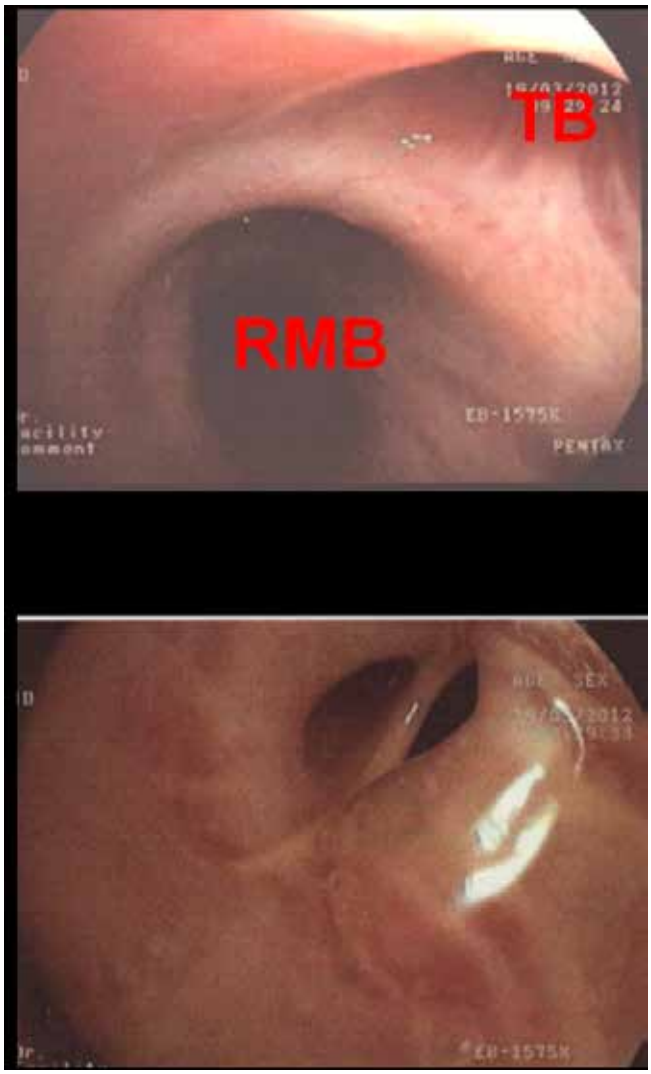

Figure 2. Bronchoscopy
The bronchoscopic image (Fig 2a) shows the origin of the tracheal bronchus (TB) nearly at the bifurcation. The proximal right main bronchus (RMB) is also visible. A view into the tracheal bronchus is provided by figure 2b. The orifice seems to be partially narrowed.

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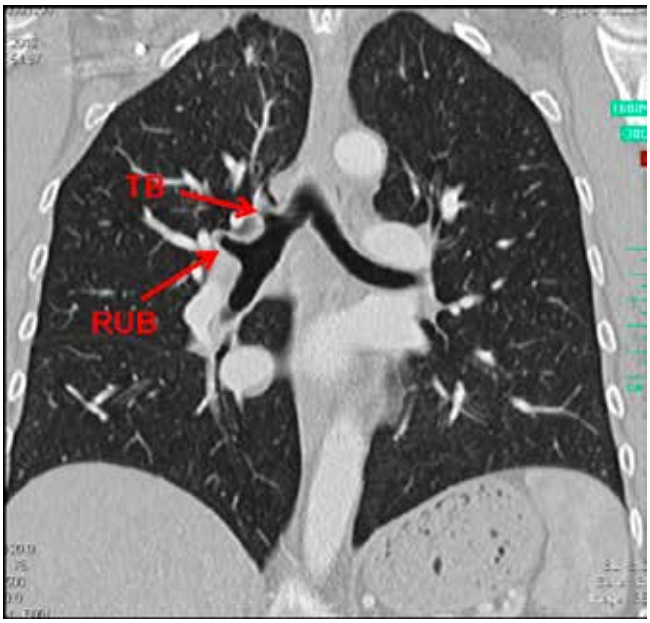

Figure 1a. Frontal CT image
The tracheal bifurcation is visible in this frontal view of the computed tomography of the chest. The origin of the tracheal bronchus is visible virtually at the carina (TB). The regular right upper lobe bronchus (RUB) itself is not displaced. There are no further recognizable abnormalities of the airways.

The pathological examination of the specimen confirmed the diagnosis of recurrent pneumonia with fresh and older inflammatory lesions without malignancy. The postoperative course was uneventful. The patient recovered fast and was discharged from hospital at the 7th postoperative day. Afterwards there were no clinical or radiographic signs of recurrent pulmonary infection during a follow up period of altogether nine months.

DISCUSSION

The first description of a tracheal bronchus derives from the 18th century anatomist Eduard Sandifort (1742-1814), who was chair of anatomy and surgery at the Dutch university of Leiden. Since then congenital abnormalities of the tracheobronchial tree have been studied by anatomist as well as by clinicians. Nowadays, the term tracheal bronchus encompasses several kinds of anomalous bronchi which originate from either the distal trachea or the right main bronchus and direct to the right upper lobe[1-3]. In case of normal branching of the right upper bronchus in combination with an accessory airway, the anatomic variant is called a supernumerary bronchus. However, displaced tracheal bronchi are more frequent. In those cases the upper lobe bronchus is devoid of a recognizable apical segmental bronchus. Therefore, the aberrant bronchus is called a displaced bronchus.

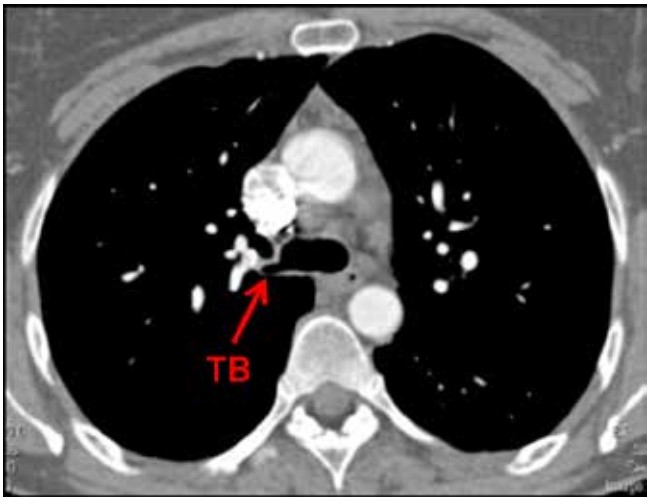

Figure 1b. Axial CT image
This axial view is situated at the level of the tracheal bifurcation. The division of the distal trachea into the two main bronchi is already identifiable. The origin of the tracheal bronchus (TB) is shown.

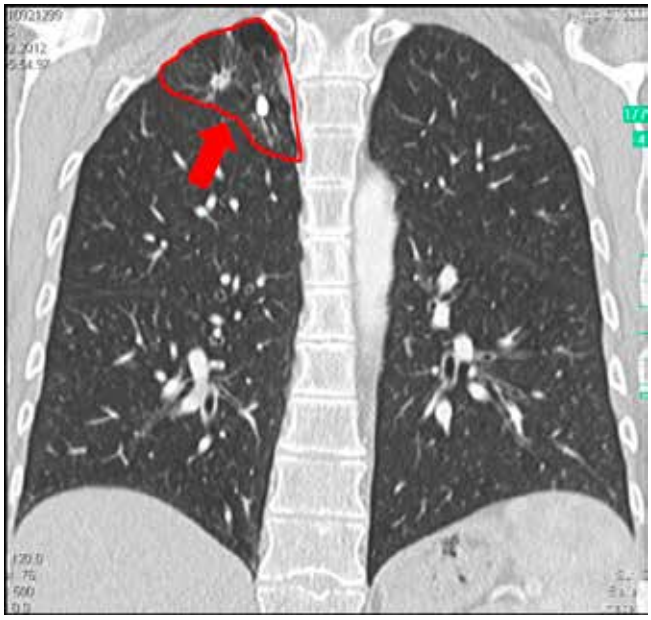

Figure 1c. Inflammatory lesions
The frontal CT image shows numerous inflammatory lesions and parenchymal changes within the right apical upper lobe segment, which is marked by a red contour (arrow). The morphological alterations comprise tumorlike lesions, calcifications and bullae. The other parts of the lung show no signs of pathological transformation.

Such congenital abnormalities are rarities. In the year 1962 Le Roux examined 1000 consecutive bronchograms, which had been obtained at the Regional Thoracic Unit in Edinburgh[4]. Altogether he encountered only 30 abnormalities of the right upper lobe bronchus. The most common disorder was an apical segmental bronchus originating from the trachea or the main bronchus. He found such a condition in 14 out of 1000 bronchograms[4]. Our patient had a displaced bronchus directing to the apical segment. The anatomy is clearly visible in the coronary CT images [Fig 1a+b].

Those congenital malformations are usually asymptomatic in adults whereas they are quite frequently associated with respiratory complications in paediatric patients. In a series comprising 18 infants with tracheal bronchus, resection of the right upper lobe due to recurrent pneumonia was eventually

mandatory in five cases[5]. Persistent or recurrent pneumonia as well as the occurrence of bronchiectasis caused by a tracheal bronchus have also been reported in adults. Furthermore, pulmonary actinomycosis and haemoptysis have reportedly been associated with a tracheal bronchus[3, 6]. Because of the rareness of the underlying condition the literature comprises mainly reports of single cases.

In our case, the tracheal bronchus was responsible for recurrent pneumonia with severe morphological changes of the lung parenchyma [Fig 1c]. The diagnosis was only established with considerable delay. Following segmentectomy the patient recuperated well. Henceforth she has been healthy and has shown no signs of pulmonary infections. This finding is in conformance with the results of the above mentioned paediatric series in which lobectomy led to resolution of the recurrent pneumonia, too. Similar outcome has been observed for surgical treatment of bronchiectasis in adults. Effective relief of symptoms is achievable by complete resection of all lung tissue with bronchiectatic destruction[7, 8]. Segmentectomy of the lung is a safe procedure without a noteworthy loss of lung capacity. Hence, resection of the affected segment in case of a bronchial abnormality associated with pulmonary infections is justified and provides definite cure.

Moreover, distinction between an inflammatory lesion, as in our case, and a pulmonary neoplasm can only be obtained by pathological examination of the specimen. Even ^{18}F-FDG-PET which is generally a valuable tool for diagnosis of pulmonary malignancies is considered to be of limited use for proper differentiation of lung cancer from pulmonary inflammation. Neoplastic as well as inflammatory nodules show increased glucose metabolism resulting in enhancing lesions on PET images. Therefore these findings have to be carefully interpreted and the conclusions are often uncertain and indeterminate with a reported accuracy of only 70%[9]. As a consequence, surgery is also indicated to rule out lung cancer[10].

In conclusion, congenital abnormalities of the bronchi are rarities among the adult population and are mostly asymptomatic. Nevertheless, a tracheal bronchus can be associated with recurrent pulmonary infections and tumorlike inflammatory lesions. Then operative management by means of segmentectomy provides cure and simultaneously rules out lung cancer.

The authors have no conflict of interest.

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Ulster Med J 2013;**82(2):**97-99

Case Report

Chemotherapy causes cancer! A case report of therapy related acute myeloid leukaemia in early stage breast cancer.

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Accepted 6 december 2012

ABSTRACT

Use of chemotherapy and radiotherapy in the adjuvant setting has improved survival for many patients with malignancy. Unfortunately multimodality treatment can come at a price, in particular therapy-related malignancies. This has importance in that patients must be made aware of this potential detriment from therapy and doctors must consider this diagnosis in those patients who are cancer survivors and presenting with health problems. We present a case report and brief overview of the literature regarding chemotherapy-induced acute myeloid leukaemia (AML) following therapy for early stage breast cancer.

Keywords: therapy-related leukaemia, breast cancer, adjuvant chemotherapy.

A 52 year old woman had a mastectomy and axillary node clearance for a T2 NO MO infiltrating ductal carcinoma of the left breast which was grade 2 and hormone receptor positive. Past medical history included ulcerative colitis, she was taking no regular medications. Subsequently she received 4 cycles of adjuvant chemotherapy consisting of doxorubicin (60mg/m^2) and cyclophosphamide (600mg/m^2), followed by a 5 week course of radiotherapy and 5 years of tamoxifen. Six years following her surgery she was referred to the haematology clinic with thrombocytopenia, (Platelet count = 60x10^9/L (150-400). This coincided with the introduction of mesalazine for a flare up of her normally quiescent colitis.

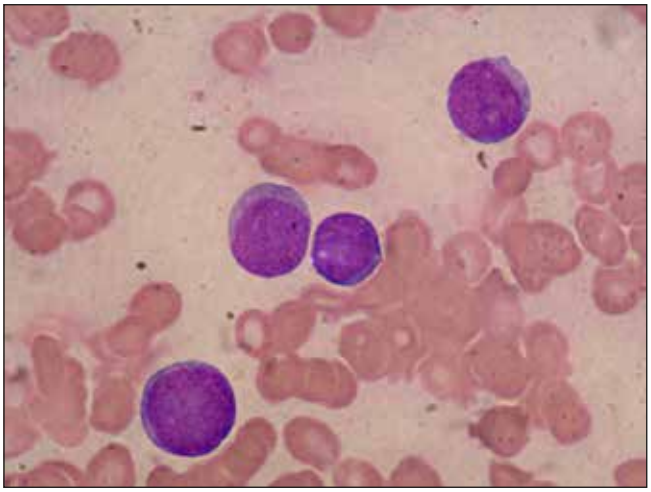

Fig 1.Peripheral blood film showing multiple myeloblasts.

An initial bone marrow biopsy was inconclusive and a presumptive diagnosis of either Idiopathic Thrombocytopoenic Purpara (ITP) or drug-induced thrombocytopenia (DIT) was made. She was reviewed 6 months later by which time her platelet count was 30x10^9/L. She was lethargic and had a petechial rash. Repeat bone marrow biopsy showed dysplastic features with 5% blasts in keeping with myelodysplasia (Refractory Anaemia with Excess Blasts-1) and she was placed on close follow up. Following an episode of dental sepsis her peripheral blood film was examined and found to contain numerous myeloblast cells (Figure 1) and the presence of mitotic figures (Figure 2).

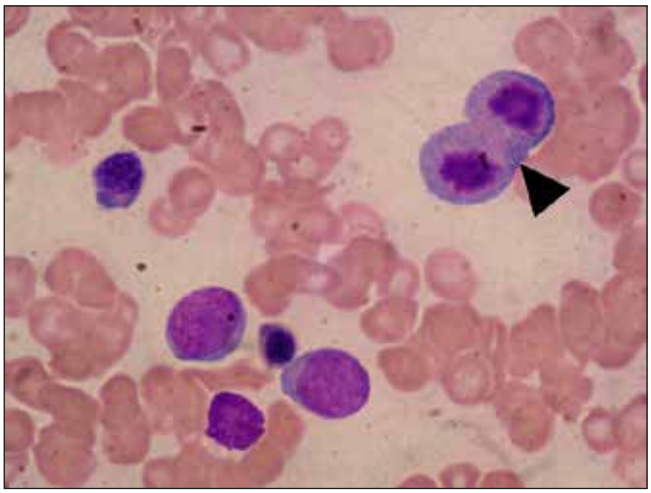

Fig 2. Mitotic figure (arrowhead) indicating high turnover rate of blast replication.

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A further bone marrow biopsy confirmed AML with a background of myelodyplasia (in keeping with therapy related AML) that was classified histologically as AML M2 (AML with maturation) in the French-American-British (FAB) classification. There were no cytogenetic abnormalities identified. Unfortunately despite chemotherapy she had unrelenting progression, became refractory to platelet transfusions and died in the hospice 9 months later, by which time her white cell count (WCC) was $330x10^9$/L. Her death occurred 8 years after adjuvant chemotherapy for breast cancer: there was no breast cancer evident on radiological staging prior to her death.

DISCUSSION

Breast cancer is the most common solid organ malignancy in females. Early detection with mammography screening and improvement of therapeutic options has increased survival rates. It is treated with a range of chemotherapies, radiotherapy, hormonal therapy and biological agents. Many patients receive these treatments in the adjuvant setting to decrease the risk of systemic relapse but in the context of modest survival gains from therapy. These treatments have well recognised early acute complications including neutropoenic sepsis, which is occasionally fatal. However long term complications from these therapeutic modalities, especially in patients who have potentially been cured of their primary cancer, are becoming increasingly important with improved survival. Patients with breast cancer often undergo chemotherapy with repetitive bone marrow suppression which unfortunately for some can result in myelosyplastic and leukaemic syndromes. Therapy-related myeloid neoplasms (t-MN) represent a unique clinical entity in patients treated with chemotherapy or radiotherapy and unfortunately carry a poorer prognosis than de *novo* disease.[1]

The incidence rate of therapy-related acute leukaemia in this setting is in the order of 0.2-0.5%. [1] A small but real increase in AML has been reported in several larger observational studies in breast cancer follow up.[2,3,4] In Northern Ireland an average of 1079 cases of breast cancer are diagnosed each year. Trends confirm that the number of women diagnosed each year is increasing by an average of 23 cases per year.[5] At least 300 patients per year receive adjuvant chemotherapy, this could equate to one or two such cases of therapy-related AML each year, making it a potentially understated and underemphasised clinical issue.

Two main types of therapy related AML and MDS were recognised depending on the putative agent according to the 2001 WHO classification of myeloid neoplasms. These were 1) those caused by radiation or by an alkylating agent (e.g. cyclophosphamide) or 2) caused by a topoisomerase II inhibitor (e.g., doxorubicin, epirubicin). These two types have distinct phenotypes. Alkylating agent related leukaemias have a long latency (4-7 years), pre-leukaemic phase and a worse prognosis. In contrast, those induced by topoisomerase II inhibitors have a shorter latency (2-3 years median), no prodromal phase and a better prognosis[6] (Table 1). In this case our patient received a chemotherapy drug from both groups which is standard practice. On balance the prodromal phase and longer latency would tend to indicate that cyclophosphamide was the more significant aetiological factor.

Table 1.

Key differences in therapy related AML by causative chemotherapy.

	Alkylating Agents (eg cyclophosphamide)	Topoisomerase II inhibitors (eg doxorubicin, epirubicin)
Onset	Long latency (median time 4-7 years)	Short latency (median time 2-3years)
FAB Subtype	M1/M2	M4/M5
Preleukaemic Phase	Two thirds present with myelodysplasia, the remainder have myelodysplastic features.	No preceding myelodysplastic phase
Cytogenetic Abormality	Chromosomal abnormalities in chromosome 5 and 7	Classically balanced translocations 11q23,21q22
Prognosis	Worse than *de novo* AML	Similar to *de novo* disease with corresponding cytogenetics

A population based study by the National Cancer Institute (NCI) analysed data for 420,000 women with breast cancer and found younger age at diagnosis and node positive breast cancer appear to confer a greater risk of AML in breast cancer survivors, potentially due to greater chemotherapy exposure or alternatively underlying genetic predisposition.[7] Several other factors can increase the risk of AML in this setting including: dose intensity of chemotherapy, use of adjuvant radiotherapy and the concomitant use of granulocyte colony stimulating factor (GCSF). The use of GCSF is increasing prophylactically to reduce the risk of neutropoenic sepsis and includes patients receiving docetaxel chemotherapy which is a current standard of care in node-positive breast disease. [8]

With the increased incidence of breast cancer and the trend for more chemotherapeutic intervention in the adjuvant setting it will be of utmost importance that patients are aware of the potential risks of secondary malignancy during the consent process. This is particularly significant for younger cancer patients. [9] It is important to add that the therapeutic benefit from adjuvant chemotherapy in early stage breast cancer is compelling, and is of a different order of magnitude than the estimated risk of secondary leukaemia.

The authors have no conflicts of interest.

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Ulster Med J 2013;**82(2):**100-108

Grand Rounds

Imaging in Cauda Equina Syndrome – A Pictorial Review

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Accepted xx January xxxx

INTRODUCTION

Cauda Equina Syndrome (CES) is an uncommon condition important because of its catastrophic consequences for the patient and its potential for medico-legal actions against medical staff. The need for prompt intervention makes research into the subject practically and ethically challenging. This article aims to provide an overview of CES with illustrations of its common causes and mimics.

DEFINITION

CES results from dysfunction of the sacral and lumbar nerve roots in the vertebral canal producing impairment of bladder, bowel or sexual function and perianal or saddle numbness[1]. It is a rare condition with a prevalence in the general population estimated between 1:100000 and 1:33000[2].

ANATOMY

A typical vertebra consists of a vertebral body anteriorly and a neural arch posteriorly. The neural arch has pedicles laterally and laminae posteriorly with transverse processes arising from the pedico-laminar junction. A spinous process arises posteriorly from the junction of the hemilaminae. These bony elements house the spinal cord and Cauda Equina in conjunction with the intervertebral discs, the posterior longditudinal ligament, ligamentum flavum and the facet joints[3]

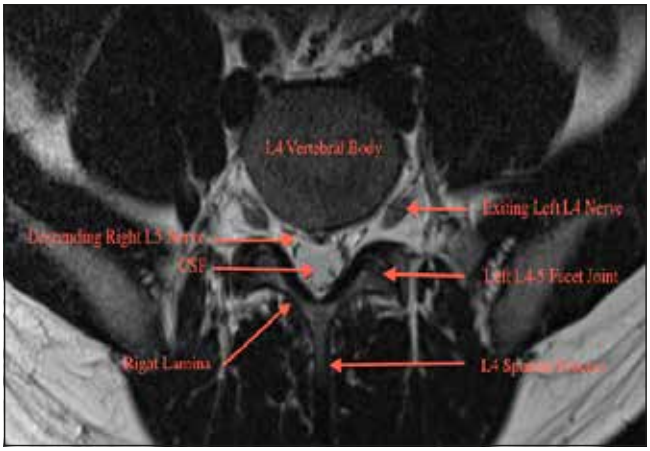

Fig 1a. Normal Axial T2 Weighted (T2WI) MR Lumbar Spine

The intervertebral disc consists of a central, gelatinous nucleus pulposus surrounded by a more fibrous annulus fibrosis (figure 1a). The annulus is relatively thin posteriorly

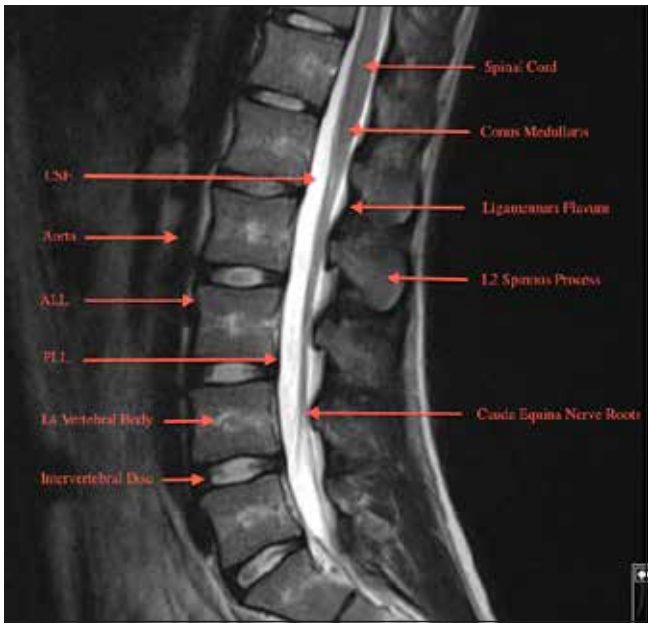

Fig 1b. Normal Sagittal T2 Weighted MR Lumbar Spine

and this is the usual site for rupture of a degenerative disc.

The spinal cord extends from the medulla oblongata to the level of T12-L1 where it terminates as the conus medullaris (figure 1b). Spinal nerves C1-C7 arise above the pedicles of their corresponding vertebrae whereas all the other spinal nerves arise below their pedicles. Spinal nerves exit the vertebral column at progressively more oblique angles due to increasing distance between the cord segment and the corresponding vertebrae. Lumbar and sacral nerves travel almost vertically to reach their corresponding neural exit foramina. The cauda equina consists of the nerve roots distal to the conus. These nerves have a dorsal root for transmission of sensation and ventral root for transmission of motor and sympathetic fibres.

The nerves in the cauda equina region include the lower lumbar and all the sacral nerve roots. Functions of these nerves include sensory innervation to the saddle area; voluntary control of the external anal and urinary sphincters and sensory and motor fibres to the lower limbs.

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The spinal cord vasculature is complex and variable. In broad terms the cord is supplied by two posterolateral spinal arteries and a single anterior spinal artery which all arise from the vertebral arteries. The spinal arteries receive further supply along their routes from radiculomedullary arteries arising from the subclavian artery and branches of the intercostal and lumbar arteries such as the artery of Adamkiewicz.

PRESENTATION

CES is defined by impairment of bladder, bowel and sexual function with perianal and saddle numbness[1].

Other symptoms that may be present include back pain with or without radicular symptoms; sensory changes or numbness in the lower limbs; lower limb weakness and reduced or absent lower limb reflexes. A thorough history should include any obvious precipitants relating to the aetiologies listed above such as trauma, underlying malignancy or recent surgery.

Saddle anaesthesia and bladder, bowel or sexual dysfunction are the key clinical findings to discriminate between CES and sciatica, which can also present with low back pain and radiculopathy[4].

Table 1:

Aetiology of Cauda Equina

Cause	
Congenital	Spinal Dysraphism Dwarfing syndromes, Congenital tumours: dermoid, epidermoid, teratoma and lipoma
Infective	Bacterial abscess Tuberculosis Schistosomiasis
Traumatic	Spinal fractures or dislocations
Degenerative	Spondylolisthesis Lumbar spinal stenosis Herniated intervertebral disc
Vascular	Arteriovenous malformations Aortic dissection
Iatrogenic	Secondary to surgery Spinal or epidural anaesthesia Spinal manipulation
Neoplastic	Ependymoma Neurofibroma Meningioma Schwannoma Lymphoma Metastases
Endocrine	Osteoporotic collapse
Biochemical	Paget's Disease
Inflammatory	Rheumatoid Arthritis Ankylosing Spondylitis
Haemorrhagic	Epidural/Subdural Haematoma
Thrombotic	Inferior Vena Cava Thrombosis

CLASSIFICATION

CES may be divided into complete or incomplete[4]. In complete cauda equina syndrome patients present with saddle anaesthesia and retention/incontinence of bladder or bowel. In incomplete CES there is saddle anaesthesia but bladder and bowel dysfunction has not progressed to full retention or incontinence. Bladder or bowel symptoms that these patients my report include loss of urgency or altered urinary sensation.

AETIOLOGIES

The most common cause of CES is lumbar disc herniation at the L4-L5 and L5-S1 levels[1]. Multiple other pathologies can damage the anatomical structures involved. An extensive list of causes is given in the table 1 below[5]:

INVESTIGATIONS

Magnetic Resonance Imaging (MRI) is the imaging study of choice for the evaluation of suspected patients with CES due to its ability to accurately depict soft tissue pathology. It can also identify potential mimics such as aortic dissection or spinal infarction. Disadvantages include lack of 24-hour availability and contraindications such as pacemakers and poor patient tolerance due to claustrophobia.

Myelography and CT Myelography can be used as an alternative for patients not suitable for MRI but have the disadvantage of being invasive techniques. Plain films are generally unhelpful in the investigation of a herniated disc but can provide valuable information in the setting of acute trauma. Inflammatory markers and CSF studies should be performed when an inflammatory or infectious aetiology is being considered.

CLASSIFICATION OF DISC HERNIATION

Standardization of language with regard to degenerative disc disease has proven difficult with many different phrases and terminologies used to describe identical findings. For the purposes of this review we have chosen to use the nomenclature and classification of lumbar disc pathology as recommended by the combined task forces of the North American Spine Society, American Society of Spine Radiology and American Society of Neuroradiology[6] . (figure 2)

Disc herniation refers to displacement of disc material beyond the intervertebral disc space. It can be subdivided using the percentage or angle of disc material herniated[6]:

For classification purposes the intervertebral disc is considered a round structure consisting of four 90-degree quadrants.

1. Bulge

A bulging disc describes eccentric expansion of the disc beyond the confines of the endplates involving greater than 50% or 180 degrees of the endplate circumference. These can be symmetrical or asymmetrical.

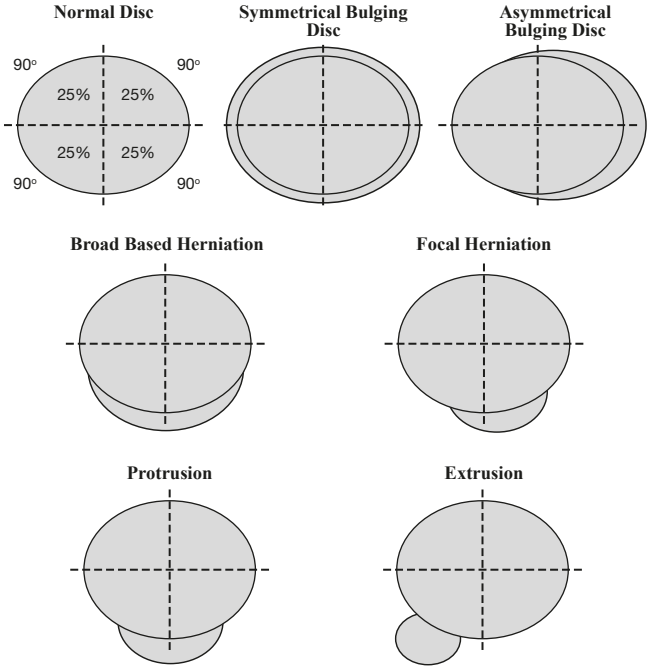

Fig 2. Schematic representation of disc herniation.

2. Broad-based herniation

A broad based disc herniation describes expansion of disc beyond the confines of the endplates that involves 25-50% of the endplate circumference.

3. Focal herniations, protrusions and extrusions.

A focal herniation describes expansion of the disc beyond the confines of the endplates involving less than 25% of the endplate circumference. Focal herniations can be subdivided into protrusions and extrusions depending on their shape. An extrusion has a narrow isthmus connecting the displaced disc material to the parent disc and protrusions have a broader base. Sequestration describes complete separation of disc material from the parent disc into the epidural space.

The location of a disc herniation should also be described in the axial plane as either central, subarticular (lateral recess), foraminal or extra foraminal. In the cranio-caudal plane it can be described as suprapedicular, pedicular, infrapedicular or at disc level.

PICTORIAL EXAMPLES

Detailed pictorial examples of all the causes listed in the table above are beyond the scope of this review. The most common causes of CES in decreasing order are[1]:

- Disc Herniation
- Tumour
- Infection
- Stenosis
- Haematoma
- Inflammatory
- Vascular

CASE 1: CENTRAL DISC HERNIATION

A 39-year-old female presents with a short history of back pain, urinary incontinence and saddle anaesthesia. (figure 3a, 3b)

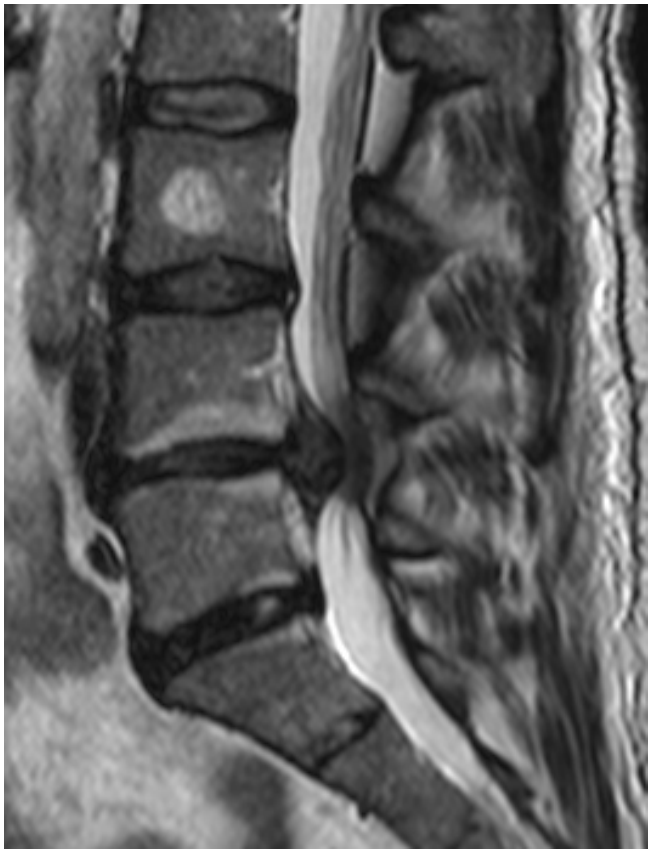

Fig 3a. Sagittal T2WI demonstrates a central disc herniation at L4-L5 with significant compression of the adjacent cauda equina nerve roots. Modic I end plate changes are also present at this level.

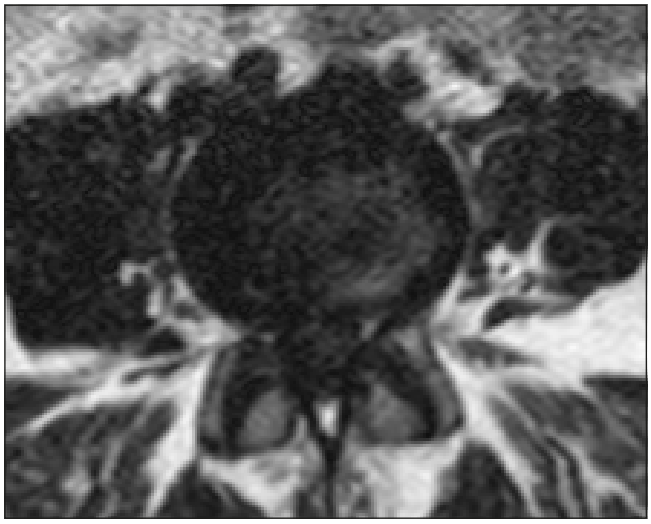

Fig 3b. The corresponding axial T2WI shows this to be a central, focal herniation (protrusion). There is no CSF visible around the nerve roots.

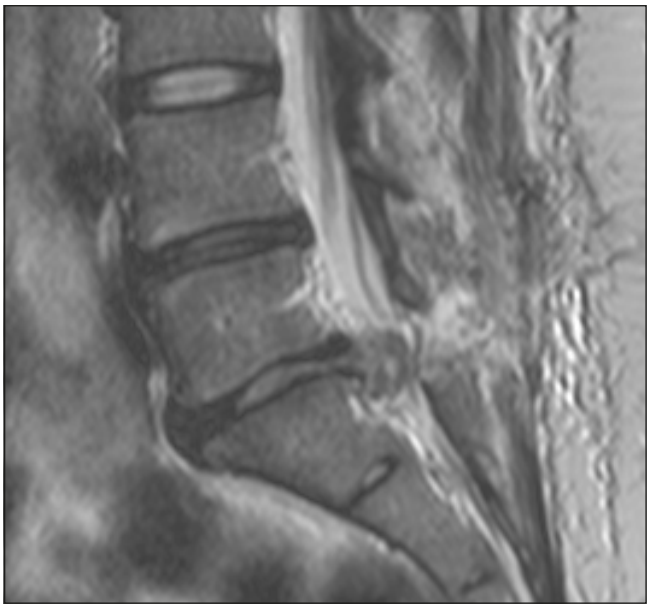

Fig 4a. Sagittal T2 WI shows a disc herniation at L5-S1 with compression of the adjacent nerve roots. Note the isthmus connecting the herniated disc to the parent disc is narrower in this case when compared to case 1. These findings are consistent with an extrusion.

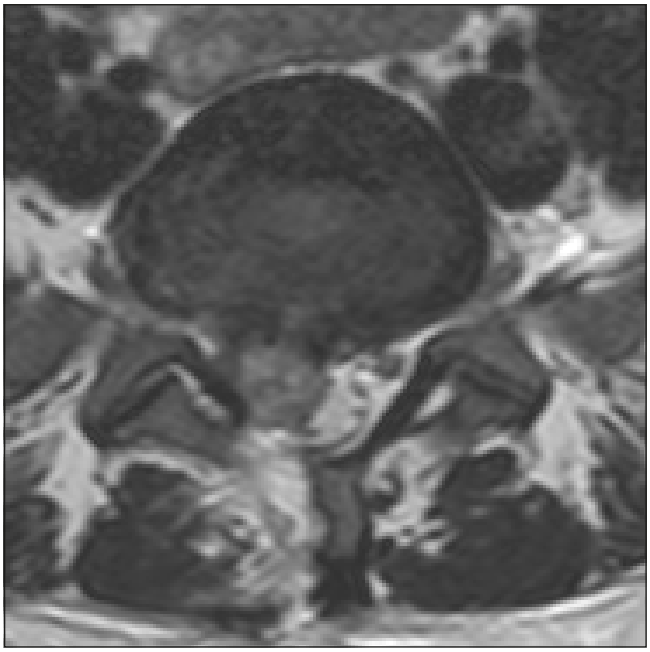

Fig 4b.The corresponding axial T2WI confirms a focal herniation with disc material centered on the right lateral recess. Note is made of a previous right laminectomy.

CASE 2: EXTRUSION

A 30-year-old female with a previous history of lumbar microdiscectomy presents with increasing low back pain and new onset urinary incontinence. (figure 4a, 4b)

CASE 3: SEQUESTRATION

A 37- year old female presents with acute onset urinary incontinence and leg weakness, more pronounced on the left. (figure 5)

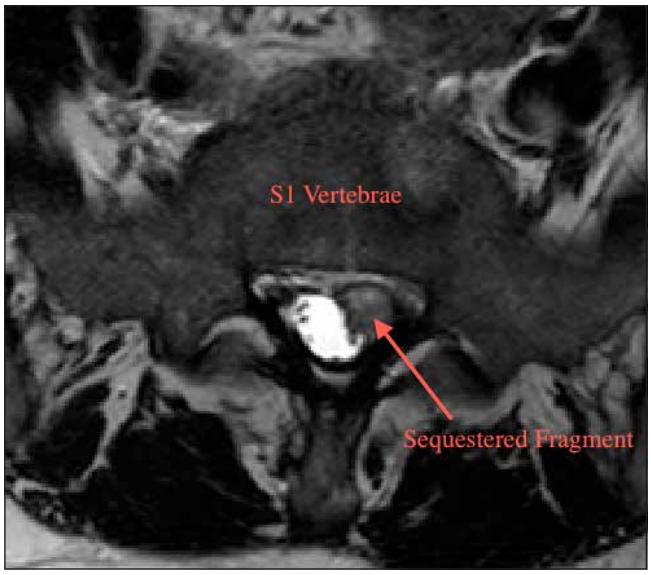

Fig 5. Axial T2WI shows a sequestered fragment of disc in the left lateral recess with displacement and compression of the adjacent nerve roots

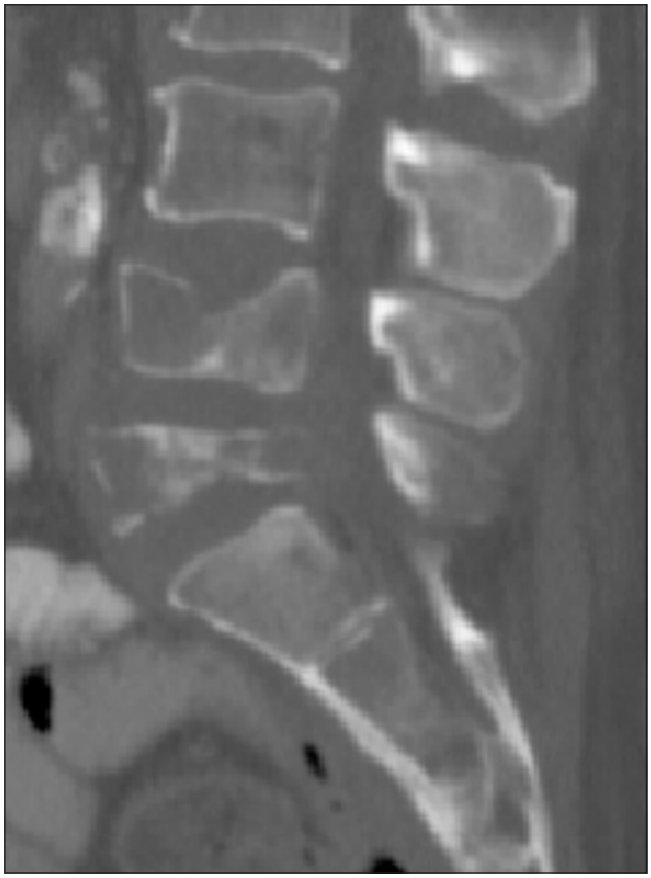

Fig 6a. Sagittal CT (bony window) shows multiple lucent lesions within the lumbar and sacral vertebrae with collapse of the superior endplate of L4 and almost complete collapse of L5.

CASE 4: SPINAL METASTASES

64-year-old man presents with abdominal pain and urinary retention. Past history of rectal carcinoma. (figure 6a, 6b)

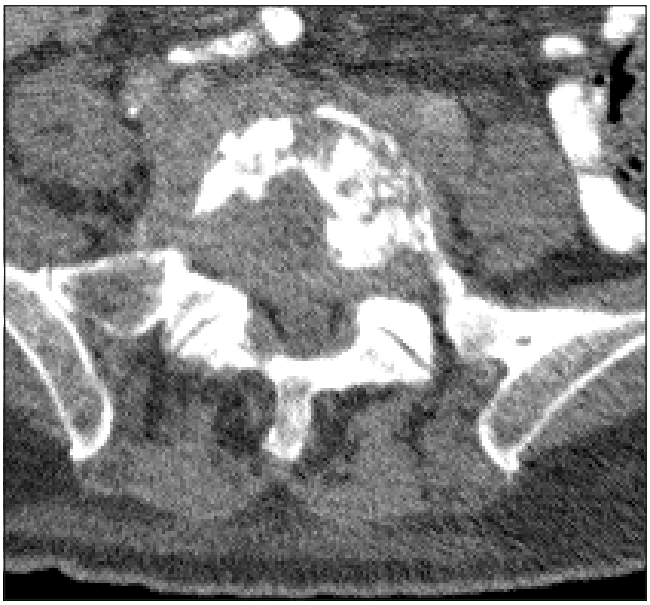

Fig 6b. The corresponding axial image (soft tissue window) demonstrate a large soft tissue component that is eroding the L5 vertebral body and extending into the spinal canal. The findings are consistent with metastatic cord compression.

The spine is the most common site of skeletal metastases[7]. Metastatic cord compression is defined as spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct expansion of malignancy that threatens or causes neurological disability[8]. Bony metastases most commonly occur with lung, breast, prostate, renal cell carcinoma or lymphoma. Metastatic cord compression is estimated to occur in approximately 80 cases per million people every year[8]. Solid primary bone tumours are much less common, accounting for less than 5% of bony malignancies. They are a rare cause of CES but cases have been reported with chordomas, chondrosarcomas and Ewing's sarcoma.

CASE 5: EPENDYMOMA

78-year-old man presents with leg weakness and increasing frequency of falls over several months. Decreased power in the lower limbs and saddle anaesthesia were noted on examination. (figure 7a, 7b)

Ependymomas arise from the ependymal lining of the spinal cord and are the most common primary spinal neoplasm of the lower cord, conus, filum and cauda equina[9]

There is often a delay in diagnosis due to slow growth. Radiologically they are well circumscribed and are classically low on T1 and high on T2 with intense, homogenous enhancement[7]. They are prone to haemorrhage and often have a "cap sign" due to haemosiderin staining. Most are WHO grade II but a rare anaplastic ependymoma is classified as WHO grade III. Other intramedullary neoplasms that should be considered include astrocytomas, haemangioblastomas and metastases.

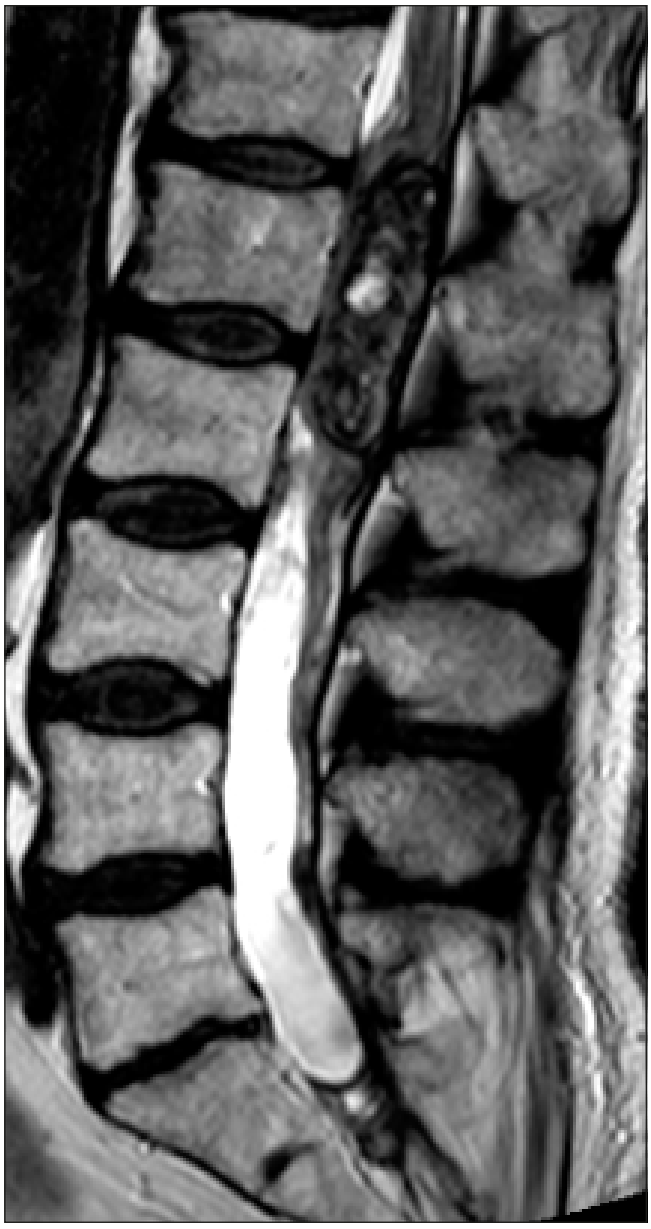

Fig 7a. Sagittal T2WI demonstrates a predominantly low signal mass with some cystic components arising from the conus. This extends inferiorly to the level of L2. T2 high signal material consistent with haemorrhage is noted between L2 and S1 with posterior displacement of the cauda equina nerve roots.

CASE 6: SPONDYLODISCITIS

34-year-old man presents with low back pain for one week and low-grade pyrexia. Examination reveals decreased anal tone and absent ankle jerks. (figure 8)

Spondylodiscitis refers to a bacterial, suppurative infection of vertebrae and intervertebral disc[7]. The lumbar region is most commonly affected and Staphylococcus aureus is the most common pathogen. The aetiology often relates to either septic emboli or direct invasion following intervention. Intravenous drug users and immunocompromised patients are predisposed.

CASE 7: SPINAL STENOSIS

An 87-year-old woman with a long history of back pain presents with a recent increase in pain and new urinary incontinence. (figure 9a,9b)

Acquired spinal stenosis describes encroachment on the spinal canal by bone or soft tissue secondary to multifactorial degenerative changes including endplate osteophytosis, disc herniation, facet joint hypertrophy and thickening of the ligamentum flavum[7]. These processes result in an hourglass appearance of the central canal effacement of the surrounding CSF spaces. Congenitally short pedicles often contribute to spinal stenosis. Exact measurements are not widely used or universally accepted in clinical practise but suggested measurements include[7]:

- Sagittal diameter of lumbar canal less than 12mm - relative stenosis
- Sagittal diameter of lumbar canal less than 10mm – absolute stenosis.

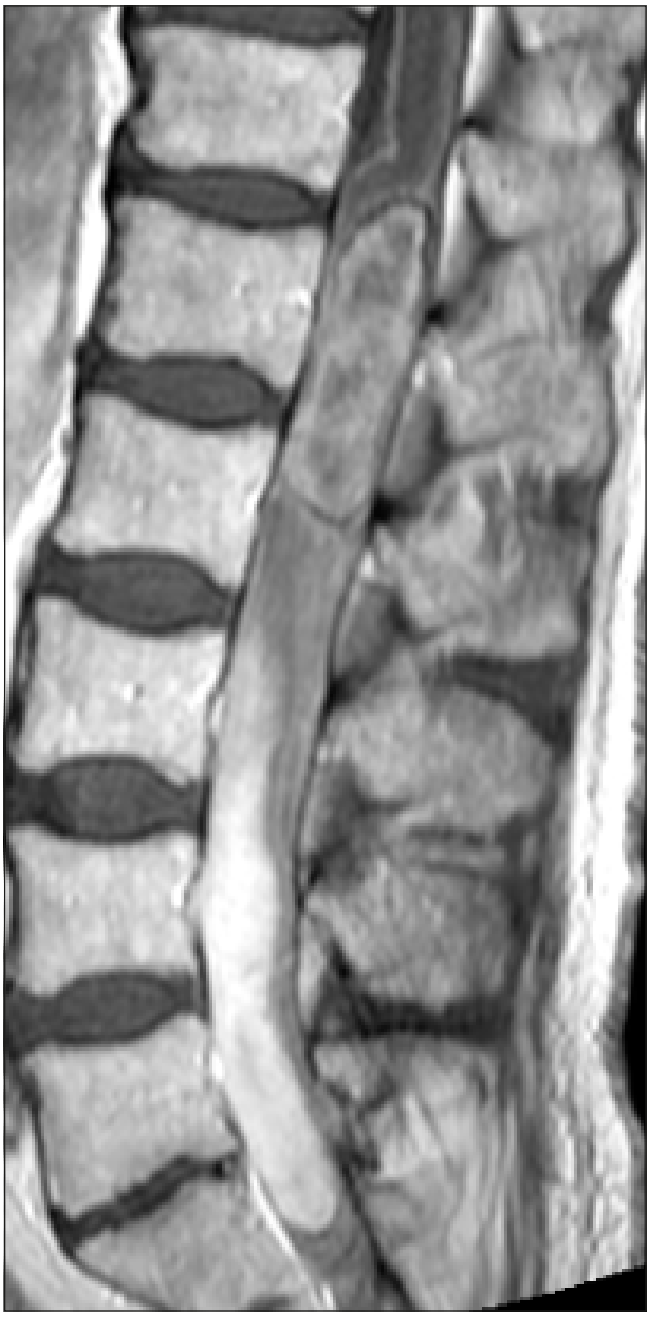

Fig 7b. The corresponding contrast enhanced T1WI shows enhancement of the mass and pial surface of the cord. The previously noted high T2 material seen anterior to the cauda equina nerve roots is also high signal on T1WI. The findings are consistent with an ependymoma with haemorrhage.

CASE 8: AORTIC DISSECTION

A 70-year-old man presents with decreased power in the power limbs, saddle anaesthesia and decreased anal tone. (figure 10a, 10b)

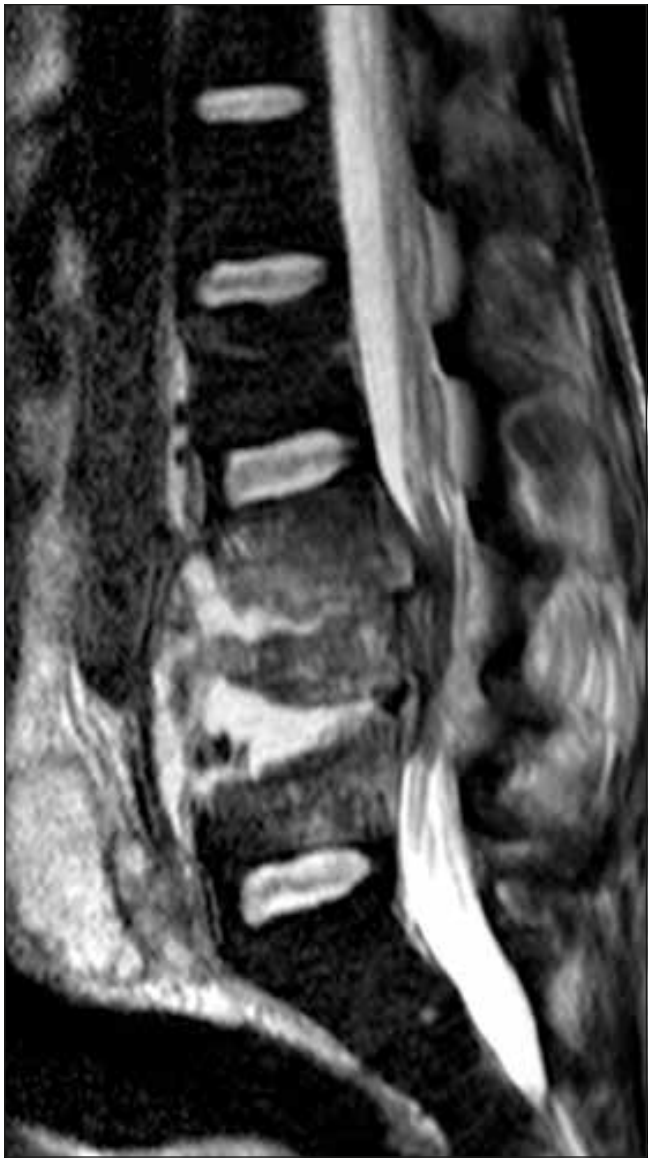

Fig 8. Sagittal T2WI shows partial collapse of the L4 vertebral body with surrounding high signal in the adjacent disc spaces. There is retropulsion of L4 into the spinal canal with compression of the adjacent nerve roots. T2 high signal consistent with oedema is noted within the L3, L4 and L5 vertebral bodies. A large fluid collection is noted anteriorly. The findings are consistent with spondylodiscitis with abscess formation.

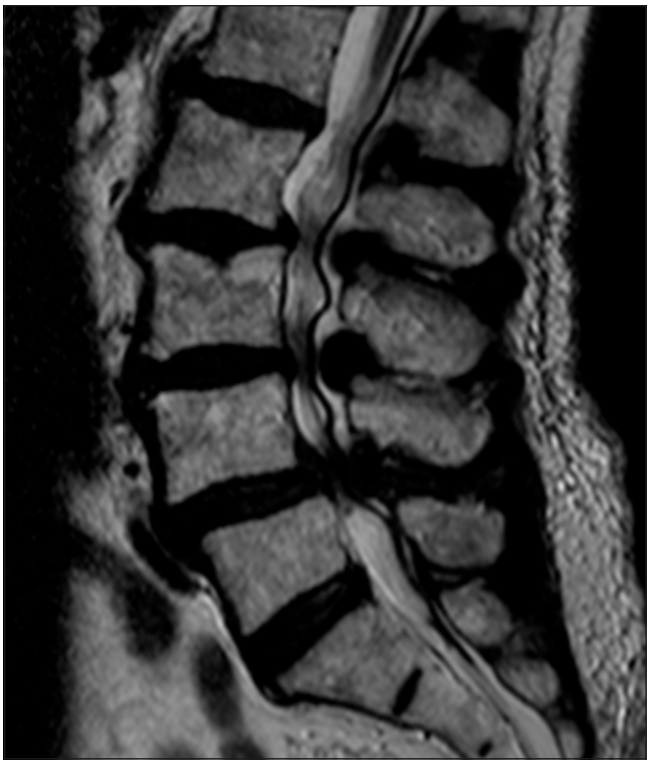

Fig 9a. Sagittal T2WI. Anterolisthesis of L4 on L5 of approximately 25%. This has caused unveiling of the L4-L5 intervertebral disc which demonstrates a generalized bulge. There is buckling of the ligamentum flavum at this level. The spinal canal is congenitally narrow.

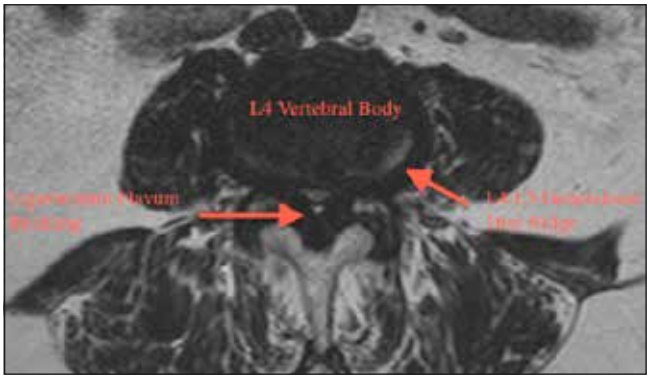

Fig 9b. The corresponding axial T2WI shows complete effacement CSF around the nerve roots. The findings are consistent with spinal stenosis

Acute aortic dissection refers to longditudinal separation of the aortic intima and adventitia by circulating blood having gained access to the media of the aortic wall. It is uncommon with an incidence of only 5-10 cases per million per year[10]. Neurological symptoms are present in 20% and it can be painless in 10% of patients. CES without chest or thoracic pain is an uncommon but recognised presentation of this condition[11]. Paraplegia that occurs in acute aortic dissection likely results from obstruction of medullary vessels feeding the anterior spinal artery[10].

CASE 9: COMPRESSION FRACTURE AND HAEMATOMA

A 79-year old man presents with increasing leg weakness following a fall. On warfarin for atrial fibrillation. (figure 11)

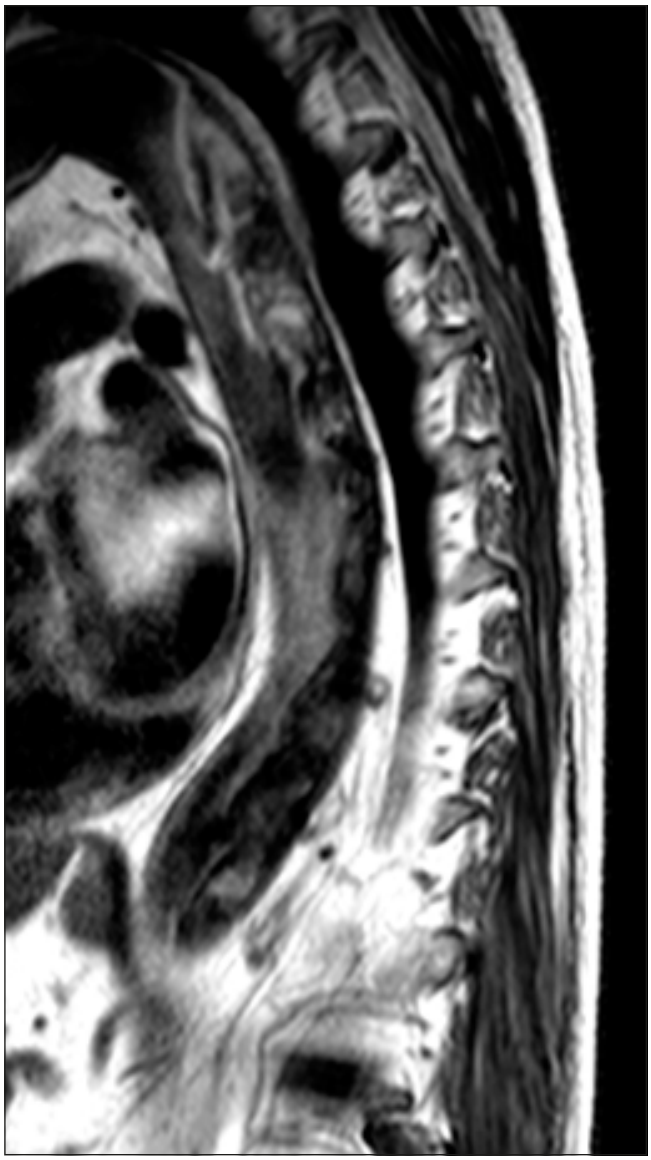

Fig 10a. Parasagittal T2WI.No significant abnormality within the spine but heterogeneous signal is noted within the thoracic aorta.

MANAGEMENT

For the purposes of this review the management discussion will be centered on lumbar disc herniation. Other aetiologies previously discussed such as spinal cord malignancy or aortic dissection are treated by addressing the underlying cause i.e. radiotherapy or vertebroplasty in the case of malignant cord compression

The role of surgery is to relieve pressure from the nerves in the cauda equina and to remove the offending elements. Treatment depends on the underlying cause with wide laminectomy and extensive decompression being the accepted surgical technique for a large lumbar disc herniation[12].

Most authors advocate emergency surgical decompression to improve outcomes in CES[5], however there is controversy with regard to the timing of surgery. Although the majority

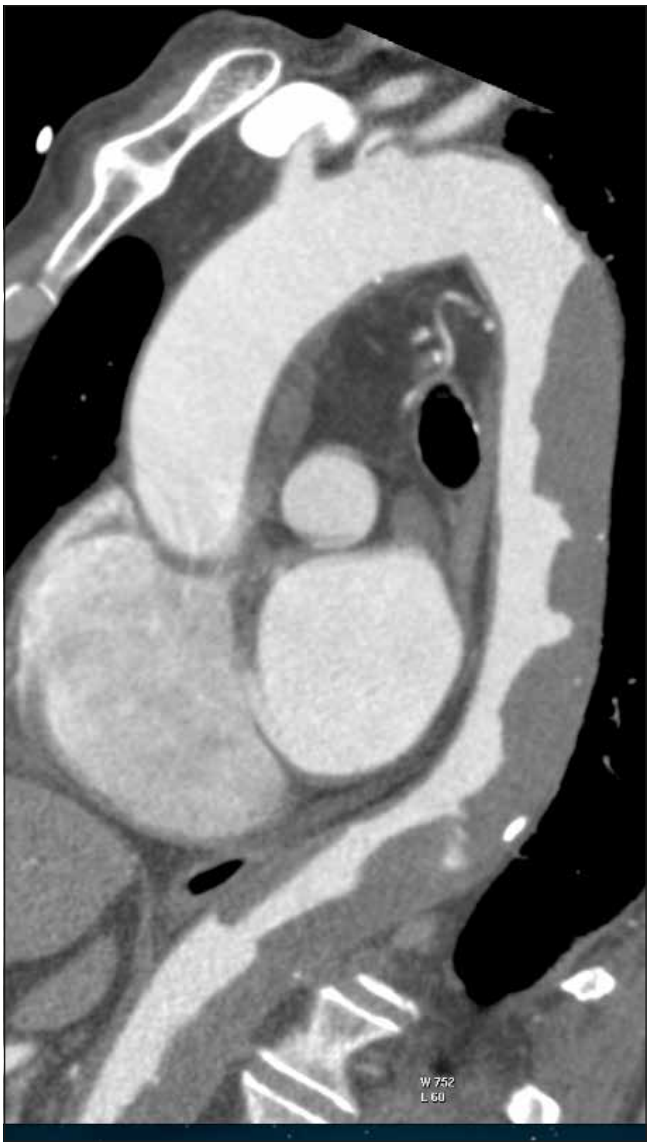

Fig10b. Contrast enhanced CT confirms the presence of an aortic dissection with extensive thrombus in the false lumen.

of authors advocate early surgery within 24 hours to improve functional outcome, several authors have shown little benefit to patients with complete cauda equina syndrome and early operative intervention.

Shapiro[13] retrospectively reviewed 44 patients with CES. These patients were subdivided depending on the time of surgery as shown in table 2 below. All patients who underwent surgery within 24 hours returned to full strength by one year. At 6 months, 95% of patients decompressed

Table 2:

Cauda Equina Syndrome: Timing of surgical interventions

Time of surgery	Number of Patients
Within 12 hours	17
12-24 hours	1
24-48 hours	2
After 48 hours	24

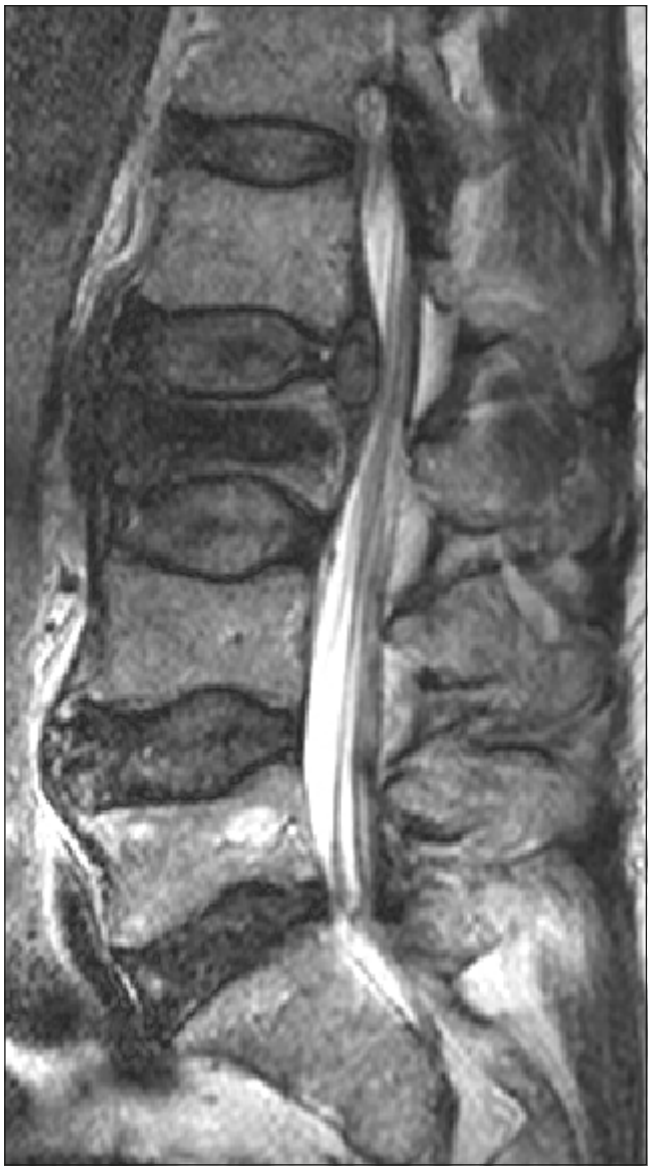

Fig 11. Sagittal T2WI shows a compression fracture of L3 with retropulsion of the posterior aspect of the vertebral body into the spinal canal. There is a convex area of low signal posterior to the L2 and L3 vertebral bodies that is compressing the adjacent nerve roots. The findings are consistent with a compression fracture of L3 with an associated extradural haematoma.

within 48 hours had normal bladder function; 100% of the men resumed sexual activity and 6/7 women resumed sexual activity. Of the patient decompressed more than 48 hours after symptom onset 58% had 0/5 to 2/5 weakness, 63% continued to catheterise, 71% had chronic sciatic pain and 31% were unable to achieve erection at one year[4,13].

Meta-analysis by Ahn and colleagues demonstrated no difference between those surgically decompressed at 24 and 48 hours[14]. In another meta-analysis, Hussain et al reported on 20 CES patients. Their study did not show any reduction in permanent disability between the group performed within 5 hours (9 patients) and those (11 patients) between 8-24 hours[15].

While there is debate about the exact timing of surgery in the literature, the consensus view is that those with incomplete cauda equina syndrome or indeterminate cases should be decompressed immediately as their neurologic and urologic outcomes are clearly improved if the patient does not progress to complete cauda equina syndrome[4,5].

CONCLUSIONS

We advocate the definition, as proposed by Fraser et al, that CES results from dysfunction of the sacral and lumbar nerve roots within the vertebral canal producing impairment of bladder, bowel or sexual function and perianal or saddle numbness. Elucidation of these findings in the clinical examination is crucial.

The number of potential aetiologies is vast but the most common causes are disc herniation, tumours, infection, spinal stenosis, inflammatory causes and vasculature occlusion.

Standardisation of language regarding lumbar disc pathology has proven difficult. We recommend the nomenclature and classification as recommended by the combined task forces of North American Spine Society, American Society of Spine Radiology and American Society of Neuroradiology.

Early surgical decompression is advocated by most authors to best aid patient recovery and reduce long term disability. There is evidence to suggest intervention within 24 hours significantly improves outcomes.

The authors have no conflict of interest.

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Ulster Med J 2013;**82(2):**109-113

Annual Oration

Thinking Otherwise

Royal Victoria Hospital, Wednesday 26th September 2012

Patrick M Bell

Accepted 15 February 2013

When asked, many months ago, if I would deliver the 2012 Annual Oration, the great sense of honour being accorded easily overcame any anxiety about what I would say. I have to tell you that as the day has drawn closer, I have struggled to appreciate the honour, as a sense of alarm verging on panic has gradually taken over.

Many of us in medicine get used to delivering talks and lectures of one sort and another in front of large audiences. What is it about this occasion that reduces grown men (and perhaps women: there have been one or two) to a state of high anxiety? As I look around, it's not hard to see the reason. Because as I anticipated this is not some anonymous audience in an unfamiliar place far from home. Here I am, in the hospital where I have spent most of my professional life, which I have grown to love despite its imperfections, surrounded by colleagues, friends, teachers, family and loved ones; in short those with whom I have shared the ups and downs of professional and personal life. I am afraid to say so, but you really are quite intimidating. Nevertheless, I am grateful to you all for coming and I will try not to keep you too long.

Veterans of these occasions will know that the origins of the Oration are in welcoming the new students to the hospital for their clinical studies – to the Belfast General Hospital, which became the Belfast Royal Hospital and then moved to what is now the Royal Victoria Hospital. Even though so-called vertical integration of the curriculum has made the distinction between pre clinical and clinical studies less clear, that purpose remains today. I attended my first Annual Oration in the 1970s having been led there by Dr John S Logan. I won't name the orator that year, but I do not recall finding it all that compelling. Orations can be something of an acquired taste and perhaps appreciation increases with age. So for those students who have made it along, you do have my understanding, but I still say a warm welcome.

You will have gathered from the title that I do have a few things on my mind, and the first thing I want to do is persuade you that it is appropriate for me to use this occasion and the format of a lecture to unburden myself. Secondly I hope to persuade you that dissent and argument remain key to both good medical practice and the advance of medical science. Thirdly I will argue that there are times when it is the duty of the doctor to bring dissenting views into the public sphere. Finally I will advise you that we should not be complacent about the freedom we have to speak out both as doctors and as citizens.

So is it really appropriate for 150 or more of us to gather here, taking perhaps two hours or more out of busy working lives? Worse still for a couple of rows in the middle it might turn out dry enough for golf. Whatever way you look at it, there are a lot of man hours involved. And then you are told you are going to have to listen to a lecture – a word that in modern usage has picked up a lot of negative connotations. More than that, there is the veiled threat within the title that a medically qualified person in N. Ireland might be at risk of saying something vaguely controversial. Worst of all there is no right of reply, so you will be exposed to the opinions of a middle aged male of a certain background and upbringing without a balancing panel of views - unless there is some heckling from the back which I do not remember as a tradition of these occasions. So I suggest you to hold onto your seats: it could get a little bumpy.

A few years ago the playwright David Hare argued, in his book "Obedience, Struggle and Revolt", that the set piece lecture remains a critical part of developing ideas and reaching the truth[1]. Hare commented on the extreme rarity of uninterrupted speech in both social and academic discourse. His contention was that it takes time to put forward a certain point of view, and that the absence of immediate counterargument should not be a cause for concern. Rapid responses can be unnecessarily defensive with a certain amount of grandstanding and posturing. Indeed, Hare suggested that if you wanted to make sure an hour would pass in which no serious thing was said about politics you would invent the television programme "Question Time". Medical educational theorists have a low expectation of students' ability to concentrate. The London Deanery programme[2] tells us that "a rule of thumb is that real concentration on one activity, such as listening to someone talk, lasts around 10 minutes without a break or change of pace. It is important therefore to keep the session flowing ..."

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I am not sure how I'm doing so far but, if only out of politeness, you are prepared to stick with me for the next half hour or so – you see I have high expectations of your powers of concentration - another question arises which is should we use this occasion, when we award some of our brightest students their well earned prizes (and may I add my own congratulations), to discuss anything remotely controversial? Indeed I have heard it said that the Oration is purely ceremonial. Well I beg to differ. If it is worth getting you all together, and so long as we avoid unnecessary and gratuitous insult, then I can see no reason why the strongest opinions should not be articulated provided they are in some way relevant to the work of this hospital, the greater Belfast Trust or the health service in general. And if there are those at the end of this morning who feel sufficiently moved to wish to mount a counterargument, could I suggest that you send your application in early to the Chairman of Staff for next year's event.

So Chairman, Ladies and Gentlemen, if I might move to my second theme; that dissent and argument, challenging orthodoxy, remain key to good medical practice and science.

The Germans have a nice word "andersdenker", one who thinks the other thought or thinks otherwise. In medicine, as in other walks of life, we should all be prepared to be, from time to time, andersdenker. History is littered with instances of great minds, and of course some not so great minds, who have run up against the prejudice of established opinion whether that opinion is held within cliques, oligarchies, majorities or even, sad to say, within democracies, for it was they, the democrats in Athens in the 5th century BC, who sentenced Socrates to death – as depicted by Jacques-Louis David in this picture now hanging in the Metropolitan Museum of Art in New York (figure 1).

Socrates chose to die rather than give up the right to express his opinion. What was that great thinker's crime? He was part of no faction, he commanded no arms. It appears he just went round Athens talking to people. It is strange how disturbing those in authority found logical argument.

And the connection here, you may ask, with medicine? Well, Plato tells us that Socrates dying wish was that a cock be sacrificed to Asclepius[3], the mythical physician-hero eventually worshipped as a god. Asclepius also came to a sticky end, struck down by Zeus with a thunderbolt for overstepping his physicianly powers and upsetting the natural order – a point I will return to.

It is not hard to find examples of less than divine physicians who ran into difficulty when they challenged conventional opinion. There may have been others thinking along similar lines to William Harvey when, in 1628, he published his great treatise, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. In just 72 pages he distilled the results of years of careful experimentation, comparative anatomical dissection and clinical observation, and described the circulation of blood around the body as we now know it.

Quite quickly, opposition arose from those who adhered to the traditional views of the ancient Graeco Roman physician Galen. In contrast to Harvey one of his most vociferous opponents Primerose managed to write his book, published in 1630, inside a fortnight[5] – no real need to check the data if there are no data, which remains the standard approach of many alternative medicine advocates today.

Fig 1. The Death of Socrates by Jacques-Louis David. With permission from the New York Metropolitan Museum of Art through the Images for Academic Publishing initiative.

Some of you may have been lucky enough a few years ago to see the Lyric Theatre production of Molliere's "Le Malade Imaginaire". Mr Diafoirus, the physician, is depicted railing against the circulators - the adherents of Harvey's view[5]. Diafoirus may well be based on the Parisian physician Gui Patin who, when not opposing the circulators, was obsessed with purgation and bleeding. That "Le Malade Imaginaire", written in 1671, 43 years after the publication of "De motu Cordis", was able to satirise critics of Harvey's ideas probably indicates that opposition to Harvey was by this stage on the decline. This ties in nicely with Max Planck's remark "a new scientific truth does not triumph by convincing its opponents but rather because its opponents eventually die, and a new generation grows up that is familiar with it"[6].

A sceptical and questioning approach is not just a matter for medical scientific inquiry. It is part of everyday medical practice and teaching. The discipline of learning by questioning is often loosely called the Socratic method, after our friend Socrates of Athens. Challenging a series of hypotheses – does the evidence fit - is usually how we establish a diagnosis. It is also the method most of us use in our bedside teaching as we challenge students with the complicated jigsaw of observations that make up the presentation of illness. Socrates was accustomed to say that he did not himself know anything and that the only way in which he was wiser than other men was that he was conscious of his own ignorance[7]. This is a good starting point for learning and perhaps emphasises that we need to come to our patients with an open mind.

But a few words of warning are also necessary. Socrates was against the absolute scepticism of the sophists. That well

known medical writer and thinker, Petr Shrabanek, made the point that too much scepticism can hinder scientific inquiry if it goes so far as to become an inability to recognise the absurd – what he called irrational scepticism. Irrational scepticism risks becoming a dogmatic belief in the absurd and a tentative unbelief in reason[8]. The danger is that one's mind stays so open that the brains fall out.

Acceptance of what is termed alternative medicine falls into this category. It is understandable for frustrated patients, with chronic or incurable illnesses, or with symptoms which doctors have failed to acknowledge or explain, to turn to alternative medicines and unorthodox practitioners. But for those, who have been trained at much expense to become medical practitioners and others who should know better, to fail to recognise what is patently absurd is scepticism gone mad.

My third theme is that there are times when it is the duty of the doctor to speak out. The need to do so may appear obvious, in other instances less so.

Let's start with a fairly extreme example. In 1946 twenty doctors and three administrators were charged with war crimes and crimes against humanity for their part in the human experimentation in the Nazi concentration camps. The defence argument was that they were engaged in necessary wartime research and that they were following the orders of their superiors. Sixteen were convicted and either hanged or sent to prison[9]. It is hard to find evidence that any wrestled with their conscience. One or two expressed remorse later. All of us can agree that , however difficult, they should have spoken out or refused to carry out their orders. Loyalty to an organisation, institution or regime was not a valid excuse.

Of course, it is an extreme example. None of us is likely to be in a position like this today. Or maybe not. Steven Miles has told us[10] that at prisons in Abu Ghraib, Iraq and Guantanimo Bay, Cuba "at an operational level, medical personal evaluated detainees for interrogation, and monitored coercive interrogation, allowed interrogators to use medical records to develop interrogation approaches, falsified medical records and death certificates and failed to provide basic medical care." The Red Cross accused physicians of flagrant abuses of medical ethics. I don't equate the Nazi doctors with those in Iraq or Cuba in any scale of evil, but it is clear that the modern doctor must remain vigilant

This applies in today's NHS in the form of so-called "whistleblowing" with respect the practice of either an individual colleague or an organisation. In all such situations we have been given clear advice by the General Medical Council about how to raise and act on concerns about patient safety[11]. So-called gagging clauses have been quite rightly condemned and doctors instructed not to sign them. And of course making concerns public must be an option, but only when other appropriate channels have been exhausted.

In the aftermath of the Mid Staffordshire NHS Foundation Trust scandal, the House of Commons Medical Committee called on the General Medical Council to send out a clear signal to doctors that they are as much at risk of being investigated for failing to report concerns about a fellow doctor as they are from poor practice on their own part[12]. No one would defend remaining silent if we become aware of poor performance by a colleague, which is putting a patient at risk. There is, however, some danger of putting this type of thinking at the heart of our practice. In building team working of health care professionals an element of trust is essential. My concern is that the Health Committee message will have the effect of creating an atmosphere of fear and distrust of the sort seen in communist block countries before 1989. In my experience nearly everyone in the NHS is trying to do their best. No amount of compulsive checking can induce excellence if motivation and morale are at rock bottom.

As opposed to speaking out about deficiencies in care, I am rather more concerned about whether the profession has contributed, or some would say been allowed to contribute, to decisions that have shaped the health service in NI over the last 30 years. As the Compton Report has pointed out we face a situation where poorly developed community services are failing to stop the flow of patients by default through the Accident and Emergency and outpatient departments of our hospitals[13]. In these same hospitals resources are spread too thinly around too many sites with the result that levels of manning of essential emergency and other rotas is at breaking point.

Could this all have been avoided? Probably not. But the unrealistic nature of much discussion about the service has not helped.

Doctors do need to use every opportunity to bring their professional opinion to bear. It is helpful if our ideas can be directed through the filter of collegiate discussion. Since the scrapping of the Specialty Advisory Committees to the Department of Health, it is not clear to me how the Department of Health in N.Ireland obtains independent medical advice. Contrast the situation in Scotland where there are close links with the medical Royal Colleges.

If we are to take a more active part in public debate, we need to make it clear in what context we speak; as doctors or as individuals. And there are dangers that, speaking as doctors, we may involve ourselves in matters that we have no business getting involved in. Michael Fitzpatrick, a General Practitioner working in London, has warned that doctors, and governments acting through doctors, have become associated with the "regulation of lifestyle in the name of health ... for deterring vice and disciplining society". In the introduction to his book[14] "Tyranny of Health" he states "On a bitterly cold February day in the winter of 1987 I had to break into the house of an elderly couple who had succumbed to a combination of infection and hypothermia. While I waited for the ambulance I found unopened on the doormat, a copy of the government's "Don't die of ignorance" leaflet which has been distributed to twenty-three million households as part of the campaign to alert the nation to the danger of

AIDS. Around half of these households contained either an old couple or an old person living alone. One elderly woman wrote to a national newspaper inquiring do you think this caring government would swap my AIDS leaflet (as new) for a bucket of coal". Fitzpatrick is perhaps a little hard on a well intentioned initiative, but it does highlight that in our professional role it is best to confine ourselves to stating professional opinion and leave it to individuals to take decisions about how they behave.

My final theme is that we should not be complacent about the freedoms that we have and think we have. There remain many vested interests which stand in the way of legitimate expression of opinion. The poet and critic Tom Paulin has argued in his book "Crusoe's secret; the aesthetics of dissent" that huge sections of English literature are a sort of coded criticism of establishments of their time[15]. You may think it fanciful if I suggest to you that we may again have to disguise reasoned scientific opinion within the pages of literature, but perhaps consider these cases. Three years ago Dr David Nutt, government scientific advisor, gave a public lecture at which he expressed the view that certain drugs, specifically ecstasy and cannabis, should be regraded from class B to class C, that is labelling them as less dangerous than previously. This contradicted the Government line and he was sacked by the then Home Secretary Alan Johnston[16].

David Nutt may have erred in making a direct criticism of the minister who did not take his advice. From what I saw of Alan Johnston he appeared to be a very competent Minister. I accept that classification of drugs is a high profile and emotive issue, and my own personal view tends to be proscriptive in the matter of drugs of abuse. But essentially Alan Johnston, in sacking David Nutt, conceded his inability either to argue the contrary case on scientific grounds, or, as a politician, articulate the view that public opinion which he represented did not agree with the scientific opinion expressed. Sadly those elected democratically to lead us, just as in Socrates day, can be oversensitive to logical argument. You might say why should Governments not appoint whom they want to give them advice? Well they can do exactly that, but of course the danger is that they appoint those whose opinions they like to hear.

As well as overbearing government, the dangers posed by claimant friendly libel laws have received much attention. For example, there are numerous instances of large pharmaceutical companies suing doctors for comments made during scientific meetings. These cases have stimulated a vigorous campaign to reform the libel laws, which currently place an onus on the defendant to prove the truth. This may not be easy. Even victory in a libel case can leave the defendant paying huge legal expenses. This goes well beyond individuals. Medical journals have felt it wiser to desist or pay up without fighting the case.

One note of optimism was the victory at the Court of Appeal by Dr Simon Singh, a medical journalist[17]. Dr Singh was sued following an article he wrote in which he criticised the British Chiropracter Association for defending chiropractors who as he put it "happily promoted bogus treatments". They finally dropped their case in April 2010. The Appeal Court judges drew on the statement of Judge Easterbrook of the US Seventh Circuit Court of Appeals; "scientific controversies must be settled by methods of science rather than by the methods of litigation. More papers, more discussion, better data – not larger awards - mark the path towards superior understanding of the world around us."

So, finally, how is the argumentative doctor to proceed? There are some lessons to be learned from the playwright Henrik Ibsen. In his play "An Enemy of the People", completed in 1882 and based on real events, Ibsen tells how the well intentioned Dr Thomas Stockmann speaks out after he learns that the spa waters of the town in which he practices are a source of typhoid and other diseases[18]. These spa waters are also the town's main source of wealth as a tourist attraction. They are run by the Baths committee, of which Dr Stockmann's rather pompous brother is Chairman as well as being mayor of the town. Stockmann sadly makes a number of mistakes. He is certainly tactless in his dealings with authority. Pinching and wearing his brother's grand mayoral hat makes good theatre, but does not improve filial love and respect, the equivalent of leaving your car in the Chief Executive's parking space. Don't let it get personal. Stockmann displays complete ignorance of the economic impact of his proposals to solve the problem, a characteristic not unknown amongst modern medical men. He is inclined to be hot headed and rushes to the press with his scoop. His near fatal mistake is to trust the press to remain on his side after the catastrophic impact of his findings on the town's house prices becomes clear. He does not mashal his evidence clearly and assumes the public will have no difficulty following the logic of the scientific argument. The public have a perfect right not to like the facts and an even more important one which is to ignore them altogether. Perhaps most seriously Stockmann allows a degree of self interest to influence his actions which extend beyond the strictly medical. He believes that publishing his findings in the press will enhance his reputation and overturn the town's ruling clique. In short his handling of the situation lacks many of the skills that would be required for survival in the modern NHS. Despite the rightness of his cause he is declared an enemy of the people, his house is stoned by the mob, and he loses his position and practice.

So if there are any new students here, and don't we all need to consider ourselves new students of something, my advice is certainly to challenge conventional opinion, and speak out when necessary. Take a little care when tackling Governments and others with big budgets and large public relations departments. Watch out for false friends in the press, and be sure that your motivation is at all times - beginning, middle and end - to improve the lot of the patients under your care.

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Ulster Med J 2013;**82(2):**114-120

Medical History

Our Blood Your Money

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Accepted 26 July 2012

SUMMARY

On June 3, 1939, Donegal-born James C. Magee was appointed U.S. Army Surgeon General by President Franklin Delano Roosevelt. On May 31, 1940, Magee appointed Professor Walter B. Cannon of Harvard University as Chairman of the U.S. National Research Council Committee on Shock and Transfusion. In 1938 Brigadier Lionel Whitby was appointed Director of an autonomous U.K. Army Blood Transfusion Service (ABTS). Whitby thereupon appointed Professor John Henry Biggart, Professor of Pathology, Queen's University, his Northern Ireland Head of Blood Transfusion and Blood Banking. Winston S. Churchill was aware that Biggart's service would be responsible for the needs of the Allied Forces and later for the United States Forces in Northern Ireland. Professor J.H. Biggart was known to Churchill from their 1926 post-prandial encounter in Belfast. The United States in 1941 determined that they were not able or prepared to fly U.S.-donated blood to Europe or Africa. The shortage of whole blood for United States forces required Whitby's ABTS to supply all the blood for the Mediterranean Theatre and in Europe from the St. Lô breakout from Normandy until after the capture of Brussels on September 3, 1944 and then again in December 1944 for the Battle of the Bulge. Winston S. Churchill took Whitby to Quebec in September 1944 to meet with President Roosevelt and the combined U.S. Chiefs of Staff. Churchill used the supply of British blood to meet the needs of American Forces to prevent the U.S. threats to bankrupt the British Empire. President Roosevelt, already involved in his fourth campaign for the U.S. Presidency, accepted most of the British proposals for further credits. By Okinawa in the spring of 1945, under ABTS tutelage, all the Allies were adept in long-range transport and storage of large, 100,000 pint quantities of whole blood. Subsequently, Whitby and John Henry Biggart were knighted; U.S. Army Surgeon General Magee was sacked.

INTRODUCTION

The principles of World War I blood banking were continued during the Spanish Civil War by the Blood Transfusion Services of the Spanish Republican and Nationalist Armies. The Republican service included 28,900 donors and used citrated and stored blood in a manner similar to "Robby" Robertson's blood banks during World War I[1-3]. The Nationalists were advised in Spain by Oxford's Nuffield Professor of Anaesthesia Robert Macintosh (Fig. 1), and by Dublin-born and Yale-trained Joseph Eastman Sheehan, Lord Nuffield's choice for Professor of Plastic and Reconstructive Surgery[5]. Elósegui's Nationalist Blood Transfusion Service transfused an estimated 25,000 times before Franco's victory[6].

Fig 1. Professor Sir Robert Macintosh and Angus Hedley-Whyte examining at the first examinations in 1952 for the Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons of England. Photograph 1952 gift to John Hedley-Whyte. Sir Robert was fluent in Spanish from his internship in Montevideo. Both Sir Robert[4] and Professor Eastman Sheehan[5] were friendly with Nuffield Professors Hugh Cairns and fellow Nuffield Professor Republican Catalan hero Joseph Raspall Trueta, an orthopedic surgeon. Both Professors Macintosh and Sheehan were awarded the White Cross of Military Merit by Franco[6].

In 1938 the British, in preparation for another war, formed, at the instigation of the Royal College of Surgeons of England, an autonomous Army Blood Transfusion Service (ABTS) under the command of Brigadier Lionel E. Whitby[2,7], already well-known for his successful treatment of King George V and his introduction of sulphonamide treatment into Britain[8-10]. Whitby had also been advisor to the Massachusetts General Hospital in the successful treatment of Franklin Delano Roosevelt, Jr.'s serious pneumonia[11]. Whitby obtained the services of his physician wife, Major Edith, as his executive officer and urged the appointment of Geoffrey Keynes to be

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Surgical Consultant to the Royal Air Force[12]. Lionel Whitby writes Oswald "Robby" Robertson "stored blood for as long as 21 days and used it with excellent results in the treatment of wound shock on the battlefield," where it was indirectly transfused during World War I[3]. Whitby continues, "It is difficult to understand why [Robby] Robertson's [and Colonel Professor Andrew Fullerton's] remarkable achievement remained forgotten for nearly twenty years till the Spanish Civil War in 1937-39"[3].

The Whitbys arranged close collaboration and their ultimate control of the U.K. Emergency Medical Services' blood donation and banking. For Northern Ireland, Queen's John Henry Biggart, Professor of Pathology since 1937, was the Whitbys' obvious choice for Director and Blood Transfusion Officer for Northern Ireland[13]. Biggart had written about blood[14,15]. He got on well with Professor Thomas Houston whose World War I blood banking with "Robby" Robertson was by now well known[16]. Moreover, Biggart had been a Harkness Commonwealth Fellow at Johns Hopkins for two years and had toured throughout the United States[13]. The U.S. forces due to be deployed to Musgrave Park were scheduled to, and arrived in 1941 and 1942, without U.S. blood banking facilities. From 1940 Angus Hedley-Whyte (RAMC) and Colonel Thomas Lanman's (U.S. Army Medical Corps) Musgrave Park surgical services[17] were to rely on Biggart's blood donors obtained through the Northern Ireland Transfusion Service of the U.K. Emergency Medical Services.

Geoffrey Keynes, in 1940 about to be Air Vice Marshall, arranged the recruitment of Dr. Gerry Nelson from Biggart's Queen's Pathology Department to the Royal Air Force (RAF)[2,13]. Winston S. Churchill as First Lord of the Admiralty, was told that Biggart's Service would provide blood for the Royal Navy, Merchant Marine and the U.S. Navy. Lionel Whitby later recounted to Churchill, now Prime Minister, of Biggart's post-prandial hazing of Churchill following the latter's 1926 Queen's honorary degree. Winston Churchill had been seized by Biggart's fellow students, "crowned with an Irish paddy hat with green ribbon, given a white clay pipe and placed in an Irish jaunting car." Before Churchill marched a cohort of Hibernians, suitably bedecked, with John Henry Biggart in charge, writes Biggart's son Denis[18].

During the 2nd British Expeditionary Forces' retreat from France in 1940, Whitby's service provided approximately 4,000 pints of whole blood[2,7]. As a result of the experience of both BEF's in World Wars I and II, and the fighting in Norway, it was estimated that 41.4 pints of blood would be needed for every 100 Allied wounded[2]. Whitby informed the U.S. Surgeon General of the Army, Major General James Magee, of this estimate through his liaison officer in Washington, D.C., Colonel Frank S. Gillespie, R.A.M.C.[19,20].

US DISPUTES

Donegal-born General James Carre Magee between 1939 and 1943 commanded a corps of 30,000 U.S. doctors as well as 20,000 nurses[21]. While on a tour of Allied Forces in the U.K. and Africa, his superiors U.S. Chief of Staff George C. Marshall and Lt. General Brehon B. Somervell, Commanding General, U.S. Services of Supply convened the Sanford H. Wadhams Committee to review "the organization and administration of the [U.S. Army] medical department"[22]. Chief of Staff Marshall and General Somervell were not convinced of the capability of the Office of the Surgeon General to manage wartime challenges, as the Surgeon General's Office had objected to limitations on personnel and supplies they had imposed[22]. Evarts Ambrose Graham, Professor of Surgery, Washington University, St. Louis, Missouri, and Dr. Lewis H. Weed, Director, Medical School, The Johns Hopkins University, were members; in addition, six civilian doctors and two retired U.S. Army doctors were added, as was only one layman, Corrington Gill, an economist and statistician. Secretary of War Colonel Henry Stimson announced the formation of the Wadhams Committee the day before its first meeting on September 25, 1942, and Surgeon General Magee was thus informed while on his UK and Africa tour of inspection[22].

The Allied Commanders and Surgeons with whom he met during this tour continued to emphasize the need for U.S. whole blood[23]. Surgeon General Magee saw that the Whitbys' ABTS was doing an excellent job of supplying whole blood for the Allies in Africa. In early January 1943, General Magee asked for a copy of the complete Wadhams Committee Report. Next month, February 1943, Lewis H. Weed and Evarts A. Graham insisted on seeing the U.S. Secretary of War Henry Stimson. Former U.S. Surgeon General Merritt W. Ireland also complained to General Marshall of "aggressively critical attitudes toward the Medical Department…and of the failure to release the Report"[22]. On June 1, 1943, Magee was relieved of his Surgeon Generalship. The replacement nominated by George C. Marshall and President Franklin Delano Roosevelt was unacceptable to the American Medical Association; it being the start of his re-election campaign, the President accepted the American Medical Association's candidate Norman Kirk, an orthopedic surgeon[21]. Magee had paid the price for requisitioning too many hotels and having Military Police arrest U.S. prostitutes to reduce U.S. Army rates of venereal disease[22].

At the request of Surgeon General Magee, Walter B. Cannon, Professor of Physiology at Harvard, who had advocated the use of gum acacia during World War I, chaired the U.S. National Research Council Committee on Shock and Transfusion[19]. By November 3, 1941, this committee agreed "that it had been the consensus of the group that [US] Armed Forces should use whole blood in the treatment of shock wherever possible", but the results of that discussion were not officially minuted until two years later, on 17 November 1943[19].

D-DAY PLANNING

On Friday, March 5, 1943, at Thirlestaine Hall, Cheltenham, the D-Day Casualty Planning Committee, including Brigadier Angus Hedley-Whyte, was told that at least 30,000 pints of

group O whole blood would be needed for D-Day and the following month, on Whitby's advice, based on the previous year's experiences at Gazala-Bir Hacheim, Alam Halfa, and El Alamein. Col. Elliott C. Cutler's memorandum dated March 27, 1943, to Brigadier General Paul R. Hawley, Chief Surgeon, European Theater of Operations, stated that "Brigadier Whitby tells me that the use of wet plasma has practically been given up, and transfusion used in its stead in the British Army"[24] (Fig. 2). The Allied planning group were shocked to be told that the U.S. would not sanction the transport of any whole blood from the United States to Great Britain; logistical problems and the efficacy of human plasma were cited as the reasons for the U.S. obduracy[19]. The fractionation of whole blood and production of wet and dry plasma had been described and overseen by Professor Edwin J. Cohn of Harvard Medical School[29,30].

Fig 2. Portrait of Elliott Carr Cutler, 1946, by Charles Sydney Hopkinson (1869-1962). Oil on canvas 124 x 90 cm (49 inches x 35.5 inches). Reproduced, with permission, from the collections of the Brigham and Women's Hospital, Boston, MA. Photography by Susan R. Symonds, Mainframe Photographics Inc., Brigham & Women's Photography Services.

Elliott Carr Cutler was born in 1888 of Puritan stock. He graduated from Harvard Medical School before World War I. He further trained in 1913-14 at Heidelberg, and thereafter served as a surgical mainstay of Harvard's 5th General Hospital[25]. Cutler's 1923 mitral valve split was "The first successful intracardiac operation in the world…"[26,27]. During World War II he was responsible for planning the overall treatment of the wounded in the European Theater of War[25]. His 1947 British Journal of Surgery obituary is laudatory: "Perhaps no surgeon of the United States ever yearned or strove more earnestly to forge lasting bonds of friendship…between the peoples of the great English-speaking countries on either side of the North Atlantic''…'Integer vitae scelerisque purus'"[28].

Col. Edward D. (Pete) Churchill of Harvard University and the Massachusetts General Hospital was incensed by the Surgeon Generals', Magee's and from June 1, 1943 Kirk's positions. Col. Churchill briefed a New York Times reporter with the aim of publicizing the need for military blood banks[31] (Fig. 3). Pete Churchill was Chief Surgical Consultant to the North African and Mediterranean Theater of the War, in an Allied Command Structure with the Whitbys' ABTS providing blood as needed. Pete Churchill thought Brigadier Whitby's service invaluable and efficient and thus informed his successive theater chiefs D.D. Eisenhower and Ulsterman Harold Alexander[20,33,34].

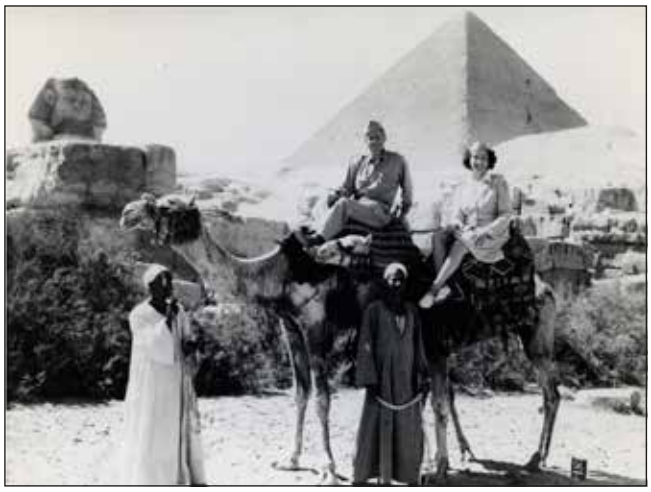

Fig 3. Col. Edward D. "Pete" Churchill on August 30, 1943, during a tour organized by the Red Cross. Photograph of Edward D. Churchill in Cairo [HMS c62, box 34, f.3] from the Edward D. Churchill Papers, The Harvard Medical Library in the Francis A. Countway Library of Medicine, reproduced with permission[32].

The Red Cross was helping the ABTS with production of whole blood in the Middle Eastern theater. Col. Churchill is accompanied by Mrs. Charlotte R. Bonner of the Red Cross. The previous day, Col. Churchill had met Mr. Banes, Director of the U.K. Red Cross in the Middle Eastern Theater, who assigned Mrs. Bonner as Col. Churchill's Cairo guide. She took Col. Churchill to the Middle East Surgeon's office where they worked on vital statistics of the wounded. They then went to British General Hospital No. 9 to see British Major Andrew Logan's group of chest injury patients, and continued on to British Hospital No. 63, together with Major Logan of Edinburgh and Col. J.S.K. Boyd. Churchill's camel's name was "Canada Dry". On August 31, 1943, Churchill left Cairo to return to his North African Post and thence to Italy: the Allies landed at Salerno on September 9, 1943[32,33].

BRITISH NEAR BANKRUPT

During early 1944 Winston S. Churchill's government were presented draconian terms and demand for the termination of Lend-Lease: on March 9, 1944, W.S. Churchill replied to President Roosevelt regarding U.K. dollar holdings: "These

U.K. dollar balances are not, as your telegram might suggest, a particular part of our assets…but our total reserves… We alone of the Allies will emerge from the war with great overseas war debts. I do not know what would happen if we were now asked to disperse our last liquid reserves at a time when British and American blood will be flowing in broad and equal streams and when the shortening of the war by even a month would far exceed the sums under consideration"[35]. President Roosevelt, in response to many in Congress and his administration, decided to temporize, having in mind the Octagon Conference and his own upcoming presidential election[36].

Initially, the D-Day Casualty Planning Committee had planned for the 30,000 pints of group O whole blood to last until the expected breakout from Normandy. The Whitbys tried to increase their collection of whole blood by donor drives by the ABTS and blood banks, especially in Cairo, Algiers, London and Belfast (Fig.3). The U.S. Armed Forces in the U.K. bled essentially every one of their available, non-combatant troops. With the unavailability of whole blood from the United States, the fighting in the Normandy bocage exhausted U.S. supplies. This dire situation was exacerbated by the RAF and USAAF short bombing of U.S. Troops before the Saint-Lô breakout. ABTS was thereafter chiefly responsible for the supply of whole blood to the Allied forces until after the Allied liberation of Brussels on September 3, 1944[19,20]. One of the keys to ABTS success was the widespread enlistment of French donors both in North Africa and metropolitan France. Almost total Allied air-superiority and a plethora of a thousand DC3 Dakotas helped immeasurably—wounded going north and ABTS blood going south, averaging 2,000 pints per day. The number of wounded reached 40,000 in a single month, and as many as 50,000 patients were air-evacuated. Nonetheless, the U.S. Armies in Normandy had to ration and allocate whole blood despite the provision to these U.S. armies of several thousands of pints of whole blood by ABTS. On the instruction of the European surgical consultants and Lieut. General Sir Alexander Hood, GBE, head of the R.A.M.C., Generals Paul Hawley and Harvard's Moseley Professor of Surgery, Elliott C. Cutler, were flown to Washington on August 13, 1944. The U.S. Surgeon General Kirk and General Hap Arnold, Commander U.S.A.A.F. changed their position while Hawley and Cutler were in mid-Atlantic. On August 21, 1944, the first pints of whole blood were flown from New York to U.S. forces in Europe. During the transition period in the fall of 1944, to compensate for U.S. inexperience in temperature control for transported whole blood, U.S.A.A.F. pilots were instructed to fly trans-Atlantic at six to eight thousand feet to preserve blood at 4 - 6°C[19,20].

OCTAGON TUITION

On Tuesday, September 5, 1944, Lionel Whitby joined Winston and Clementine Churchill's family party on the Cunard liner *Queen Mary*, en route to the Quebec Conference known as "Octagon". On Wednesday, September 6, Lionel Whitby was asked to dine en famille with W.S. Churchill and Hastings (Pug) Ismay. Churchill suggested that Whitby instruct the "Yanks how to fly blood long-ways big time" in Quebec[37]. At that September 6 dinner, Whitby recounted the R.A.F.'s dropping of whole blood to the ongoing Polish insurrection in Warsaw, which had started the previous month on August 1. Ismay suggested that Whitby also describe A.B.T.S.'s services to the U.S. personnel in Normandy, the rest of France, North Africa, Sicily, Salerno and Anzio.

Winston Churchill knew of his namesake Pete's briefing by the U.S. Surgeon General Magee and his staff in January 1943. Sir Alexander Hood had told him how the Pete Churchill legend had begun in 1929 at Harvard, with Pete's first successful U.S. pericardiectomy—the stripping of the pericardium in a patient dying of constrictive pericarditis[27,38]. W.S. Churchill added that he had learnt more of Robby Robertson and Elliott Cutler in World War I at the Club of Odd Volumes, watering hole of bibliophile Brahmins, after receiving his Honorary Harvard LLD on September 6, 1943[26,39].

The *Queen Mary* docked in Halifax on Sunday, September 10, 1944 and the Octagon conference started in Quebec City on Tuesday, September 12 (Fig. 4). After Whitby's presentations, President Roosevelt told Admiral Leahy to tell Brigadier Whitby he should hereafter "request and require on behalf of the Commander-in-Chief" (as Ismay told JHW). Thus, on Thursday, September 14, Admiral Leahy came as the sole American, to Churchill's "vast household dinner" [42*]. Later that evening, Churchill told his secretary Colville that their gambit "our blood for your money" had, as Colville put it, succeeded "beyond the dreams of avarice". Winston Churchill replied, "Beyond the dreams of justice"[42].

On Sunday, September 17, the Winston Churchills left for Hyde Park. On Wednesday, September 20, the Churchill party and 9,000 U.S. troops left New York, again on *The Queen Mary*. At Churchill "domestic" dinner parties on Thursday, September 21, finishing at 3:00 a.m. and on Sunday, September 24, Whitby was debriefed by Churchill in his "old spontaneous form"[42]. President Roosevelt was no longer proposing British bankruptcy. During the Battle of the Bulge in December 1944 and January 1945, A.B.T.S. was again given control of all west European blood matters. Montgomery and Patton were delighted that U.S. three-star general Lee no longer, at least temporarily, had a say in blood transport and distribution[43].

PACIFIC WAR

U.S. blood transport and preservation were a shambles at Leyte—essentially all blood was destroyed by tropical heat. In all, about 3,000 pints of preserved whole blood were used during the first thirty days of the Leyte liberation[19,20,44].

* During 1915-1916, Lahey and F.D.R. had frequently sailed together on the East Cost as far as Campobello. F.D.R in 1916 dispatched Leahy in the Dolphin, the Secretary of the U.S. Navy's dispatch boat, to pick up F.D.R.'s family at Campobello and sail them up the Hudson to their home in Hyde Park, New York. Leahy discretely completed this 600 mile sail.

At Iwojima there was a shortage of whole blood for both wounded marines on land and on board U.S. Navy ships. Okinawa was different: for 46,000 U.S. wounded, 46,000 pints of whole blood were successfully transported, preserved and transfused. Whitby's 1940 estimate of 41.4 had become100 pints of whole blood per 100 wounded[2]. Between March 24 and the middle of June 1945, the American Army Divisions lost 4,000 killed on Okinawa and the U.S. Marine Corps reported almost 3,000 dead. Japanese army casualties were 110,000 dead. The Japanese lost 7,800 planes around Okinawa, of which 1,000 were kamikaze. Okinawan civilian casualties were at least 70,000, and possibly as many as 160,000[19,45].

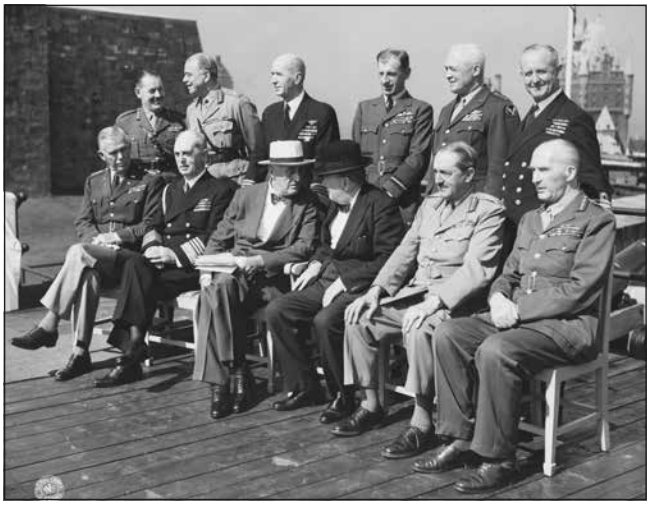

Fig 4. This photograph was taken on the boardwalk of the Citadel near the Château Frontenac, Quebec City, when the U.S. Joint Chiefs of Staff met with the British Chiefs of Staff as the Allies' Combined Chiefs of Staff Committee at the Octagon Conference in September 1944. Seated (left to right) are General George C. Marshall, Admiral William D. Leahy, President Franklin D. Roosevelt, Prime Minister Winston S. Churchill, Field Marshal Sir Alan Brooke, and Field Marshal Sir John Dill; standing (left to right) are Brigadier Leslie C. Hollis, Lieutenant General Sir Hastings Ismay, Admiral Ernest J. King, Air Chief Marshal Sir Charles Portal, General Henry H. Arnold Chief of the U.S. Army Air Corps, and Admiral Sir Andrew B. Cunningham.

Leahy was instructed by U.S. Commander in Chief Franklin D. Roosevelt to tell Brigadier Lionel E. Whitby, also present at the Château, that it was F.D.R.'s wish that henceforth the advice of the Whitbys be followed in all Allied areas of combat. Leahy was Chair of the U.S. Joint Chiefs of Staff and Chief of Staff to the Commander in Chief, F.D.R.

Both Alan Brooke and Bill Leahy suffered grievously in World War II. Twelve of twenty-seven "Fighting Brookes of Colebrooke", County Fermanagh, were killed[40]. Louise Leahy died postoperatively in Vichy, France, on April 21, 1942, after F.D.R. had urgently recalled her husband of thirty-eight years from his ambassadorship to Pétain, following Laval's assumption of power. The Leahys had planned to return to Washington, D.C. as soon as Mrs. Leahy had sufficiently recovered, but Admiral Leahy embarked for New York on May 22, 1942 with his wife's remains[41].

U.S. Army Signal Corps photograph 194469 2. Courtesy of the George C. Marshall Foundation, Lexington, Virginia, USA.

Presidential and U.S. chiefs of staff estimated that the casualties during the invasion of Japan would amount to 268,000 of the 767,000 of the U.S. troops committed, and therefore they needed 300,000 pints of blood[45]. Blood and plasma, 100,000 pints of each, were ready[19]. After VJ day, the Japanese and Allied prisoner burns survivors were recipients of this trove: there were between 500,000 and one million burns survivors of the U.S. bombing raids[46,47]. Transfusions began as occupation forces arrived.

The American Red Cross collected 13.3 million pints of donor blood during World War II, of which 10.3 million was converted into plasma and 3 million into whole blood: of this, soon after the liberation of Brussels, 197,712 pints of whole blood were flown from the U.S.A. to the Allied forces in Europe[19]. Using ABTS cooling techniques only 3-4% were spoiled and only another 4,000 pints discarded as past expiration date.

POST WAR

In November 1946, Brigadier Lionel Whitby became visiting Professor of Medicine at Harvard University, and subsequently Regius Professor of Physic and Vice Chancellor, Cambridge University[48,49]. On May 17, 1946, Elliott Cutler addressed the Annual Meeting of the Academy of Medicine, Cleveland, Ohio, saying, "I do not believe the American People will tolerate in another war the entirely secondary position relegated to the medical department by many generals in this war, as if the lives of American citizens were totally expendable[50]". Professor Cutler died of cancer on August 16, 1947.

In 1948, J.H. Biggart, having been overlooked in the Churchill's 1945 dissolution honours, was appointed C.B.E. by Atlee's Labour administration. The citation stated the award was for his part in "organizing the Blood Transfusion Service and emergency medical services in Northern Ireland"[18].

On August 12, 1959, John Hedley-Whyte was appointed Clinical Fellow, Acting Resident at the Massachusetts General Hospital; on December 18, 1961, he was appointed to Professor Edward D. "Pete" Churchill's Harvard Department of Surgery as an Assistant.

Donegal-born Magee's wife died in 1946. He thereafter lived at the Army-Navy Club in Washington, D.C., by day mostly in a corner arm-chair. John Hedley-Whyte, when staying there was told by staff that the Army Surgeon General always warmly greeted his sons, General Mervyn M. Magee, and Col. James C. Magee, Jr., Marine Corps and two grandchildren on their frequent visits. Army Surgeon General Magee was buried with full U.S. Military Honours in Arlington National Cemetary on 20 October 1975[21].

ACKNOWLEDGMENTS

The authors thank Mr. Jack Eckert and Ms. Jessica B. Murphy of the Center for the History of Medicine, Countway Library of Medicine, an Alliance of the Boston Medical Library and

Harvard Medical School, for their expert assistance with the Elliott C. Cutler and Edward D. Churchill Archives. The authors thank the reference staff at Lamont Library, Harvard University for assistance with the William D. Leahy Diaries. The authors thank Ms. Catherine Pate, Brigham and Women's Hospital Archivist, Countway Library of Medicine, and Ms. Anne Fladger, Director, Brigham and Women's Hospital Medical Library, for their assistance in arranging photography of the portrait of Elliott Carr Cutler, on view in the Bornstein Amphitheater of the Brigham and Women's Hospital, Boston, MA.

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Letters

INCREASINGLY HARD TO SWALLOW - 18 YEARS OF CHANGING TONSILLECTOMY PRACTICE IN NORTHERN IRELAND.

Editor,

The clinical and economic value of tonsillectomy has been the subject of debate for decades. The McKinsey Report[1] considered tonsillectomy (along with a number of other procedures) to be a 'relatively ineffective, and often unjustified' procedure, stating that reducing tonsillectomies by 90 percent could save the NHS £45 million each year. Subsequently ENT UK[2] showed an association between a decreasing number of tonsillectomies performed within the UK and an increasing number of hospital admissions for tonsil-related complications.

The aim of our study was to determine if there was an association between the number of tonsillectomies performed and the number of admissions for tonsillitis and peri-tonsillar abscesses in Northern Ireland. Using a computer-aided system data was collected and analyzed for all tonsillectomies performed within the Southern Trust from 1994 until 2012, and compared to the admission rate for tonsillitis and peri-tonsillar abscesses during the same time period.

From 1994 until 2001 the number of tonsillectomies performed decreased from 1,235 to 497 per year, while the number of admissions for tonsillitis and peri-tonsillar abscesses increased from 226 to 452 per year. The decrease in the number of tonsillectomies performed was largely attributed to financial constraints and waiting-list times within the Trust. From 2001 until 2012 the number of tonsillectomies performed increased from 497 to 973 per year, while the number of admissions for tonsillitis and peri-tonsillar abscesses decreased from 452 to 239 per year. Our results show a general trend between the decreasing number of tonsillectomies performed and an increased number of admissions for tonsillitis and peri-tonsillar abscesses, and vice-versa, over the 18 year period assessed (**Figure 1**). Studies in England and Wales have shown similar results with admissions for tonsillitis increasing over the last decade while the number of tonsillectomies has generally declined.[3,4]

With ever increasing pressure on governments to curtail spending in healthcare budgets it is important for both doctors in primary and secondary healthcare practices to be aware of the potential impact on the quality of life of their patients from reducing the number of operations

performed that are deemed "ineffective" by government. The impact of tonsillitis and peri-tonsillar abscesses on both the patients' quality of life and the economy is considerable with the debilitating nature of these conditions resulting in an average of 35 million days being lost from school and work in the UK each year[2].

Effective referral and selection practices are essential for members of the medical profession to justify the procedures they perform and ensure autonomy of our practice is continued and not dictated by government budgetary policies. Evidence-based national guidelines are available to aid clinicians in identifying patients who are suitable for referral and would benefit most from surgery across a number of specialities[5]. Within Otorhinolaryngology increasing the annual number of tonsillectomies performed in selected patient groups is likely to result in an overall decreased number of hospital admissions for tonsil-related pathology and potential cost savings as a result.

The authors have no conflict of interest.

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CLOSED TALAR DISLOCATION AFTER LOW ENERGY TRAUMA

Editor,

ABSTRACT

A closed dislocation of the talus, without fracture, occurring after low energy trauma is extremely rare. We report our experience of a 47 year old gentleman who presented with a closed posteromedial dislocation of his talus following forced pronation of his foot while playing football. This was reduced urgently in the Emergency Department under conscious sedation and managed in a short leg cast for 6 weeks. Early CT imaging revealed osteochondral injury to the talar dome, not visible on plain radiographs. There are few reported

cases in the literature and no guidelines regarding the optimal method of treating this injury. We advocate attempted urgent reduction to preserve function and early CT imaging to assess for injuries that are not apparent on plain radiographs.

CASE REPORT

A 47 year old gentleman presented to our Emergency Department (ED) after sustaining a forced pronation of his foot while playing football. Clinical examination in the ED revealed a closed deformity of the ankle with tense skin over the medial aspect.

Plain radiographs revealed a postero-medial dislocation of the talus with no obvious associated fracture (Fig1a). He underwent urgent closed reduction under conscious sedation in the ED. Reduction occurred relatively easily on the first attempt and was confirmed with plain radiographs (Fig1b).

A short leg cast was applied for six weeks. Outpatient CT scan at two weeks revealed an osteochondral injury to the midlateral talar dome with resultant small intra-articular loose body.

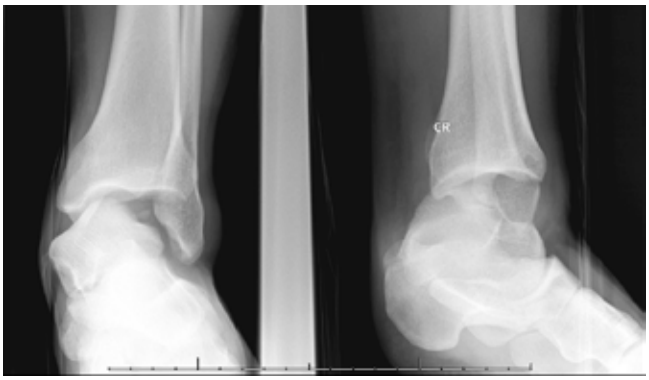

Fig1a

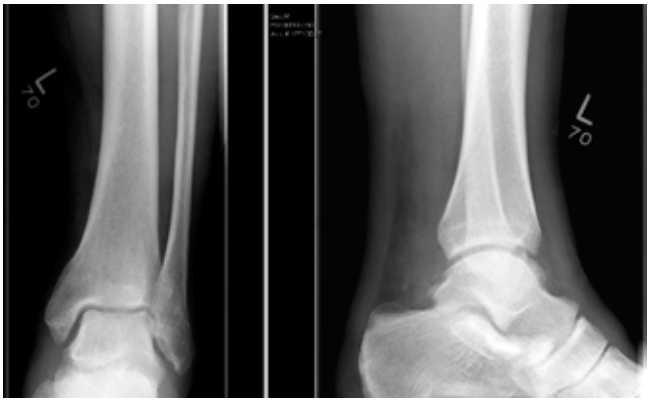

Fig1b.

DISCUSSION

Complete dislocation of the talus is an extremely rare injury that normally occurs after high energy trauma[1, 2] and most reported cases are open injuries.

Total talar dislocation is thought to be the endpoint of maximum pronation or supination coupled with a plantar-flexion force placed across it[4]. Forced supination will cause antero-lateral dislocation (most common) and pronation will dislocate postero-medially[3]. Leitner[5] described a three-stage mechanism of dislocation; firstly dislocation of the subtalar joint, followed by talonavicular and then total extrusion as supination or pronation forces progress.

For closed injuries, Ritsema suggests a rapid open reduction is optimal[6]. A further argument for open reduction is the possibility of tibialis posterior tendon preventing reduction of lateral dislocations[4], or extensor digitorum brevis or peroneals blocking lateral dislocations[8]. However, Taymaz and Gunal[2] report excellent results of a case treated by closed means and Hadji et al[7] report positive findings at 3 year follow up of a closed reduction.

De Palma[9] suggested that final functional outcome may also be related to the direction of dislocation. While medial dislocations generally have good outcomes, lateral dislocations have been associated with the more significant disability. These injuries are most commonly complicated by Avascular necrosis (AVN), post traumatic arthritis and infection.

SUMMARY

Closed dislocation of the talus is an extremely rare injury. We advocate early attempted reduction under sedation in the ED, thus preserving talar blood supply, before considering surgery, and routine early CT scanning to look for osteochondral injury not seen on plain radiographs.

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The authors have no conflict of interest.

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THE GREAT PRETENDER: GASTROINTESTINAL STROMAL TUMOUR IN PREGNANCY PRESENTING WITH LIVER METASTASES

EDITOR,

Gastrointestinal Stromal Tumours (GISTs) constitute approximately 3% of all neoplasms of the gastrointestinal tract (GIT). Reported incidence is estimated between 1 and 20 per million people.[1]

CASE

A 22-year-old woman presented to surgical outpatients at 21 weeks gestation reporting a 17 month history of a 'lump' in her upper abdomen, associated with abdominal pain, nausea, early satiety and vomiting. A swelling in the left upper quadrant of her abdomen was noted in addition to tender hepatomegaly. Abdominal ultrasound confirmed multiple liver lesions, the largest in the right lobe of the liver measuring 10 cm *(Figure 1a)*.

Inpatient OGD demonstrated submucosal tumour of the stomach, and MRI of the abdomen confirmed the liver lesions and a 4.4 cm lesion arising from the stomach *(Figure 1b)*. Examination of core liver biopsies revealed metastasis from a GIST thought to be of gastric origin. Tumour cells showed positive immunoreactivity for c-Kit, DOG1 and CD99. Mutational analysis demonstrated it was wild type for c-Kit, platelet-derived growth factor receptor α (PDGFRA) and B-Raf. A diagnosis of GIST, stage 4 was concluded.

A repeat MRI scan at 25 weeks gestation demonstrated rapid progression of the tumour within the stomach and liver. Subsequently, treatment with Imatinib was commenced.

The patient reported increasing pain due to pressure exerted by the gravid uterus on her liver. Antenatal steroids were administered at 28 weeks gestation and an elective caesarean section was performed. A live male infant was delivered weighing 1200g. He was transferred to the neonatal intensive care unit where he remained for six weeks. Our patient was admitted to the palliative care unit for symptom control.

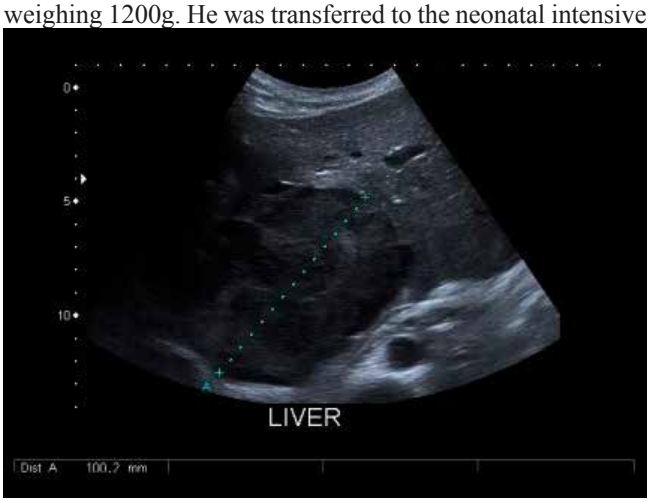

Fig 1a. Ultrasound of liver: Well-defined heterogenous lesion measuring 10 cm within the right lobe of the liver.

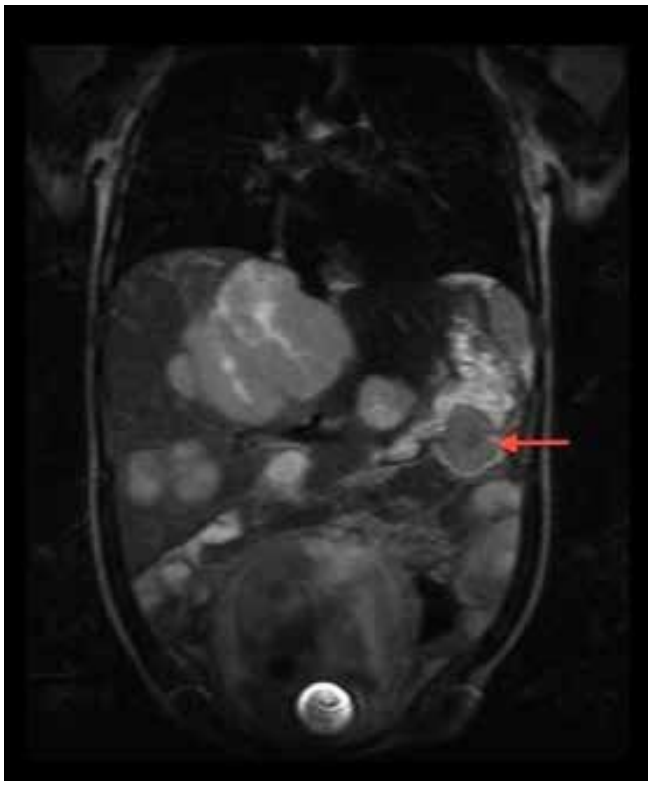

Fig 1b. MRI of abdomen: Coronal T2 weighted sequence demonstrating an extra-hepatic lesion arising from the greater. A repeat MRI scan at 25 weeks gestation demonstrated rapid progression of the tumour within the stomach and liver. Subsequently, treatment with Imatinib was commenced.

DISCUSSION

Discerning a diagnosis of GIST in pregnancy is difficult as symptoms mimic complaints associated with uncomplicated pregnancy. Lesions are found most commonly in the stomach (50%) however they may arise throughout the GIT.[1] Due to the potential risk of fetal carcinogenesis, MRI is the preferred investigative method in pregnancy.[2]

We note little consensus as to how these women should be managed. Primary surgical resection forms the mainstay of treatment for limited disease; more recently, Imatinib mesylate, a targeted molecular therapy which inhibits the KIT receptor tyrosine kinase, has improved management of GIST in patients expressing KIT or PDGFRA mutations.[3] Tumour response to Imatinib is poor in patients with wild-type GIST. Nilotinib, a second generation tyrosine kinase inhibitor has been developed to overcome Imatinib resistance. Trials examining its effectiveness as a first-line treatment for patients with metastatic or inoperable GISTs are ongoing.[4]

The effects of Imatinib in pregnancy are largely unknown; Pye *et al* report 180 cases of women on Imatinib for treatment of chronic myeloid leukaemia in pregancy. Outcome data for 125 cases were known (69%); there were eight live births and one stillbirth with congenital abnormalities. Three infants

displayed similar findings of exomphalus, craniosynostosis and bony abnormalities.[5]

Managing GIST in pregnancy is fraught with uncertainty: the effect of pregnancy on GIST, timing and mode of delivery, initiation of Imatinib, its effects on the fetus and the long-term prognosis for the patient and her child.

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The authors have no conflict of interest

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A CASE OF SEVERE HYPOCALCAEMIA

EDITOR,

ABSTRACT:

There have been increased reports linking the use of Proton Pump Inhibitor Drugs (PPIs) to electrolyte disturbance. We report a case of a 71 year old lady who was troubled by intermittent pins and needles for six months before she was found to be severely hypocalcaemic. Further investigations suggested that her low calcium level was secondary to hypomagnesemia which, in turn, was secondary to treatment with Omeprazole.

CASE REPORT:

A 71 year old woman was referred to hospital after she was found to be severely hypocalcaemic by her General Practitioner (GP). She had attended her GP with a six months history of intermittent sensation of pins and needles in her legs and arms. Her past medical history is of folic acid deficiency, hypertension, depression, and bladder cancer. She was taking the following medications: Aspirin 75 mg, Bisoprolol 10mg, Flurazepam 30mg, Dosulepin 150mg, Doxazocin 4mg, Ramipril 10mg, Pravastatin 40mg, Omeprazole 20mg, and Ropinirole 250mcg.

She was still complaining of numbness on arrival to hospital but Chvostek's and Trousseau's signs were not present. Her blood tests showed a magnesium level of 0.19mmol/L (0.7-1), a calcium level of 1.39mmol/L (2.1-2.6) [corrected levels], and a potassium level of 3.2mmol/L (3.5-5.3).

She was initially treated with intravenous magnesium and calcium supplements, and oral potassium. Following correction of her magnesium levels she became hyperkalemic with potassium of 6.3mmol/L. Her Ramipril was therefore stopped. When her electrolyte levels were normalised her tingling stopped. Further investigations showed a vitamin D level of 13nmol/L (<25 is defficient), a parathormone level of 65pg/ml (15-65), a negative coeliac screen, and a normal vitamin B12 and folate levels.

Her medications review raised the possibility that Omeprazole was causing her electrolyte disturbances. She had been on Omeprazole for six years. This was changed to Ranitidine during her admission.

She was discharged home on calcium and vitamin D supplements.

Her electrolytes were repeated two months following her discharge and they were all in the normal range.

DISCUSSION:

The patient's electrolyte abnormalities resolved after Omeprazole was withdrawn. There have been previous reports linking Omeprazole and other PPIs to electrolyte disturbance[1,2]. The presumed mechanism is impaired intestinal absorption since urinary magnesium excretion is usually appropriately low[1]. The resulting hypomagnesaemia may cause hypoparathyroidism, hypocalcaemia, and hypokalaemia[3].

The symptoms of magnesium deficiency relate to the central role of magnesium in ATP metabolism and neuromuscular transmission[2]. However, symptomatic magnesium depletion is often associated with multiple biochemical abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis[3]. As a result it is often difficult to ascribe specific clinical manifestations solely to hypomagnesemia[3]. The organ systems commonly affected by magnesium deficiency are the cardiovascular system and the central and peripheral nervous systems[4].

The U.S Food and Drug Administration currently recommends that healthcare professionals should consider obtaining serum magnesium levels prior to initiation of PPIs treatment and checking levels periodically thereafter for patients expected to be on prolonged treatment or who take PPIs with medications such as Digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics)[5].

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The authors have no conflict of interest

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So you want to be a **medical student in Europe?**

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Accepted 27 February 2013

WHY PEOPLE CHOOSE FOREIGN MEDICAL DEGREES.

So you want to be a doctor? Well of course you do, but perhaps you're exploring options beyond the usual UK courses. This could be for a variety reasons; perhaps you dropped a grade - or got the grades but not the offer. Maybe the costs of university courses are giving you (or your parents) cold feet - or perhaps you'd like to experience life abroad before you settle into your medical career? No matter what your reasons for applying to a foreign English language medical degree, there are a growing number of European Universities hoping to help you fulfil your dreams of medical success.

WHY FOREIGN UNIVERSITIES OFFER ENGLISH LANGUAGE COURSES.

Primarily based in former Eastern Bloc countries, the universities concerned have been running medical degrees since their creation – some over 600 years ago. There's a long tradition of producing graduates and well established medical schools. Broadly, here's what's on offer – they teach you (in English) their medical course as given in the native language and your fees make up some of the shortfall in university funding.

FUNDING.

But let us not be naïve – all medical degrees are not created equal. Different countries and cities have different courses with different curricula and therefore differing popularity, naturally reflected in the cost of tuition fees. The longest established universities in the most picturesque and "westernised" cities could cost double that of a degree from a non-capital city, meaning those looking for the most economical option may find themselves at the most easterly reaches of the EU.

TRAINING.

In line with the differences in price and popularity, it's harder to gain a place at some European Universities than others. You'll be competing with candidates from most European countries plus people from the US, Russia and the Far East. This is mainly based on performance in the entrance exams plus a fairly rudimentary interview – and of course your ability to pay. Once accepted, the hard work starts. Many courses operate on assumed attrition rates with students graded on a curve and only the top performers going through. Course structures vary widely, with some courses closely modelled on UK versions, but you must remember that many European countries have different healthcare models to the UK and therefore teach students differently. Your chosen country may well not have anything approaching foundation training and instead go straight to speciality training. This can result in longer courses and more in-depth knowledge required. In addition to this, in an expense-conscious healthcare system, less emphasis is placed on costly tests and scans, with a greater reliance on good old fashioned clinical examination. Don't worry – it's invaluable for PACES. A final thought on course structure; you're expected to follow the same curriculum as the native students, usually substituting English language classes for those of the country. And don't forget Latin, Ancient Greek, History of Medicine and a healthy dose of Philosophy in with your ethics classes.

CLASSMATES.

In my own experience, I studied alongside students from Ireland, Norway, Sweden, Germany, Portugal, Greece, Cyprus, the US, Russia, Taiwan, Malaysia, Syria, Jordan, Israel, Sri Lanka and India. Think of it as an elective squared. The opportunity to learn about healthcare in other countries has been invaluable for me in the way I approach issues in the NHS and my attitude to patients and the kind of service they receive. Also I have a welcome holiday home in numerous far flung destinations, which is always nice.

EXPERIENCE.

Studying medicine abroad might appear like an easy entrance to medicine, but it isn't for the faint-hearted. University in general and especially a medical degree are hard enough at any age, even in your own country. Living abroad is tough; really tough at first and there won't be anyone there to hold your hand. Make no mistake, these universities want to produce high quality graduates but your personal satisfaction is not in their modus operandi – there are many people waiting to take your place. Pastoral care is improving but students in difficulty for any reason may not find the sympathetic ears more common in the UK.

TRANSITION BACK TO UK/IRELAND.

A straw poll of my colleagues who studied in Europe reveal some common themes: we don't have OSCEs for example, and such scenarios can be very daunting at the outset. Ditto buzz words, acronyms and even descriptions of common conditions. You may well feel that your knowledge is substandard, but scratch the surface and you'll find that you know the same but learnt it in a different format. The attitudes of your future colleagues are a different matter - I've experienced everything from intrigue to scorn. EU law means that we no longer have to pass the dreaded PLAB exam, but if anything this previously helped our fight for recognition as competent doctors.

CONCLUSION.

If you don't want to, or aren't able to study medicine in the UK, medical degrees abroad are a valid option. Becoming a doctor isn't supposed to be easy, but if you feel that you can rise to challenges of living abroad whilst maintaining your workload you can enjoy a wonderfully enriching university experience in addition to gaining your medical qualification – and after all, life is about the journey, not just the destination.

Curiositas

IN THE NEWS

A phone kiosk in Crossgar, County Down has taken on a new life. In partnership with the British Red Cross, Queen's University Belfast, Down District Council and British Telecom - the kiosk has had an automated external defibrillator (AED) installed. Together with a series of training events for the local community - Crossgar is prepared for such an emergency. Let's hope they never actually have to use the device in the first place.

HISTORICAL QUIZ

Who is this famous Northern Irish physician born in a town just 5 miles away from Crossgar? Amongst his many noted contributions to society, some include bequeathing his vast collections of books, specimens and curiosities that provided the foundation of the British Museum. He is also credited with inventing milk chocolate.

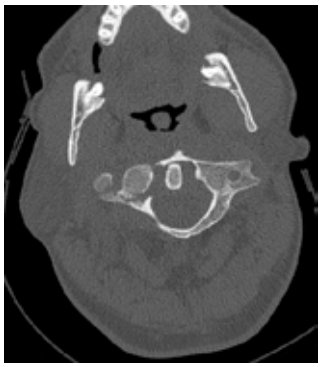
RESEARCH QUIZ

You may recognise this famous Northern Irish building in the background. However how has the device in the foreground helped to improve physical activity levels of some of our local civil servants?

CONSIDER CONTRIBUTING TO CURIOSITAS?

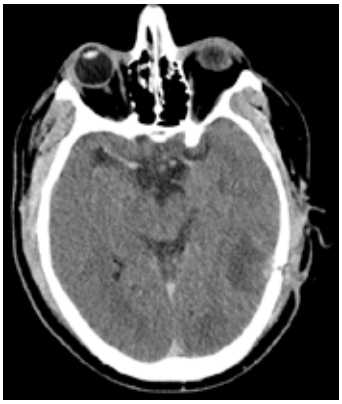
Please refer to '*Curiositas: Guidelines for contributors*' http://www.ums.ac.uk/curiositas.html and email *curiositas@ums.ac.uk* with your ideas and submissions

POSTGRADUATE QUIZ



A 40-year old male presented to his local Emergency Department with neck pain following a fall. A CT scan of his neck was performed. What key abnormality do you notice on this CT scan? What is the recommended surgical treatment for this condition?

Three months later the patient presents with tonic-clonic seizures and undergoes a CT Brain (with contrast). What does the scan reveal and what is the underlying mechanism?

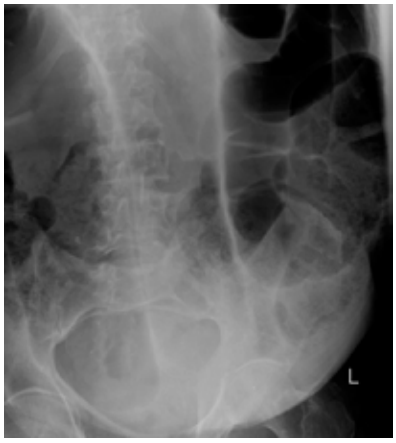


Mr Tom Flannery, Consultant Neurosurgeon and Senior Lecturer,

Royal Victoria Hospital, Belfast Health and Social Care Trust and Queen's University Belfast

MEDICAL STUDENT QUIZ

A 74 year old male present to the Emergency Department with a 24 hour history of a distended abdomen, abdominal pain and absolute constipation. An abdominal x-ray was performed. What are the key clinical features in this radiograph?



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ANSWERS See page **

Book Case

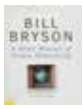
The editor considers six books that exemplify the popularisation of science and philosphy

THE FLY IN THE CATHEDRAL

Brian Cathcart (Penguin, 2005)

The famous description of the size of an atom's nucleus given by Ernest Rutherford, Brian Cathcart's vivid narrative recounts the events that led Rutherford, John Cockcroft, Ernest Walton (Ireland's only physics Nobel laureate) and James Chadwick to the splitting of the atom in 1932. The Cavendish laboratory in the 1930's is presented as a more genteel, impecunious environment than possibly many contemporary scientists might recognise.

A SHORT HISTORY OF NEARLY EVERYTHING



Bill Bryson (Doubleday, 2005)

As he wrote himself, Bill Bryson's challenge was 'to take subjects that normally bore the pants off most of us, like geology, chemistry and particle physics and see if there wasn't some way to render them comprehensible to people who never thought they could be interested in science'. His sense of wonder never depreciating, this skilled wordsmith effortlessly converts tricky science into brilliant prose.

COSMOS

Carl Sagan. (MacDonald, 1989)

In this extraordinarily accessible book, Carl Sagan considers the billions of years of our cosmic evolution; earth's cornucopia of peoples, their histories, intellectual and scientific achievements. From the shores of 'The Cosmic Ocean' he sees a small blue world, inhabited by a species that is just beginning to discover its commonality, its precarious position and its potentially glorious future.

ON GIANTS' SHOULDERS

Melvyn Bragg (Hodder and Stoughton, 1998)

Melvin Bragg, a polymath if ever there was, assembles distinguished groups of scientists to consider and distill the contributions of Archimedes, Galileo, Newton, Darwin, Poincare, and Einstein thus producing an everyman's understanding of their world.

THE CONSOLATIONS OF PHILOSOPHY

Alain de Botton (Penguin books, 2001)

Echoing Boethius's 6th century masterwork, 'The Consolation of Philosophy', de Botton considers the philosophies of six individuals that might serve as a remedy for our many worries, frustrations and, well, human weaknesses. They are Socrates (unpopularity); Epicurius (poverty); Seneca (frustration); Montaigne (inadequacy); Schopenhauer (a broken heart) and Nietzsche (difficulties).

THE HITCHHIKERS GUIDE TO THE GALAXY

Douglas Adams (Pan Books, 1992)

Cheating I know, but anyone who has understood the concepts of the Babel Fish, the Infinite Improbability Drive and the Pan Galactic Gargle Blaster cannot fail to be heartened. As Arthur Dent said, just before discovering that a fellow diner was spending a year dead for tax reasons, 'It's not so much an afterlife, its more an après vie." This eventual five-part trilogy launched thousands of science careers and there are, at least, 42 reasons why you should read it.

Curiositas: Answers

HISTORICAL QUIZ

Sir Hans Sloan, born in Killyleagh 1660. For further information read Dr Stanley Hawkins article on Sir Hans Sloane's life and legacy. *Ulster Med J* 2010;**79(1):**25-29.

http://www.ums.ac.uk/umj079/079(1)025.pdf

(Image of painting of Sir Hans Sloane, Ulster Medical Society Rooms)

RESEARCH QUIZ

Queen's University Belfast researchers from the Centre for Public Health investigated the impact a 'physical activity loyalty card scheme' had on a sample of Northern Ireland government office workers. Participants swiped their physical activity 'loyalty card' on sensors around Stormont grounds and earned 'points' which could be redeemed for retail vouchers based on the amount of physical activity completed. The authors concluded that the scheme led to a short term change in physical activity and demonstrated the potential for physical activity promotion and business engagement in health. *(Hunter RF, Tully MA, Davis M, Stevenson M, Kee F. Lancet 2012;380;4)*

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60360-8/abstract

(Images courtesy of Dr Mark Tully and Dr Ruth Hunter; Centre for Public Health, Queen's University Belfast)

POSTGRADUATE QUIZ

This patient has sustained a right-sided lateral mass C1 fracture (Jefferson type). He required a Halo-Vest Brace for immobilisation of the upper cervical spine. Three months later the patient presented with tonic-clonic seizures. A CT scan revealed cerebritis (early abscess formation) secondary to pin-site infection (due to penetration of dura and bone) from their Halo brace. Follow this link for further information about this clinical case and image findings

http://www.ums.ac.uk/curiositas/082(2)cur.pdf

MEDICAL STUDENT QUIZ

Sigmoid volvulus with resultant large bowel obstruction. Follow this link for further information about this clinical case and radiograph findings

http://www.ums.ac.uk/curiositas/082(2)cur.pdf

THE ULSTER MEDICAL JOURNAL

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Volume 82 No. 2 **May 2013**
ISSN 0041-6193

Cover legend: 'Death of Socrates'. See review on page 108.