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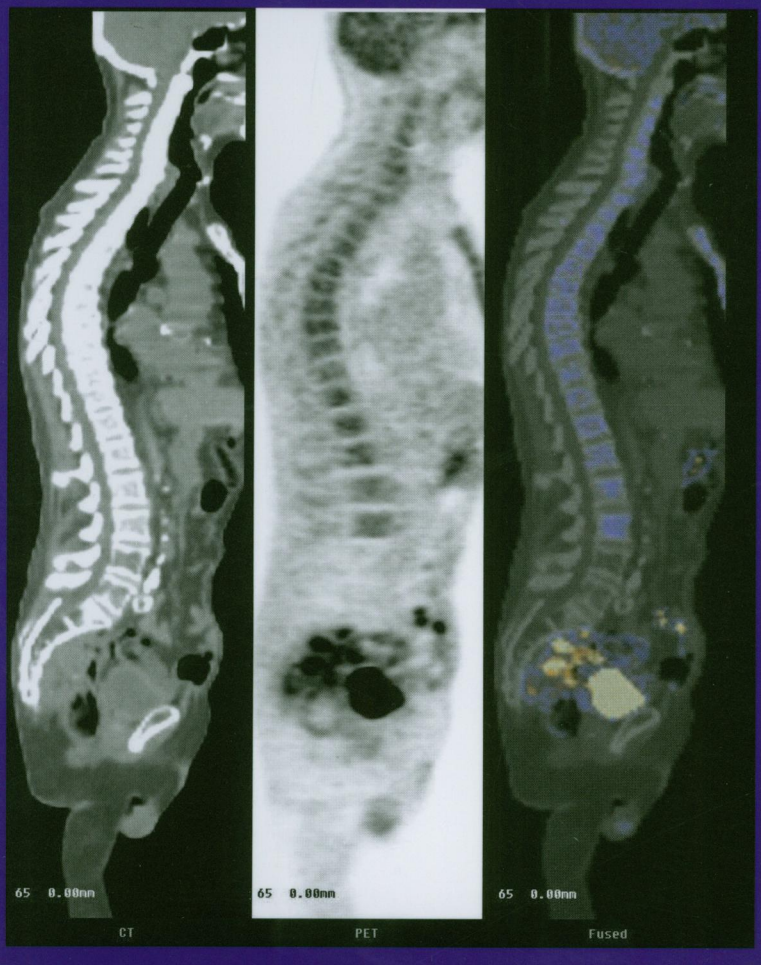

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The Ulster Medical Journal

The Journal of the Ulster Medical Society. First published in 1932.
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The Ulster Medical Society was founded in 1862
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THE ULSTER MEDICAL JOURNAL

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Legend for cover pic:

"PET-CT (sagittal section) demonstrating a pre-sacral mass with soft tissue density (CT) and abnormal FDG uptake (PET) within the pelvis. The fused (PET-CT) image shows abnormal activity with the pelvis". See paper by Skelly in this issue (Skelly RT, McClintock CM, Hughes SJ, Irwin ST. PET-CT in the diagnosis of recurrent rectal cancer complicated by left thigh abscess. *Ulster Med J* 2005; **74 (2)**: 105-107).

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THE ULSTER MEDICAL SOCIETY

Autumn Programme – 2005

President Dr Stanley Hawkins, BSc, FRCP

Contemporary Topics in Medical Practice, Research and Education

Thursday 13th October 8.00 pm — North Lecture Theatre MBC QUB

PRESIDENTIAL ADDRESS

"The History of Neurology in Belfast"

Dr Stanley Hawkins, Reader in Clinical Neurology, Queen's University Belfast

Thursday 27th October 8.00 pm — Ulster Medical Society Rooms

"Undergraduate Medical Education, the GMC, the University and the NHS"

Prof Maurice Savage, Director of the Medical Education Unit, QUB.

Thursday 17th November 8.00 pm — Ulster Medical Society Rooms

Joint meeting with the ULSTER OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

"Inherited Thrombophilias and Pregnancy"

Prof John Higgins, University College Cork

Thursday 24th November 8.00 pm — Ulster Medical Society Rooms

JUNIOR MEMBERS FORUM

Thursday 8th December 8.00 pm — Beech Hill Country House Hotel

THE DESMOND WHYTE LECTURE

"Postgraduate Medical Education"

Dr Terry McMurray, Postgraduate Dean

Northern Ireland Chest, Heart and Stroke Association

Research Grants 2006 for chest disease, heart disease and stroke

The Northern Ireland Chest, Heart & Stroke Association is inviting research proposals for funding of work which will commence after 1st August 2006.

Funding is available for heart disease projects and stroke research projects to the total value of £125K.

Up to £125K is available for research in this year's priority area of chest disease.

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Scientific research grants are available to researchers working in Northern Ireland carrying out research that will primarily benefit the people of Northern Ireland.

The Scientific Research Grants Committee of the Association will be meeting in March 2006 and May 2006 to discuss the applications. Applicants will be notified before June 2006.

To download an Application Form, Guidance Notes and other information, please visit our website www.nichsa.com or contact Sara Morrow, Research and Advocacy Co-ordinator by email: researchassistant@nichsa.com or by phone: on 028 90266714 / 028 9032 0184 ext 248.

The closing date for receipt of applications is

Wednesday 26th October 2005

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PAUL JOHNSTON
(*Honorary Secretary*)

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Editorial

We are like Dwarfs standing [or sitting] upon the shoulders of giants . . .

A former editor once complained to me that the phrase 'standing on the shoulders of giants' was a little overused, judging by the number of manuscripts that were being submitted to the journal with that title or variations thereof. It is unprintable what he planned to do with the next such submission (and I do not know whether he did take any action if one arrived!) but the phrase is overused. The use of Google search engines has increased dramatically over the last 5 years and to 'Google' is almost a household word. Google have just released a beta version of their new search engine 'Google Scholar' for slightly more academic use and their motto proudly states 'Stand on the shoulders of Giants' at the top of the internet page.[1] The term was also literally coined by the Bank of England when in 1997, it introduced the £2 coin with 'standing on the shoulders of giants' on the rim.

One giant whose shoulders I am standing on, is Dr Mark Gibson, editor of this journal from 1995 - 2005. His term of office finished in May 2005 with the completion of issue 1 of this volume, and he has left the journal literally larger than when he started. He modestly ascribes the transition from the old small page format to new A4 format to 'supplies of the old paper were running low'[2] but in this modern age of the electronic journal, maintaining a small society produced journal is a feat in itself and he will be remembered for not only increasing the size of the journal, and thus allowing better formatting of tables and graphics and the modern two-column text format, but also for maintaining a steady hand through times of competitive publication of journals worldwide. His rigorous peer review of manuscripts, with up to 50% of papers being rejected, has ensured that good quality papers are published.

During the Gibson years, the readership has learnt several important facts, seen great changes in both the medicopolitical and educational fields, watched medical progress of sorts, learnt about a Professor who never turned up,[3] and saw the first comprehensive index of the journal produced.[4]

This period has covered four major historical events; the 50th anniversary of the NHS, the Bristol case, the Omagh bomb and the Good Friday agreement. All these are major issues and described as 'the four horsemen of the apocalypse' by Dr Henrietta Campbell in her editorial commentary in 1998.[5] In the late 1990's the phrase clinical governance first creeps in,[6] and in this century, the biggest reorganisation of clinical ethics committees ever[7] followed by our own move into the 21st century with the Ulster Medical Society website.[8]

Some journal papers have published facts that can be documented with accuracy much better in the Northern Ireland population than elsewhere, for example, the knowledge that 1 in 600 children are born with Down syndrome in Northern Ireland, of whom 4% have a mild mosaic type which can be difficult to recognise at birth.[9] Conversely novel prevention suggestions made several years ago by experts here but implemented better elsewhere include a prospective observational study on thrombolytic therapy for myocardial infarction by mobile coronary care. This paper found that more could be done to improve services here, and was published in the same year that the originator of the idea, Professor Frank Pantridge, another Ulster 'Giant', – sadly died.[10]

The phrase 'standing on the shoulders of giants' is often attributed to Sir Isaac Newton in 1675 or 1676. Some scholars suggest that it was a jibe at his rival, Robert Hooke who had invented the inverse square law. Hooke was of short physical stature and Newton may have tried to imply lack of intellectual stature. Like all attributed quotes, earlier sources exist and the earliest may be Bernard of Chartres who in around 1130 said "We are like Dwarfs standing [or sitting] upon the shoulders of giants, and so able to see more and see farther than the ancients]".[1] I feel like that Dwarf, starting afresh in this job with expectations of journal editors increasing daily.

Our thanks are due to Dr Gibson for his steady hand, and also to his able Editorial assistant Carol

McKelvey, who has also retired this year. We wish them both well and are in their debt. The journal content however, is made by the readership, not the editor, so the new editorial board encourages you to keep sending in your good papers and reviews so we can build on the strengths of the journal that Dr Gibson has laid down, and will allow us to stride giant-like into the future.

Patrick J Morrison, Honorary Editor.

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Ulster Med J 2005; **74 (2)** *75-77*

Commentary

Management of Hyperkalaemia in Adults

G McVeigh

Accepted 5 August 2005

The reported incidence of hyperkalaemia in hospitalised patients is between 1 and 10%.[1] The vast majority of cases are related to patients prescribed angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARBs) in conjunction with spironolactone with pre-existing or new renal failure. Most other cases are related to potassium supplementation and prescription of diuretic/drugs with potassium-sparing properties.[2] It is the most serious of all electrolyte abnormalities as symptoms can be non-specific or absent, even in severe hyperkalaemia, before causing cardiac arrest.

The Cochrane Collaboration recently reviewed the evidence forming emergency management of hyperkalaemia.[3] None of the studies of clinically-relevant hyperkalaemia reported on mortality or cardiac arrhythmias. Studies were conducted in convenience samples of patients and many of the trials were methodologically flawed. Adverse events were rarely reported and no serious adverse effects were reported with any intervention. One single episode of hypoglycaemia with insulin use was reported in one study. These results reflect the fact that most studies have been conducted in mildly hyperkalaemic individuals and contrast with case reports attesting to the deleterious cardiac effects and adverse effects of treatment in patients with severe hyperkalaemia.[4,5]

A decrease in the serum potassium is the most frequently reported outcome in clinical trials.[3] For this outcome intravenous insulin and glucose and beta-2 agonists are effective therapies with the combination being more effective than either intervention employed alone. The evidence supporting the use of intravenous bicarbonate is equivocal and administration of potassium absorbing resins will not lower potassium acutely. Despite the lack of compelling evidence to support the efficacy of intravenous bicarbonate and the potential to do harm, the Oxford handbook of Acute Medicine (often used by junior staff) recommends the use of 8.4% sodium bicarbonate administered via central line![6]

Haemodialysis represents the most effective but also the most invasive approach to lower the serum potassium. Although there is no randomised evidence to support the use of intravenous calcium gluconate, this measure is employed to stabilise the cardiac membrane.[3]

Many of the studies reviewed by the Cochrane collaboration reported before 1999. Since then the incidence of hyperkalaemia has surged, in part due to recommendations for the treatment of chronic heart failure, presenting major management problems.[7,8] These patients are often prescribed spironolactone in addition to angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockade. Simultaneous prescription of NSAIDs, digoxin or heparin, associated renal failure, diabetes mellitus (type IV renal tubular acidosis), old age, dehydration and severity of heart failure greatly magnify the risk of developing severe hyperkalaemia.[8] This clinical scenario is likely to be encountered with increasing frequency by junior doctors on the acute medical take. Given the serious cardiac outcomes, the heterogeneity in expert treatment recommendations and the potentially serious adverse effects associated with treatment, local guidance for the management of hyperkalaemia produced by Clinical Resource Efficiency Support Team (CREST) is therefore welcome.[9]

The guidelines and accompanying wall chart (*Figure*) provide information on the classification

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Figure

EMERGENCY MANAGEMENT OF HYPERKALAEMIA IN ADULTS

Incidence between 1 and 10% in hospitalised patients. Majority of cases are related to pre-existing or new Renal Failure, potassium supplementation or diuretics/drugs with potassium - sparing properties. Classified as mild (K^+ 5.5 - 6.0), moderate (K^+ 6.1 - 6.9), severe (K^+ ≥7.0) Consult senior colleagues in clinical team

COMMON CAUSES OF HYPERKALAEMIA IN ADULTS

TRANSCELLULAR SHIFT OF POTASSIUM

- Acidosis (including Diabetic Ketoacidosis)*
- Drugs (digoxin poisoning, succinylcholine)

RENAL CAUSES

- Acute or Chronic Renal Failure*
- Hyperkalaemic RTA (Type IV)*
- Drug induced inhibition of K^+ excretion (eg amiloride, spironolactone)*
- Drugs inhibiting R-A-A system (ACE inhibitors, ARBs, NSAIDs heparin)*

INCREASED CIRCULATING POTASSIUM

- Exogenous K^+ (K^+ supplements in drugs)
- Endogenous (tumor-lysis syndrome, rhabdomyolysis)

* = **MOST COMMON CAUSES**

STEP 1: COMPREHENSIVE HISTORY AND EXAMINATION ❶ to determine and treat reversible causes of hyperkalaemia: **ALWAYS TREAT THE UNDERLYING CAUSE.**

- Non-specific symptoms include fatigue, weakness, paresthesias, palpitations (may be absent even with severe hyperkalaemia).
- Focus on past history of renal problems and medication usage: **Stop K^+ containing fluids / foods and drugs inhibiting K^+ excretion.**
- Exclude urinary tract obstruction (examine for bladder distension/prostatic hyperplasia). Catheterise if appropriate.

STEP 2: QUESTIONS AND INITIAL INVESTIGATIONS

Q: Is hyperkalaemia really present?: Pseudohyperkalaemia (e.g. haemolysed sample). Repeat K^+ urgently but do not delay treatment if **renal failure** or if **hyperkalaemic ECG changes**.

Q: Is Emergency Treatment needed?: **Yes** if ECG changes present (Peaked T waves, PR prolongation, decreased or absent P waves, QRS widening, AV block, sine wave QRST) **A normal ECG does not obviate the need for therapy - the ECG can be normal in severe hyperkalaemia.**
Yes if severe hyperkalaemia. Acute changes in K^+ are more likely to cause cardiac arrhythmias.

A 12-lead ECG with cardiac monitoring, **repeated** assessment of **glucose** (BM testing), urea and electrolytes is mandatory. Creatinine kinase/blood gas analysis (if indicated).

STEP 3: MANAGEMENT

1. **Protect the Cardiac Membrane:** **Administer 10ml calcium gluconate** 10% solution IV over 2 minutes. Effects noted 1 to 3 minutes and last approximately 30-60 minutes. **Caution if patient taking digoxin.**

2. **Shift Potassium into Cells:**
   (a) Insulin **Withdraw 10 units of Actrapid® insulin using an INSULIN syringe. Always** obtain a check of volume from a senior nurse before proceeding. Add to 50ml glucose 50% and administer by slow IV injection over 5 minutes. Effects observed in 15 minutes and last 4-6 hours. Monitoring – blood glucose should be measured after 30 minutes and then hourly up for six hours after completion of the infusion.

   (b) Beta 2 Adrenergic Therapy **Administer 10mg nebulised salbutamol**. Effect observed 15-30 minutes. May not always reduce K^+ and not used as a single agent. Synergistic K^+ lowering effect when used with insulin/glucose above.

   Calcium gluconate, Insulin and Beta-2 agonists buy time and can be repeated multiple times while definitive measures are pursued.

3. **Stop Potassium intake:** Stop potassium supplements and potassium containing drugs. Avoid potassium rich fluids or foodstuffs in diet.

4. **Remove potassium from the body:**
   (a) Use dialysis Required only in exceptional circumstances were severe hyperkalaemia persists despite appropriate management. Ask senior colleague to consult with renal team.

   (b) Use the gut Calcium Polystyrene Sulphonate (Calcium Resonium® rectally or orally) limited efficacy and delayed action (BNF for details).

of hyperkalaemia, address common aetiologies and direct patient assessment and therapeutic strategies to safely and effectively manage hyperkalaemia. The safe and effective use of insulin/dextrose in the treatment of hyperkalaemia is highlighted with particular emphasis placed on the requirement to always use an insulin syringe and have a check of volume by a senior nurse before administration to the patient. The administration of sodium bicarbonate to lower the serum potassium is not recommended. Cardiac monitoring is mandatory. However a normal reading does not obviate the need for calcium gluconate as the ECG does not always demonstrate findings even in severe hyperkalaemia. Caution is required with the administration of calcium gluconate if the patient is taking digoxin. Perhaps the most important message for junior doctors relates to early consultation with senior colleagues responsible for the patient.

The guidance in the CREST document provides clear and concise information to enable physicians to safely and effectively manage patients presenting with hyperkalaemia. I would urge all junior doctors to use and follow this guidance and would like to thank all the professionals who contributed to the development of these guidelines.

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Ulster Med J 2005; **74 (2)** 78-80

Extended Commentary

A failure of leadership? Why Northern Ireland must introduce a total ban on workplace smoking

Martin McKee

Accepted 5 July 2005

The decision by Shaun Woodward, Northern Ireland's Minister for Health, Social Services, and Public Safety to opt for only a partial ban on smoking in public places has been greeted with widespread incredulity. Smoking kills about 3,000 people in Northern Ireland every year, nearly as many as died in all the years of "the troubles", and his decision flew in the face of a widespread public consultation in which 91% of over 70,000 people responding supported a complete ban.[1] Ironically, as policy-makers from all over the world have travelled to the Republic of Ireland where they can see, and are increasingly copying, the successful ban introduced there, the Minister seems unaware of what has been achieved a short drive across the border. There is, however, a glimmer of hope, as the Minister has stated that there will be a further period of reflection that could lead to a total ban. Given the wealth of experience of the benefits of such bans, why any more reflection should now be needed seems a mystery. In fairness, however, it must be conceded that it is easy to become confused given the torrent of misinformation emanating from the tobacco industry and its associates.

Our knowledge about second-hand smoking and how best to tackle it has increased greatly in recent years, largely as a result of a series of American court rulings that forced the tobacco industry place many of its internal documents in the public domain.[2] This has revealed the enormous scale of deception that the industry has been involved in for decades. For example, in 1994 the chief executives of seven of the largest tobacco companies testified to the US Congress that nicotine was not addictive even though their own internal documents clearly showed that it was.[3] We now know how, for years, the tobacco companies were manipulating the content of cigarettes to increase the nicotine kick to speed the onset of addiction among new smokers. We also know how, since at least 1977, industry executives from different companies would meet, often in secret,[4] to discuss ways of keeping alive the illusion that there was genuine scientific controversy about whether tobacco was harmful. These tactics, coupled with even more unsavoury activities, including complicity in smuggling,[5] mean that the credibility of the tobacco industry is in shreds. As a consequence, the industry has increasingly resorted to the use of other organisations, especially in the hospitality industry, to make its case for it, often with the support of generous funding.[6]

So what are the arguments being used by the tobacco industry and those speaking on its behalf? The first is that the risks of second hand smoke have been exaggerated. Here it is necessary to step back and review the nature of the evidence. The early research showing the harm caused by second hand smoke was conducted on non-smoking wives of smoking men. The argument was that this represented a group who, although not actively smoking, was exposed to the smoke of others at home.

Although groundbreaking research at the time, these studies are, of course, subject to certain limitations, which the industry worked hard to exploit. A key objective was to attempt to show that non-smoking

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wives of smokers were in some way different from the rest of the population. They also sought to identify anything else that these women might be exposed to that would explain their increased risk of disease. The effort they went to was immense, although hardly surprising given how much they had to lose. When the International Agency for Research on Cancer produced what many people regard as the definitive study on the harm caused by second-hand smoke,[7] the industry spent $4 million in a campaign to undermine it.[8]

The main limitation of these studies was that they assessed exposure to second-hand smoke indirectly, asking about whether people lived with smokers but not measuring what they were exposed to. In fact, this was likely to under-estimate any effect. However this weakness has now been overcome in a recent study that measured levels of cotinine, a by-product of nicotine, that gives a much more accurate measure of exposure. This showed that the danger was far greater than had been suspected, with those exposed most to other people's smoke having a 60% increase in the risk of a heart attack, after other risk factors had been taken into account.[9]

Other research sheds light on the mechanisms underlying these risks. We have recently revealed the existence of a testing plant in Cologne that is owned by Philip Morris, but managed through a complex web of relationships that have concealed its links to the parent company.[10] In this plant, studies on animals found that sidestream smoke, such as that from smouldering cigarettes in ashtrays, is about four times as harmful as directly inhaled smoke. The explanation is the lower combustion temperature, leading to production of volatile organochlorines, compared with smoke produced when the smoker is sucking air through the cigarette. This is analogous to the situation in which burning garden waste creates dangerous dioxins while burning the same waste in a high temperature incinerator is much safer. Thus it is apparent that second hand smoke is much more dangerous than had previously been assumed.

A second argument is that the problem of second-hand smoke can be solved by ventilation. Much of the evidence they produce is their own research, from studies almost guaranteed to give the results they want. In contrast, independent studies show that it requires fans blowing with the force of a wind tunnel to reduce exposure to safe levels.[11] It is important to recall that, although ventilation may remove the smell of smoke, about 90% of the harmful components of tobacco smoke, such as cyanide and carbon monoxide, are odourless. In contrast, smoking bans do make a difference to air quality. Preliminary results from research undertaken in Dublin pubs has found a reduction of 45% in the level of carbon monoxide in the breath of non-smoking bar staff since the ban was introduced, with a 36% fall among ex-smoking bar staff.[12] Another study of the ambient air in Dublin bars found a reduction of 88% in particulate material under 2.5μm and a reduction of 53% in material under 10μm.[13] This particulate material is increasingly recognised as being very harmful to health.[14] Not surprisingly, the tobacco industry has worked hard to reduce the smell of environmental tobacco smoke to encourage the idea that ventilation works.[15] The contrast between the speed with which authorities act when alerted to risks of exposure to asbestos contrasts with the complacency that allows bar workers to remain exposed to this noxious combination of toxins.

A third argument is that smoking bans in bars and restaurants will lose money, and so increase unemployment. Again this is nonsense. The majority of people are already non-smokers and many avoid bars precisely because they are so smoky. In New York, in the nine months after the smoking ban was introduced, sales tax receipts on food and drink increased by 12% and the hospitality industry took on several thousand new employees.[16] In Ireland there has been a long term downward trend in pub sales that predates the ban, but in the months after smoking was banned, the percentage of the Irish people who had visited a pub in the preceding weeks increased.[17] By the end of 2004, eight months after the Irish ban was implemented, the number of workers in the hospitality industry was 0.6% higher than it had been in 2002.[17] Contrary to the predictions of the hospitality industry, the number of tourists visiting Ireland increased by 3.2% between 2003 and 2004.[17]

So why do so many people believe the opposite? A comprehensive review of research on the economic effects of smoking bans found 97 studies of this subject.[18] Every one of the 37 studies that found a fall in sales had been funded by the tobacco industry or was written by consultants known to have industry links. Few of these studies had appeared in a scientific journal. None of the 60 independent studies found an adverse economic impact.

Finally, the industry argues that a partial ban will be more acceptable, as it protects both the health of non-smokers and the rights of smokers. All sorts of combinations have been proposed, none

of which have any merit. A major problem is that of enforcement. When, as in Ireland and many other countries, a government implements a clear and unambiguous policy, then it is essentially self-enforcing. In Ireland, compliance with the ban rapidly reached 94%. Polls have found that 93% of people think the ban is a good idea (80% of smokers), 96% think the law has been successful (89% of smokers), and 98% believe that workplaces are now healthier (94% of smokers).[17] Quite simply, there is no argument. On the other hand, poorly thought out policies such as that being proposed in England, permitting smoking in bars where food is served, lead to endless and probably insoluble arguments about what constitutes food. Furthermore, the English proposal will widen health inequalities as it is those bars in the poorest areas that are least likely to serve food.[19] The industry also suggests having demarcated smoking areas although, given the evidence reviewed above about the limitations of ventilation, as many commentators have noted, this is the equivalent of having a urinating area in a swimming pool.

The Minister may have tactical reasons for delaying the introduction of a comprehensive smoking ban that he has not shared with the people of Northern Ireland. However, given both the overwhelming support for a ban, and the weight of scientific evidence in its favour, one can only hope that this is a very temporary delay. When I was a child growing up in Belfast I remember the signs prohibiting spitting on Belfast buses. Those have gone and, in time, there will be no need for similar signs saying "no smoking". The tobacco industry and its associates will, of course, argue against effective action, to which we should simply reply "why on earth should we believe anything you say?"

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Editorial Note

Taking issue with the 'Vancouver style' into the twenty-first century

The Ulster Medical Journal has, for many years, been a proponent of 'Vancouver style', as described in Uniform Requirements for Manuscripts Submitted to Biomedical Journals [1] - devised by the International Committee of Medical Journal Editors.[2] A standard journal article is referenced with the authors/editor, followed by the title, journal name (as abbreviated in *Index Medicus*), year, volume, month, issue number (in brackets) and pages as illustrated in the following example:

> O'Neill SB, McCann JP. Unrecognised spinal cord compression as a cause of morbidity. *Ulster Med J* 2004; **73(1):** 89-91.

The Vancouver system of referencing allows that a journal with continuous pagination throughout a volume (as most journals do), may omit the month and issue. In the Ulster Medical Journal, the sub-editor checks all references for accuracy, and (although not written policy) inserts the issue number after the volume (if not added already by the author).

We have, from this issue, updated our instructions to authors to inclusion of the issue number as journal policy. What difference does adding the issue number make? Until recently, when manually searching for articles using hard copy bibliographic references such as *Index Medicus*, or the bound copies of the journals themselves, inclusion or omission of the issue number was immaterial - continuous pagination enabled the reader to quickly find the article in question in a specific volume.

The advent of online journals and digital searching media has changed how articles are published. Many journals are available online, and are accessed using menu selection. Initially the required year is selected, followed by the issue and thereafter the page numbers. Often menu selection does not include page numbers, though invariably the issue number is included instead.

In the Ulster Medical Journal, we are updating ourselves in line with other journals (at present mostly those published on line but increasingly those which publish both online and print versions). This small alteration in the policy should assist writers locate their source material more easily.

The Vancouver system includes instructions on referencing other material obtained from the Internet.[1] These follow the principles behind citing print sources, namely, a reference is a detailed description of the item from which you obtained your information and is used to acknowledge the work of others. Lastly, it should contain sufficient information for someone else to trace the item. Thus quoting a website's address e.g. www.nap.edu is similar to quoting a journal title alone. The proper reference may be as follows:

> Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

We hope readers will find this change helpful for both submissions to the journal and for those searching it online.[3]

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Patrick J Morrison, Honorary Editor
Mary Crickard, Sub Editor

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Review

Age-related macular degeneration

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INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative macular disorder most often clinically apparent after 50 years of age, characterized by certain fundal features and after exclusion of other disorders e.g. high myopia etc. Drusen (deposits of extracellular material lying between retinal pigment epithelium (RPE) and the inner collagenous zone of Bruch's membrane – *Figure 1*), hyperpigmentation and hypopigmentation of the RPE, without visibility of choroidal blood vessels are regarded as features of early AMD. Although drusen are the hallmark of AMD one or more hard drusen were found in at least 95% of the aged populations assessed in the larger Caucasian studies with small hard drusen being the most common in all age groups. The two stages of late AMD include exudative/neovascular (wet) and non-exudative/geographic atrophy, GA (dry) with an 80:20 ratio being observed in the majority of AMD prevalence studies (*Figures 2* and *3* respectively). Exudative AMD, which is characterised by choroidal neovascularization and

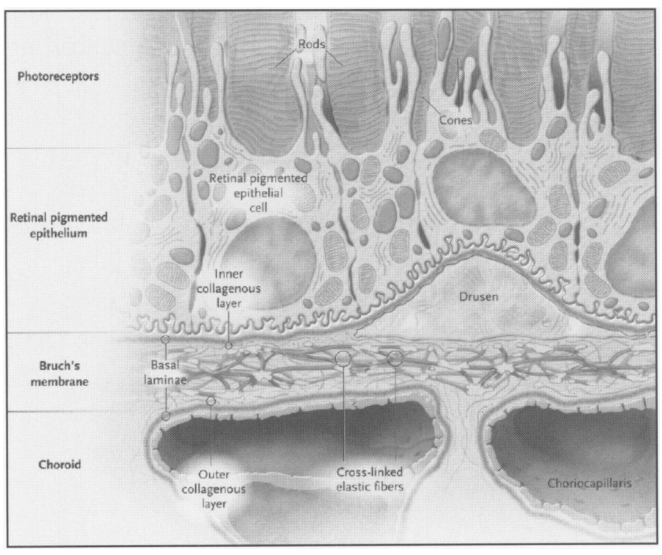

Fig 1. Interface between retinal pigment epithelium and Bruch's membrane demonstrating drusen location.

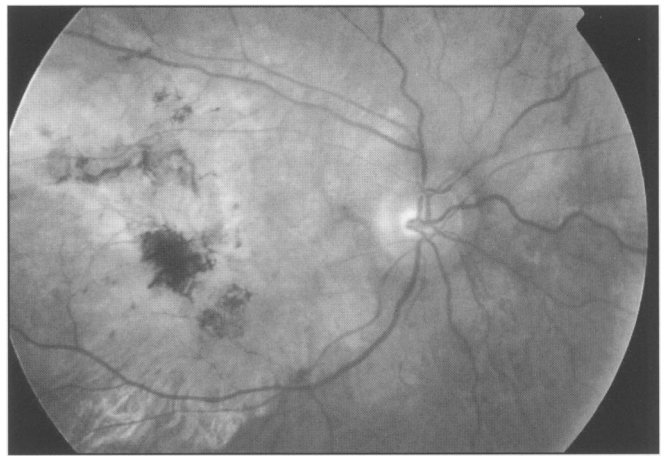

Fig 2. Retinal stereoscopic fundal photograph illustrating the features of wet AMD.

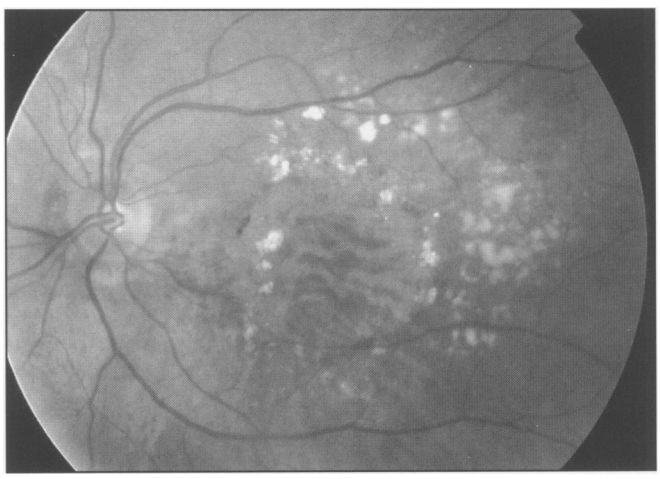

Fig 3. Retinal stereoscopic fundal photograph illustrating the features of dry AMD.

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fibrous scarring of the macula, is responsible for 80% of the AMD-related blindness.

AMD is the leading (54.4%) cause of blindness in Caucasians, compared to only 4.4% and 14.3% of cases in black and Hispanic persons, respectively.[1]

The prevalence (1.6%[2]) and incidence of late AMD (1.1% over five years[3]), in association with the increasing longevity of populations, is impacting significantly on patients, their carers and National Health Service. AMD affects 420,000 people in the United Kingdom with an estimated 214,000 people having registrable visual impairment secondary to AMD.[4] Apart from the more obvious disabling effects of AMD associated with loss of central vision, a frequently overlooked effect is depression (33% of affected individuals), which becomes particularly high on involvement of the second eye.[5]

Age is the most consistent and significant association with AMD and related lesions and is widely supported in population-based AMD prevalence and epidemiology studies, irrespective of ethnic/racial background.[2] This increase is less significant for non-white groups. A steep rise in prevalence rates of early and late AMD occur in the ≥70years.

Although numerous studies have failed to detect a significant gender difference in the prevalence of early or late AMD, females appear to have a slightly increased risk of developing late AMD.[2]

AMD is a multifactorial disease involving the interaction of genetic and environmental factors. Difficulties in classification of AMD phenotype continues to be problematic with a negative impact on unravelling the complex genetic aetiology.

HISTORICAL BACKGROUND

Hutchinson and Tay in 1875 were probably the first ophthalmologists in the English literature to describe what is presently called AMD, when they described the symmetrical fundal changes in senile patients. It was not until 1885 that AMD was recognized as a discrete clinical entity by Otto Haab and called "senile macular degeneration (SMD)". This term has been extensively used through the generations by ophthalmologists to describe the very common macular changes observed in the elderly. Various names have been used over the years for SMD,[6] with age-related maculopathy (ARM) and AMD being the interchangeable terms used today.

AMD has been difficult to classify and until recently a lack of standard classification has made it difficult to compare and review progress in the research field. The publication of an international classification and grading system for ARM and AMD in 1995,[7] based on the morphological changes observed on stereoscopic (30° or 35°) colour fundus transparencies in individuals ≥50 years has facilitated this to a certain extent. This system is based on the Wisconsin age related maculopathy grading system with the macula area being defined by a standard grid facilitating the locations and measurements of the previously mentioned AMD features[8] (refer *Figure 4*). Although this was the first standardised

TABLE I

Classification of mutually exclusive stages of AMD taken from van Leeuwen et al, 2003[9]

Stage	*Definition*
0a	No signs of AMD
0b	Hard drusen (< 63μm) only
1a	Soft distinct drusen (≥ 63μm) only
1b	Pigmentary abnormalities only, no soft drusen (≥ 63μm)
2a	Soft indistinct drusen (≥ 125μm) or reticular drusen only
2b	Soft distinct drusen (≥ 63μm) with pigmentary abnormalities
3	Soft indistinct (≥ 125μm) or reticular drusen with pigmentary abnormalities
4	Atrophic or neovascular AMD

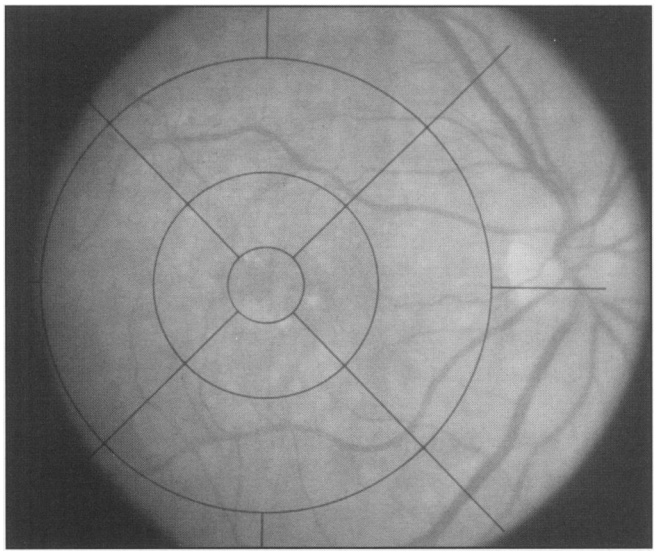

Fig 4. Standard retinal fundus grid for classification and grading of AMD.

classification and grading system for AMD, a more practical AMD phenotyping system with "affected" AMD status being designated as stage ≥ 2a i.e. soft indistinct drusen (≥ 125μm) or reticular drusen was developed recently (*Table 1*).[9]

GENETICS

Evidence of the genetic basis to AMD is well established as a result of many different types of studies over the preceding twenty years.

Case reports of concordance for AMD phenotypes within monozygotic twin pairs were perhaps the earliest indication of a genetic basis for AMD.[10]

Numerous twin studies have significantly supported the genetic component of AMD[11] with late AMD having a higher heritability (quantitative measure of innate genetic predisposition to a disease) in addition to a moderate to large unique environmental component in the largest twin study involving 840 elderly male twins.[12]

Familial aggregation studies have also demonstrated the genetic component to AMD with a lifetime risk ratio of 4.2 for late AMD in relatives.[13]

Loci on chromosomes 1q31 and 10q26 have been consistently identified in AMD genome wide scans and supports the hypothesis of genes within these loci contributing to AMD.[14-15]

The first disease locus for non-exudative AMD, (gene symbol ARMD1),[16] on chromosome 1q25-31 was discovered in a multigenerational pedigree in which ten members were affected with non-exudative /dry AMD. Subsequently a Gln5345Arg mutation in the gene Hemicentin-1 was shown to segregate with this AMD phenotype.[17] Hemicentin-1 (also known as Fibulin 6/FBNL6), a member of the fibulin protein family, encodes for extracellular matrix proteins with a potential role in drusen formation and therefore AMD pathogenesis. However, mutations in Hemicentin-1 have not been found to be associated with AMD in three other separate studies.[15,18-19] Although support for the ARMD1 locus, is substantial in the genome wide scans, it seems likely that another gene other than Hemicentin-1 may be responsible.

The first putative disease locus for exudative AMD was detected between 17-19.35 megabases (Mb) on chromosome 16p12-13 using familial linkage in a large Northern Irish pedigree.[20] The familial mutation remains undetected. Association studies in a case-control study of sporadic AMD cases from Northern Ireland added slight support to this identified linkage region.[20]

Three other genes, Fibulin 5, APOE and Complement Factor H have been reported to be associated with AMD phenotypes.

Missense mutations in the Fibulin 5 gene were found in 1.7% of 402 patients with AMD in a case-control study.[21] Further studies analyzing fibulin 5 are required in order to verify the significance of this. Fibulin 5 is a candidate gene for AMD due to its role in extracellular matrix proteins and in particular the polymerization of elastin which is a major component of Bruch's membrane and involved in AMD pathogenesis.

There is substantial evidence to show that the APOE ε4 allele has a protective effect with AMD, while APOE ε2 allele is associated with a modest increase in risk of exudative AMD.[22] APOE is a functional candidate gene due to its role in lipid transport and distribution, involvement in drusen formation and high expression levels in the retina. The opposite effect of APOE in AMD to its role in coronary heart disease remains unexplained at present.

Recently a 2.45-5.57 increased risk for AMD with a Tyr402His polymorphism in the gene encoding Complement Factor H (CFH) has been reported by independent research groups, although the existence of other coding or splice site variants within CFH that may modulate the AMD risk could not be excluded .[23-26] CFH is involved in the complement pathway and in particular impacts on C3 convertase enzyme. Evidence for deposition of components of

this complement pathway in drusen and choroid of eyes with AMD is extensive.[27,60-61]

Despite the phenotypic similarities between the hereditary monogenic macular dystrophies and AMD e.g. Best disease, with the exception of ABCA4, none of the causative genes was found to be responsible for a significant percentage of AMD cases. The ABCA4 screening consortium[28] assigned a threefold and fivefold risk of AMD in D2177N and G1961E ABCA4 carriers respectively, however replication of these findings have not been possible, leading to much controversy surrounding its potential role in AMD. The observation that some inherited macular dystrophies may have widespread retinal dysfunction, and the possibility of several genes acting synergistically or being ubiquitous, are among the suggestions by Michaelides *et al*, 2003[29] for the non-significant role of these genes in the genetic predisposition to AMD.

The above studies have clearly established that genetic predisposition plays a major role in the aetiology of AMD. Despite this, genetics of AMD are regarded as complex with the possible involvement of one or more genes enhancing an individual's susceptibility for developing the condition. The possibility that there may be other genes that modify the age of onset or phenotypic features of AMD has also to be considered. These genes may act independently or in conjunction with environmental factors e.g. smoking.

Genetic studies of AMD involve consideration of the clinical heterogeneity associated with AMD and correlation with genetic heterogeneity i.e. dry and wet AMD may have different genetic aetiology and specific phenotypes within AMD pedigrees may run true within families.[30] The recent surge in genetic studies from 2000 with nine AMD genome-wide screens published within the last eighteen months may be attributed to the growing awareness of genetics in a number of other complex late-onset medical disorders e.g. Alzheimer's disease. Unravelling the genetics of AMD will facilitate the possible expansion of the knowledge of the pathophysiology of AMD, identification of at risk individuals prior to the onset of clinical findings, and the development of preventive treatments and therapeutic strategies.

NON-GENETIC RISK FACTORS

In addition to age, gender and race/ethnicity, there are several other risk factors which have been implicated in AMD.

Evidence for a significant association between smoking and late AMD is extensively provided in numerous types of studies.[31-32] Current smokers had the highest risk of AMD compared to ex-smokers or non-smokers across all studies. This was particularly highlighted in the meta-analysis of three prospective studies,[32] the association with current smoking being stronger with exudative AMD (OR=4.55, 95% CI, 2.74-7.54) than with non-exudative AMD (OR=2.56, 95%CI, 1.26-5.2). In addition, current smokers had about a 2.5 fold increased risk of developing AMD[33-34] and were more likely to show progression of early AMD (RR=1.34, 95% CI, 0.94-1.91), to develop pigmentary abnormalities (RR=1.32, 95% CI, 0.89-1.98) and large soft drusen (≥250μm) (RR=2.19, 95% CI, 1.44-3.32) than ex smokers.[35] A significantly earlier age of developing AMD (67 years) in current smokers than in ex (73years) or never smokers (77years) was detected in the Blue Mountain Eye Study population.[36] In addition a trend for increased risk of AMD with increasing number of smoking pack years, with the risk of AMD remaining increased until at least 20 years after smoking cessation was observed .[34] The causal relationship of smoking with AMD can be explained by its recognised ability to increase oxidative stress either directly or indirectly with lowering dietary intake of vitamin C and ß-carotene, and the associated lower macular pigment density.

Population-based incidence studies have provided useful predictors of progression to AMD which include soft distinct/indistinct (≥ 125-250μm) and reticular drusen and hyperpigmentation.[9,37-38] Additional AMD risk factors highlighted by these studies included ≥10% macular area involved by drusen, ≥ 5-10 drusen and depigmentation. Two of these studies, demonstrated an increased risk between 3-11 fold of large areas of small hard drusen developing into large (≥125μm) drusen.[37-38]

A J-shaped relationship between body mass index (BMI) and AMD development and rate of progression has been illustrated with the leanest (BMI< 22) and particularly the obese (BMI>30) being at significantly increased risk.[31]

Although evidence is conflicting, there may be an association with hyperopia with AMD, albeit minor, which would alert ophthalmologists to this slightly increased risk group of individuals. There is no hypothesis for this association at present.

It would appear that cataract, particularly the nuclear type, is associated with a moderate risk of early AMD.[31] Although cataract surgery can exacerbate

AMD[39] removal of the cataract improves quality of life and visual function improvement even in end-stage disease.[40] The association of AMD in eyes that have undergone cataract surgery may be due to better detection secondary to easier visualisation of the fundus, the increased risk of photic retinal damage from the lights of operating microscopes[41] and lastly the possible inflammatory changes post cataract surgery that may predispose to the increased exudative AMD risk.[39]

Assessment of the relationship of light exposure and AMD has been fraught with many difficulties. However sunlight exposure appears to increase AMD risk, but ultimately this may be through the increased incidence and progression of early AMD and related lesions i.e. soft indistinct drusen and retinal pigment. Advice about protective gear and length of sunlight exposure may help reduce this risk.

A significant number of studies have demonstrated a weak association between hypertension and AMD which may be attributed to the various methods and definitions used.[31-32] Overwhelming evidence does not support an association with cardiovascular disease and AMD prevalence [32,43] and development and progression despite some common risk factors.[44]

Dietary fat intake may influence the risk of developing AMD by predisposing to atherosclerosis and altering the composition of Bruch's membrane rendering it less permeable to diffusion of nutrients and waste products to and from the RPE.[45-46] In addition there is a protective association (OR= 0.52, 95% CI, 0.22-1.24) between higher fish consumption and AMD.[46] There is sufficient evidence therefore to recommend dietary alterations in those individuals with mild to moderate signs of AMD to reduce progression with the added benefit to the cardiovascular system.

The effect of statins in AMD remains unresolved-with some studies reporting an inverse relationship between statins and AMD i.e. protective with individuals taking statins having a 1/11 risk of AMD[47] but unsupported in other studies.[48]

There are conflicting reports of the effect and type of alcohol consumption on the development of AMD.[49-50] The different relationships that have been identified between AMD and types of alcohol may be indicative of dietary (antioxidants) or life style factors e.g. smoking has been strongly associated with heavy drinking[50] or alcohol consumption patterns of different populations studied.

PATHOGENESIS OF AMD

Physiological ageing in humans is a generalised process associated with cumulative oxidative stress. The retina and RPE are particularly susceptible to oxidative stress due to their high oxygen consumption and levels of cumulative irradiation exposure in addition to proportion of polyunsaturated fatty acids and chromophores.[51]

Oxidative stress is the most likely primary event in AMD pathogenesis, in addition to inflammation and angiogenesis on the background of genetic and environmental influences as depicted in Figure 5.

Evidence for the role of inflammation in AMD is extensive and is inclusive of anatomical[52] and molecular studies and more recently animal models.[53] However, it is largely the molecular studies that have contributed to the current understanding of the

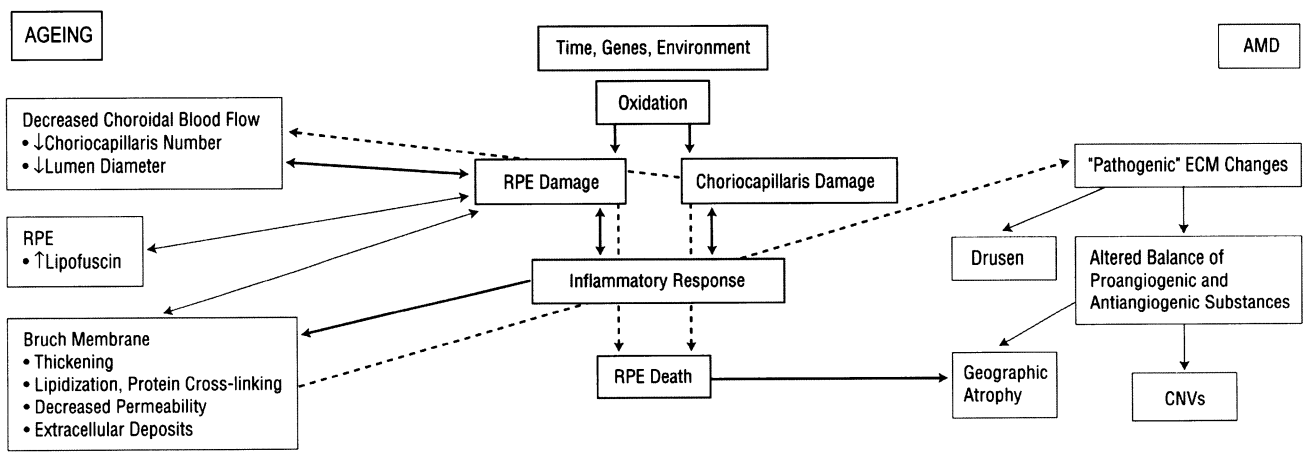

Figure 5 Ageing versus AMD (Taken from Zarbin MA, 2004[27])

TABLE II

Major molecular constituents of drusen (from Zarbin et al, 2004[27])

α_1 Antichymotrypsin
α_1 Antitrypsin
Alzheimer amyloid ß peptide
Advanced glycation end products
Amyloid P component
Apolipoproteins B and E
Carbohydrate moieties recognised by wheat germ agglutinin, Limax flavus agglutinin, concanavalin A, Arachis hypogaea agglutinin, and Ricinis communis agglutinin
Cholesterol esters
Clusterin
Complement factors (C1q, C3c, C4, C5, C5b-9 complex)
Cluster differentiation antigen
Complement receptor 1
Factor X
Heparin sulphate proteoglycan
Human leucocyte antigen DR
Immunoglobulin light chains
Major histocompatibility complex class II antigens
Membrane cofactor protein
Peroxidized lipids (derived from long-chain polyunsaturated fatty acids ie. linolenic acid and docosahexanoic acid, which are usually found in photoreceptor outer segments)
Phospholipids and neutral lipids
Tissue inhibitor of matrix metalloproteinases-3
Transthyretin (major carrier of vitamin A in the blood)
Ubiquitin
Vitronectin

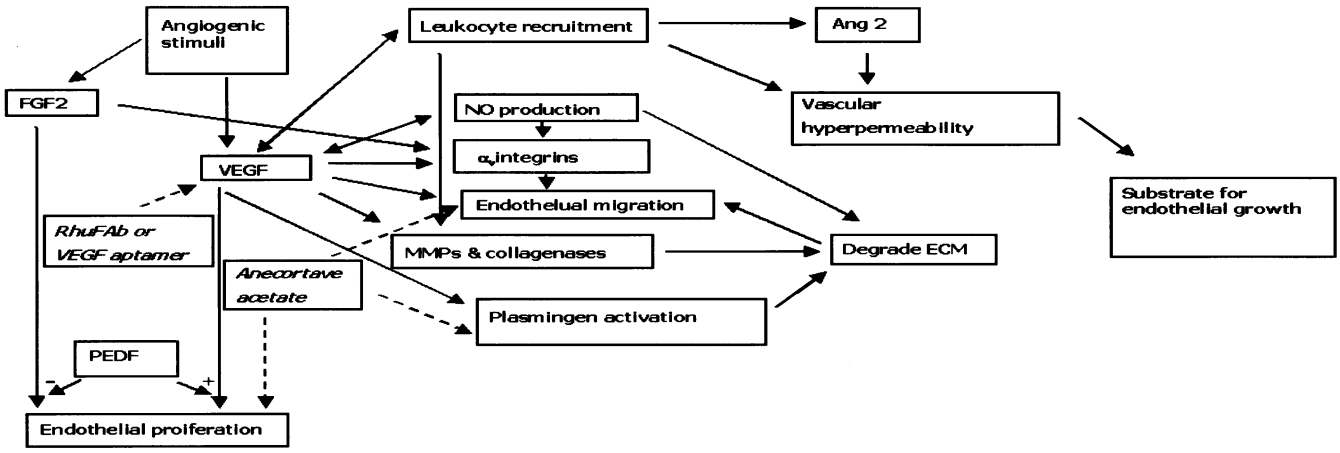

Figure 6 Angiogenesis in choroidal nevascularisation (Taken from Ambati *et al* 2003[53])

inflammatory role in AMD and the development of a local inflammation model of drusen biogenesis.[54-55] The extensive range of inflammatory constituents identified in drusen further support this (*Table 2*). AMD has been postulated to represent another chronic age-related inflammatory disease due to the striking compositional similarities between drusen and the deposits or plaques associated with Alzheimer disease, atherosclerosis and glomerular membrane disease.[56-57]

The role of angiogenesis in AMD is well documented although much remains unknown. A summary of angiogenesis in CNV is provided in Figure 6. CNV, which represents a non-specific response to a specific stimulus in nearly forty ophthalmic conditions, including AMD is a result of an altered balance between proangiogenic and antiangiogenic factors.[58]

AMD pathogenesis has been extensively investigated in an attempt to unravel the disease, however much remains unknown.

CLINICAL ASPECTS OF AMD

A degree of overlap between the two types of late AMD is well recognised, with both sometimes occurring in the same eye or at once in different eyes in the same person.

A typical history of a patient with non-exudative AMD is of a lengthy process of gradual visual loss interrupted by periods of deterioration. Sparing of the foveal centre occurs late in the course of the disease[59] with the primary visual impairment arising from scotomas (blind spots) which correspond to geographic atrophy (GA). In the early stages of GA, the patient's ability to read and recognise faces is compromised, with the size and position of the atrophic area determining the level of impairment.[60] Sudden loss of central vision in a patient with GA may indicate the presence of an exudative component or the final involvement of the central macula in geographic atrophy.

The primary event in exudative AMD is choroidal neovascularization (CNV), referring to the growth of new choroidal blood vessels, usually located beneath the RPE or rarely in the subretinal space. CNV is usually classified by both its location relative to the foveola i.e. subfoveal, juxtafoveal or extrafoveal and its pattern of fluorescence (classic, occult or mixed) on fluorescein angiography (Figure 7). CNV appears as a greenish–grey lesion on ophthalmoscopy, often accompanied by sensory

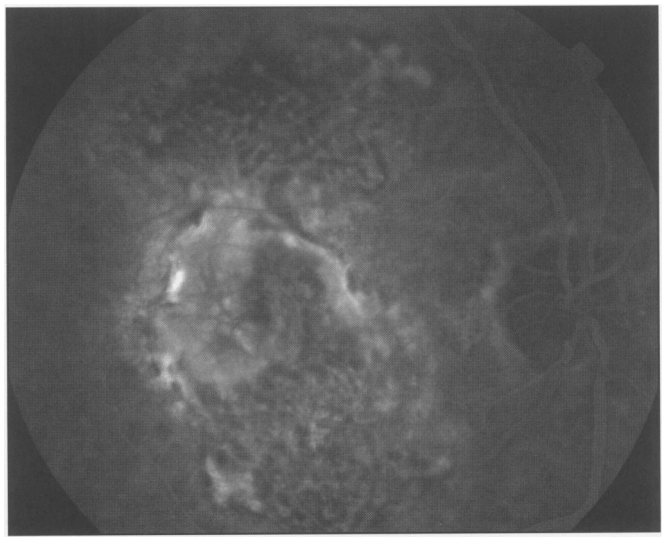

Fig 7. Fluorescein angiogram illustrating wet AMD.

retinal detachment. There may be additional signs of subretinal exudate and blood. Although the patient may be asymptomatic, the majority complain of the sudden onset of distortion and loss of central vision. CNV may precipitate detachment and tears in the RPE. Fibrovascular disciform scar tissue formation occurs with repeated leakage of blood and serum from the CNV, and represents the end-stage. The degree of RPE and photoreceptor degeneration is proportional to the diameter and thickness of the disciform scar.

TREATMENT

Treatments in AMD can be divided into the well recognised categories of preventative, established and innovative.

Lifestyle changes demonstrated to be beneficial in reducing occurrence and progression of AMD include cessation of smoking and antioxidant vitamin and mineral supplementation. A modest benefit of antioxidant vitamin and mineral supplementation in people with moderate to severe signs of AMD was the conclusion of the Cochrane review.[61] However it has been shown that individuals without AMD could not delay or prevent the onset of disease by taking antioxidant and mineral supplements.[62] Other lifestyle factors such as more exercise, alteration in type and amount of alcohol consumed, use of sun protective measures and a diet of regular fish consumption, low total and altered fat dietary intake await further research prior to any recommendations. Screening using the Amsler grid facilitates early detection of choroidal neovascularisation AMD signs in the patient with pre-existing disease particularly in the other eye and can as such be regarded as preventative.

Presently the five-year results of the Complications of Age-related Macular Degeneration Prevention Trial, evaluating the effect of low-intensity laser treatment as prophylaxis in high-risk patients with numerous large drusen in both eyes is eagerly awaited.

Presently there is no established treatment for non-exudative AMD.

Laser photocoagulation is a well-established and widely accepted treatment for CNV, largely as a result of the Macular Photocoagulation Studies.[63] This treatment is only beneficial when the CNV lesion is well demarcated and located in the juxtafoveal or extrafoveal regions, although small subfoveal lesions may benefit. Approximately 10-15% of patients with exudative AMD are eligible for this treatment. Despite persistent and recurrent CNV in over 50% of laser-treated eyes within 3-5 years of treatment,[63] laser photocoagulation continues to remain the standard of care for these lesions.

Photodynamic therapy (PDT) with verteporfin has recently been acknowledged as an approved treatment for classic subfoveal CNV.[64] NICE guidelines provide eligibility criteria for NHS funded PDT.[65] There are a number of advantages to PDT, including the ability to treat subfoveal lesions due to less destruction of the retina compared to conventional laser photocoagulation, and minimal ocular and systemic side effects. However, at best PDT seems to stabilize vision. The high persistence and recurrence rate following PDT leads to multiple repeat treatments, and adds to the cost of treatment.

Numerous experimental therapeutic interventions are under investigation including surgical intervention, anti-angiogenic and angiostatic agents, transpupillary thermotherapy and gene therapy. To date until further large scale, controlled clinical trials have been completed no consensus of the risks and benefits of such treatments can be reached.

CONCLUSIONS

AMD is the leading cause of blindness in elderly Caucasians, impacting significantly on patients, their carers and National Health Service. Treatment is limited mainly to reducing the disease progression. The multifactorial aspect of AMD is well established with age, smoking and genetics being the most consistent associations. The difficulties of phenotyping AMD have been well recognised for many years and may explain the limited progress in identifying the underlying complex genetic aetiology. Presently the debate continues as to whether non-exudative AMD is a separate disease and perhaps a different aetiology to exudative AMD or whether they both represent a continuous spectrum of AMD i.e. clinical heterogeneity. However drusen size of $\geq$125μm appears to be the most discriminating feature in AMD phenotyping for progression to AMD.

AMD impinges on the practice of medical practitioners from various specialities, particularly ophthalmology, geriatrics, psychiatry and general practice. The recognition of the familial and sporadic forms of AMD by medical practitioners is paramount with the relevant preventive and screening interventions.

AMD was first recognized 130 years ago, however much remains unknown. It will continue to present a major challenge to clinicians and researchers in the future.

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Papers

A study of current fluid prescribing practice and measures to prevent hyponatraemia in Northern Ireland's paediatric departments

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SUMMARY

Guidance on the prevention of hyponatraemia in children was issued by DHSSPSNI in March 2002. Two years later Dr Henrietta Campbell, the Chief Medical Officer, wrote to the Chief Executives of acute and combined trusts to seek assurances that the guideline had been incorporated into clinical practice and its implementation monitored. This paper reports the findings of the first prospective study undertaken to examine practice following introduction of the guidance. The evidence suggests that implementation has so far been incomplete and highlights problem areas. The paper reflects on potential explanations for the findings and makes practical suggestions for improvement.

INTRODUCTION

In November 2004, following the broadcast of the UTV Insight programme 'When Hospitals Kill' alleging that three children had died unnecessarily, the Minister with responsibility for Health, Social Services and Public Safety, Angela Smith announced that she had appointed Mr John O'Hara QC, to lead an inquiry into their hyponatraemia-related deaths. Examination of the care and treatment in relation to the management of fluid balance and the choice and administration of intravenous fluids will be a key component of the Inquiry in all three cases. Earlier in the same year Dr Henrietta Campbell, the Chief Medical Officer (CMO), had written to the Chief Executives of acute and combined trusts to seek assurances that the guidance issued by DHSSPSNI in 2002 on the prevention of hyponatraemia in children receiving prescribed fluids[1] had been both implemented and incorporated into clinical practice. In 2003, to promote further awareness and also to elaborate on the rationale underpinning the guideline, Jenkins and colleagues[2] in an Editorial in this journal highlighted the clinical situations where children are at greatest risk for developing elevated vasopressin levels, described associated risk factors and discussed how the choice of prescribed fluids can contribute to dilutional hyponatraemia. Specifically the guideline recommends 0.9% saline as an appropriate crystalloid for resuscitation; directs that the anticipated Na^+, K^+ and glucose requirements, for which age is an essential factor, should determine the type of maintenance fluid and proposes that for most replacement scenarios fluid with minimum sodium content 130mmol/l should be used. Also incorporated is advice on patient assessment that includes checking the weight of the child; advice on how to calculate fluid requirements and details of the clinical and biochemical monitoring required while in receipt of IV fluids.

In response to the CMO's request for assurance that the guidance had been implemented the prospective

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study described in this paper, the first to examine guideline adherence in local paediatric units, was undertaken to examine practice and to identify any component(s) presenting implementation difficulty and if present to in turn reflect on possible practical solutions.

METHODS

All eight acute paediatric inpatient units in Northern Ireland were invited by one of the authors (JMA), through a lead clinician, to participate in a simultaneous snapshot of paediatric practice around the Province and readily accepted. It was proposed that the management of all patients in receipt of intravenous (IV) fluids between 12.00 and 14.00hrs on the same day in May 2003, and who had also been in receipt of IV fluids in the previous twenty-four hours, would be assessed for compliance with the guidance. This time window was chosen in the expectation that a morning ward round would normally by then have been conducted, thus providing a pragmatic method of targeting a high risk group requiring ongoing therapy post baseline assessment and for whom there would have been adequate opportunity for management plans, monitoring and associated decision making to have been put in place. Neonates and intensive care patients, whose management is different, were excluded. The lead clinicians were asked to inform the relevant Clinical Director(s) that the study was being planned; asked to identify a medical assistant for local data collection and to ensure that the date was kept confidential in order to avoid a positive influence on clinician behaviour. To facilitate maximum participation coordinators were reminded of the study date in the preceding week. The same single page data collection form, previously piloted and refined by a paediatric SHO (RK) during two one week trial periods at Antrim Hospital, was used in each contributing unit. Details of diagnosis, presence of dehydration, weight recording, fluid prescription and clinical and biochemical monitoring were transcribed from the case notes, fluid prescription and fluid balance sheets.

Details of the specific elements involved in monitoring, such as records of urinary output and vomiting were, for practical reasons, not included. Instead it was assumed that a documented record of any reassessment of requirements indicated that assessment of all the key components had occurred.

Consistency of data interpretation for the purpose of comparing actual management with expected guideline management was facilitated by having the same experienced clinician (JMA) analyse the returned data forms and cross reference the diagnosis and assessment of fluid balance status against the record of prescription for each individual patient. Also, when the adequacy of data return permitted all calculations of fluid volumes prescribed were recalculated by JMA. To facilitate collation of information a prescription for maintenance fluids was judged to be inconsistent with the guideline if the volume prescribed was greater than +/- 5% and inappropriate if greater than +/- 10% of the guideline calculation. The rationale for this percentage limit is that in terms of degrees of dehydration a larger variation could correspond to incorrect management e.g. treating a moderately dehydrated patient for mild dehydration or vice versa.

As the recruitable numbers able to satisfy the strict inclusion criteria were small an identical exercise was repeated on two further days, one in June 2003 and one in January 2004.

RESULTS

There were thirty-eight eligible children for whom forms with complete/near complete data were returned. All units contributed at least one patient. Twenty-six children had a medical diagnosis and twelve had a surgical problem, eight of whom were in the post operative period. Four children had conditions for which not all elements of the guidance were relevant (see sections b, e). The grades of staff prescribing the fluids were PRHO (4); first term SHO (19); second term SHO (5); SpR (5); SAS (1); consultant (3) with one unknown. The results for adherence to each key component of the guideline are described below with the main findings summarised in table 1.

a. Was the child's weight recorded?

   Data were returned for thirty-five children. Weight was measured in 33 cases and estimated in 2.

b. Was the calculation for maintenance IV fluid volume consistent with the guidance?

   Of the thirty-seven children with this data returned there were two children receiving fluid treatment in association with chemotherapy and one with a diagnosis of benign intracranial hypertension in whom an alternative protocol was being followed and for whom the guideline maintenance calculation was not applicable. Eighty-two percent of relevant calculations

TABLE I

Guideline adherence question	*Total*	*yes*	*no*
b. was maintenance calculation consistent with guidance?	34	28	6
c. was IV fluid composition appropriate?	35	35	0
d. were maintenance & replacement prescribed separately	7	2	5
e. was fluid balance assessed at least 12 hourly?	33	15	18
f. was U&E checked at least once per 24 hours?	34	30	4
g. was oral intake considered in IV prescription?	23	12	11

Adherence to DHSSPSNI guidance[1] on prescribed fluids and hyponatraemia

were consistent with the guidance. There were three calculations judged guideline inconsistent and three others judged inappropriate.

c. Was the composition of IV fluids used appropriate?

Data were returned for thirty children who had received either maintenance fluids alone or both resuscitation and maintenance fluids plus five other children who also had a prescription for replacement and/or ongoing losses. The electrolyte and glucose content of the fluid utilised was suitable in all thirty-five cases.

d. Were maintenance and replacement fluids prescribed separately?

The return for this question provided information on a further two children i.e. a total of seven, who had both maintenance and replacement losses prescribed. Two of the seven had replacement prescribed separately but five did not.

e. Was fluid balance assessed at least every twelve hours?

Of thirty-seven data returns the guidance was considered applicable only to thirty-three as three were following an alternative fluid regimen and one was terminally ill. Forty-five percent had documented evidence of reassessment of requirements in the first twelve hours of treatment. Sixty-six percent had reassessment within the first twenty-four hours. Thirty-three percent had no record of reassessment.

f. Was U&E checked at least once per twenty-fours?

There were thirty-four data returns for whom the guidance was applicable. Twelve percent had not had a U&E checked any time in the preceding 24 hours. There were no children with severe hyponatraemia (Na+ <130mmol/l) though nine children had a Na+ <135mmol/l at some point.

g. Was the oral fluid intake considered in the most recent IV fluid prescription?

Allowance for oral intake occurred in only fifty-two percent of the twenty-three children for whom the guidance was relevant.

h. What oral fluids were used during this period?

Information was provided for seventeen of the twenty-three treated with both oral and IV fluids and is summarised in table 2.

Table II

Fluid type	*n*
Water	2
water and juice	4
water and soup	1
Juice	2
juice and milk	1
Milk	5
rehydration solution	2

Types of oral fluid administered concurrently with IV fluids

DISCUSSION

While the number of children in the study was inevitably small the information obtained should be a valid reflection of clinical practice following issue of the guidance and it is consequently important. As the study period included three induction periods for new/ changing medical staff it is reasonable to conclude that there was sufficient opportunity for the guideline to be both fully disseminated and introduced. Also the patients reported were those with the highest risk of fluid therapy associated complications for whom greatest awareness and attention to the application of the management guidelines would be expected.

The standard for weight, namely that it should always be measured or estimated in a bed bound child, was met. However this may not necessarily reflect guideline conscious behaviour as recording of weight has become part of normal paediatric practice regardless of diagnosis.

The standard achievement rate (82%) for maintenance fluid calculation was also high but with some evidence of the co-existence of potentially significant variation from advised practice. Jenkins and colleagues[2] acknowledge that guidance on maintenance fluid requirements is general guidance and emphasise that assessment should be individualised. We allowed for this in our evaluation by accepting a total calculated volume within +/- 5% of the guideline value as meeting the standard. Of the six children whose calculation was outside the guideline there were three whose prescriptions were classified as inappropriate, two being underestimates and the third an overestimate. The two underestimates were in a fifteen year old (-17%) on day 1 post appendicectomy with a first term SHO as prescriber and in a thirteen year old (-19%) with urinary infection and prescriber not indicated. The overestimated child was a six year old (+27%) admitted with vomiting and constipation but no dehydration and for whom the prescriber was a first term SHO. The management of his child is of concern though close monitoring did take place with the U&E checked on four occasions and the lowest Na+ recorded was 134mmol/l.

While there was full compliance in implementing the standard for appropriate fluid choice problems were encountered at the next step, namely recording the prescription. A separate prescription for maintenance and replacement fluids is recommended to reduce the potential risk of excess fluid administration resulting from a combined prescription inadvertently over running the deficit correction period. Separation of the prescriptions did not occur in seventy percent of relevant situations. While this may reflect lack of clinical awareness, another factor may be lack of user friendliness of available prescription sheets.

Monitoring of hydration status and fluid balance is essential. The guideline specifies that reassessment should occur at least twelve hourly but this was only recorded in the minority of cases. It is unlikely that this finding is attributable more to poor record keeping than lack of reassessment as there were four children identified who had no U&E checked during twenty-four hours of IV therapy, three of whom had actually been on full maintenance. These three included two post-operative, hence relatively high risk, patients aged 6 weeks and 11 years and a 8 year old with septic arthritis. The rigour of some assessments is also of concern as, contrary to advice, no consideration had been allowed for the oral intake in fifty percent of relevant prescriptions.

The guidance mentions hyponatraemic risk in association with use of inappropriate oral fluids but there were only two children whose oral fluid was a commercial rehydration solution (*Table 1*). The prevalent use of hypotonic solutions in this high risk group suggests that common practice needs to be reviewed.

In summary the evidence is that implementation of the Regional guidance has so far been incomplete. This could indicate that there is inadequate guideline awareness due to failure of training programmes and/ or failure of units to provide direction to junior staff. An alternative explanation is that there may be intrinsic operational hindrances to implementing the guideline. If not done already, units should organise a review by nursing, pharmacy and medical staff, both junior and senior, to identify the difficulties and possible solutions. Relevant issues for discussion and action could include: the redesign of prescription sheets to facilitate separation of prescriptions when only one IV infusion/line is present; the facility to indicate required infusion finish times; the provision of action boxes on fluid balance sheets to trigger clinical and biochemical reassessments; appending for reference a simplified maintenance fluid calculation formula on the back of prescription sheets; outlining clinical descriptions for assessment of hydration status on the back of fluid balance forms; provision of oral fluid management information and advice for carers and the introduction of a method for effective nursing and medical handover of management plans for all children receiving IV fluids. Redrafted or new documentation could be

standardised in all trusts and a consensus should be developed on the appropriate use of hypotonic oral fluids with the original guideline Working Group providing a strategic overview.

To conclude, it is probable that the current guidelines will be modified in conjunction with the developing evidence base on appropriate fluid therapy in situations where physiology is not normal, such as illness or postoperatively. Internationally best practice is still controversial[3,4] and preparation of definitive protocols is not yet possible, unlike hyperkalaemia where a consensus is now being reached.[5] Until then it is essential that all clinicians in Northern Ireland caring for children in receipt of fluid therapy know of the associated risks and are aware of our Regional best practice guidance and that paediatric departments initiate a process of regular monitoring of guidance adherence as part of their multidisciplinary audit and clinical governance programme.

The Authors have no conflict of interest.

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Paediatric Femoral Fractures –

The Royal Belfast Hospital for Sick Children Experience

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INTRODUCTION

Trauma is a leading cause of morbidity and mortality in children.[1] Only acute infections cause more morbidity than trauma in childhood.[2]

Although femoral fractures account for less than 2% of all orthopaedic injuries in children,[3] they have a significant impact not only on the patient and their family network, but also on regional trauma resources.[4,5]

The aim of this study was therefore to obtain baseline epidemiological data and evaluate the management of patients admitted with a femoral fracture to the Royal Belfast Hospital for Sick Children (RBHSC) fracture unit. We present and discuss our findings.

PATIENTS AND METHODS

We reviewed the charts and radiographs of all admissions to the RBHSC with a femoral fracture over a 12 month period.

From the charts, the following general data was recorded for each patient: age, gender, affected side(s), referring accident and emergency department, month of admission, relevant orthopaedic history and duration of inpatient stay. Specific to the femoral fracture the following data was recorded: mechanism of injury, associated injuries, whether the fracture was open or closed, the presence of neurovascular complications, initial management, transfusion requirements, definitive treatment and secondary interventions e.g. re-manipulations or revision of fixation.

From the radiographs, the site of the fracture was classified as proximal (portion superior to the distal aspect of the lesser trochanter), distal (distal femoral metaphysis, physis and epiphysis) or mid-shaft (section between the proximal and distal femur). The duration of time to fracture union was estimated from the date of the initial femoral radiograph taken at the time of injury to the first radiograph demonstrating evidence of bony union.

RESULTS

Over the 12 month period, 43 patients were admitted to the RBHSC with a femoral fracture. One child sustained a fracture of both femurs during the period of the study but at different times. There was one case of bilateral femoral injuries. This therefore equated to a total of 44 admissions (45 femoral fractures) treated during the time frame of the study. The right femur was affected in 18 cases, the left in 27 cases.

There were 33 male and 11 female admissions (ratio- 3:1). Overall age ranged from 5 days - 13 years (average, 4.7 years). For males, age ranged from 5 days - 13 years (average, 5.1 years) whilst for females the average age was 3.7 years (range, 4

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months – 12 years). The number of males and females in each age group are summarised in Table 1.

TABLE I

Gender breakdown for each age group

Age Group	*Number of males*	*Number of females*
0-5	16 (48.5%)	7 (63.6%)
5-9	13 (39.4%)	3 (27.3%)
9-13	4 (12.1%)	1 (9.1%)

Nineteen admissions (43%) were via the RBHSC accident and emergency department (*Table 2*). Twenty-two admissions (50%) resulted from trauma due to falling. Road traffic accidents (pedestrian versus motor vehicle) and direct trauma accounted for accounted for 15 (34%) and 4 cases (9%) respectively. The remaining three cases were caused by a variety of modes of injury (*Figure 1*). Table 3 summarises the mechanism of injury for males and females in each age group.

Figure 2 demonstrates the observed seasonal variation of femoral fracture admissions. A peak was found in the spring and summer months, April through August, accounting for 59% of the total admissions. When comparing the mechanism of injury to the month of admission, 15 of the Spring/Summer admissions were due to traffic trauma (58%) compared to only 4 (22%) of those in Autumn/Winter.

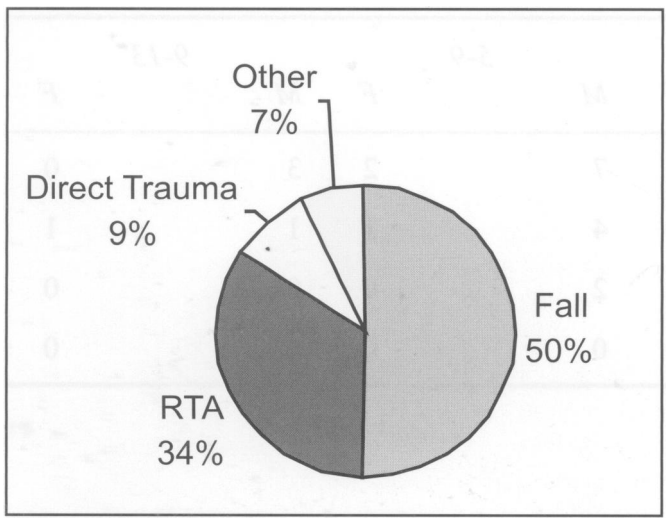

Fig 1. mechanism of injury for femoral fracture.

Table II

Referring accident and emergency departments to the RBHSC fracture unit

Accident & Emergency Department	*Number of Patients*
Royal Belfast Hospital for Sick Children	9
Antrim Area Hospital	7
Craigavon Area Hospital	5
Daisy Hill Hospital	4
Downe Hospital	2
Mid-Ulster Hospital	2
Mater Infirmorum Hospital	1
Lagan Valley Hospital	1
Whiteabbey Hospital	1
Coleraine Hospital	1
Letterkenny General Hospital	1

Trauma due to falling was more common in the Autumn/Winter months (50% compared to 35% for Spring/Summer). When considering gender, there was no marked difference between the number of males and females admitted during the Autumn/Winter and the Spring/Summer months (72% males, 27% females and 77% males, 23% females respectively). However, the average age for the Autumn/Winter admissions was 3.8 years compared to 6.3 years for the Spring/Summer group.

On evaluating the injury radiographs, 25 fractures affected the mid-shaft portion of the femur with the distal and proximal regions of the femur being involved in14 and 6 fractures respectively. Table 4 summarises the site of fracture when compared to age and mechanism of injury.

Five patients had additional injuries including an open fracture of the contralateral tibia, a closed fracture of the ipsilateral tibia, a fracture of the ipsilateral clavicle and scalp haematoma, a fracture of the contralateral distal radius and a basal fracture of the contralateral femoral neck. In four of the cases the mechanism of injury was due to a pedestrian

Fig 2. Seasonal variation in femoral fracture admissions.

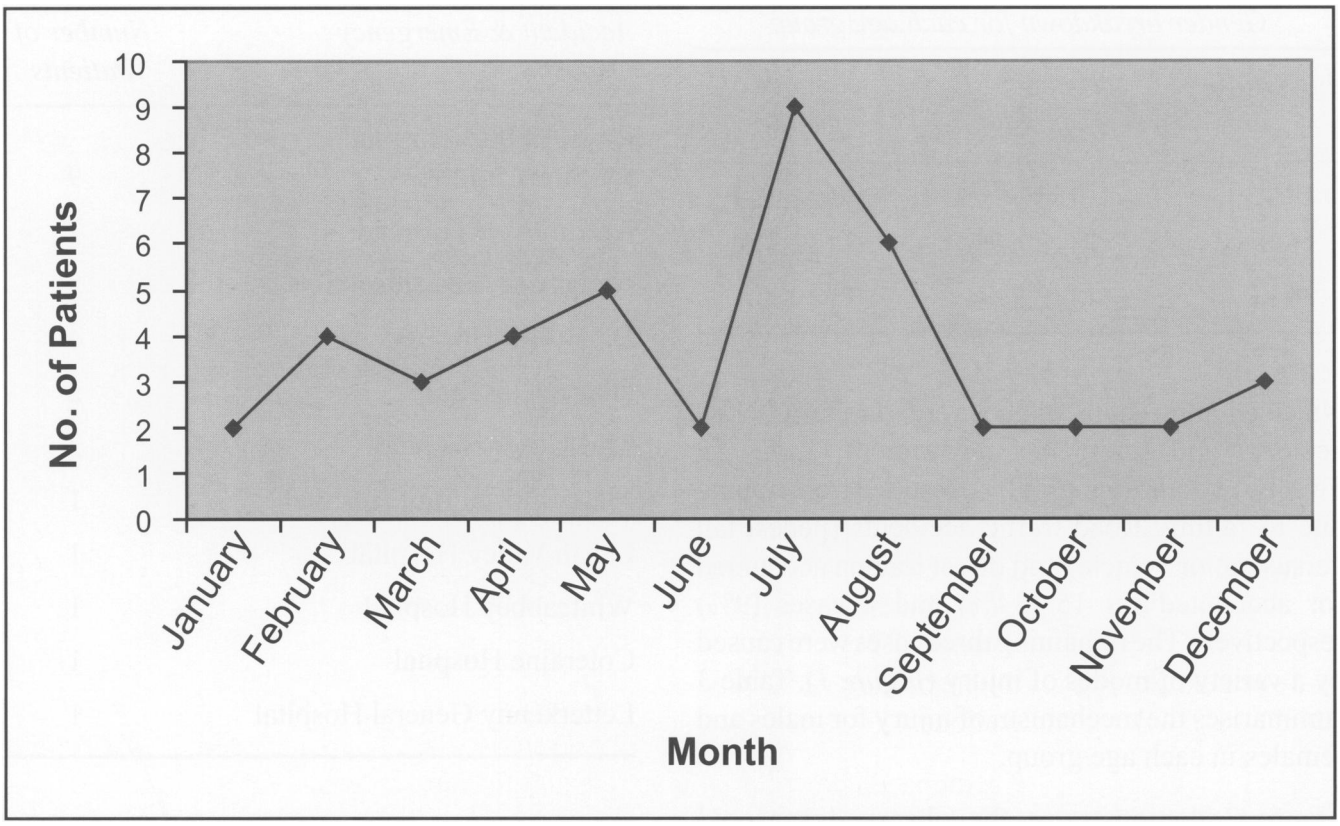

TABLE III

Mechanism of injury versus gender for each age group

Mechanism of injury	*0-5 years*		*5-9*		*9-13*	
	M	*F*	*M*	*F*	*M*	*F*
RTA	2	1	7	2	3	0
Fall	10	5	4	1	1	1
Direct trauma	1	1	2	0	0	0
Other	3	0	0	0	0	0

TABLE IV

Site of fracture compared to patient age and mechanism of injury

Site of Fracture	*Age*	*Mechanism of injury*
Distal	4 months - 13years, 6years	RTA 7 Fall 3 Direct trauma 3 Other 1
Midshaft	5 days - 13years, 3.5 years	RTA 5 Fall 17 Direct trauma 1 Other 2
Proximal	5 - 12years, 7.8 years	RTA 4 Fall 2

versus automobile road traffic accident (RTA). The remaining case was due to a fall from a height. There was only one open femoral fracture in the study population (2.3%). None of the patients had any neurovascular complications.

Two cases had associated orthopaedic conditions, which may have contributed to their femoral fracture. In one case, a subtrochanteric fracture occurred through a multicamaral bone cyst. In the other case, a child with severe spina bifida and bilateral talipes equinovarus sustained a mid-shaft fracture of the right femur and a mid-shaft fracture of the left femur at the age of five days and four months respectively.

Initial management of the femoral fracture included the application of a Thomas splint,[26] Gallows traction,[9] long-leg cast,[6] skeletal traction,[1] skin traction,[1] closed reduction and percutaneous wiring[1] and insertion of flexible femoral nails.[1] Table 5 summarises the methods used for the definitive management of the femoral fracture.

Of the 45 femoral fractures 11 (24%), were treated by operative management. Time to theatre ranged from 0 - 4 days (average, 1.3 days). No operative complications were encountered. None of the patients required the transfusion of blood products.

For those treated in hip spica, the mean time to application of spica was 9.8 days (range, 2 - 21 days). Three patients returned to theatre for change of hip spica due to loss of fracture alignment (one patient returned twice).

The average inpatient stay in the acute fracture unit was 9 days (range, 1 – 38 days). Nine children were transferred to the Children's ward in Musgrave Park Hospital for further rehabilitation.

Estimated time to union was on average 3months, ranging from 1 - 11 months. Average time to union for each age group: 0 - 5 years, 45 days; 5 - 10 years, 65 days; and 10 - 13 years, 108 days. There were no cases of fracture non-union.

TABLE V

Definitive treatment methods for femoral fracture patients

Definitive Treatment	*No of Fractures*
Hip Spica	24
Long-leg Cast	8
Nancy Nails	5
Closed reduction plus k-wiring	3
Cannulated screws	2
Thomas Splint	2
ORIF [plating]	1

DISCUSSION

In this study, femoral fractures represented 5.1% of the total fracture admissions to the RBHSC, a figure that is comparable with other published series.[2,6]

However, despite representing only a small proportion of the overall fracture admissions, the resource consumption of femoral fractures is considerably higher than all other childhood fractures.[2] In this study the average length of hospital stay was 9 days compared to only 1.5 days on average for children admitted with an uncomplicated forearm fracture.

The seasonal variation in femoral fracture admission rate that we observed is a well-recognised phenomenon.[2,4,7,8] There is a peak in the admission rate in early summer and a trough in winter (*Figure 1*). The fall in admission rate at the end of October most likely coincides with the change from summer to winter time, whilst the peak in July and August suggests that it is related to the vacation seasons, with a higher rate of both free-time activities and traffic.

When comparing age and gender to the seasonal distribution, a comparable number of males and females were admitted during the Autumn/Winter and Spring/Summer months. However, the overall average age of those sustaining a femoral fracture during the Spring/Summer months was 6.3 years compared to 3.8 years for the Autumn/Winter group. This difference is probably related to the fact that traffic trauma is more common in the Spring/Summer months and that traffic trauma is more common in 5 - 13 year old children.

Overall, we found a male preponderance for femoral fractures which, concurs with other reported series.[4,6,8-10] This is also consistent with the general finding that males predominate in childhood injuries.[11,12]

Traffic trauma, falls, abuse, incidental findings, sporting injuries and pathologic fractures are the most commonly reported mechanisms of injury, with traffic trauma and falling accounting for the majority of cases.[4,8,10,13,14] In this series, traffic trauma and trauma associated with falling accounted for 84% of femoral fracture admissions. Although in this study child abuse was neither reported nor suspected from the case notes, it is reported that femoral fractures in children less than 1 year are often secondary to child abuse[15,16] and should therefore be considered in such instances.

The aetiology of femoral fractures in children, the seasonal distribution and the region of the femur affected varies with the age of the child.[4,6,8,10,13] In early childhood, the femur is relatively weak and can break under load conditions reached in normal play. However, during childhood, through a process of remodeling, children's bone changes from primarily weak woven bone to stronger lamellar bone. Strength is also increased by a change in geometry.[17] Thus, in older children and adolescents, high-velocity trauma is required to reach the stresses necessary for fracture.

We found that for children under the age of 5 years, a fall was the most common mechanism of injury (65%) regardless of sex. This may be due to the fact that young children may have unprotected falls as a result of incompletely developed motor skills. However when considering the 5 - 13 years group, traffic trauma accounted for 75% femoral fractures with males having a five times greater incidence of femoral fracture at this age due to road traffic accidents. Furthermore, when comparing the age of the child and the mechanism of injury (*Table 4*) with the region of the femur affected, midshaft fractures were seen more commonly in younger children (average age, 3.5years) and were more commonly associated with trauma due to a fall. Injuries to the proximal and distal femur were seen more commonly with older children (average age, 7.8 years and 6 years respectively) and were much more commonly associated with road traffic accidents. These findings can be explained partly by the changes in femoral osteology that occur with development as described but also by the difference in play and free-time activities between over and under five year old children and indeed between the two sexes.

Pathological femoral fractures are relatively uncommon in children but may occur as a result of generalised osteopenia in association with osteogenesis imperfecta, or neurological diseases such as cerebral palsy or spina bifida. Benign or malignant neoplasms may also give rise to pathological fractures. One child in this series with severe spina bifida sustained a fracture of both femurs

at different time intervals (5 days and 4 months). The first fracture may have been the result of birth trauma whilst the second fracture occurred during routine physiotherapy. One child fractured through the site of a multicamaral bone cyst, although there was a definite history of a fall.

When a child is struck by a car, the femur is at the level of the bumper, the trunk is at the level of the hood and as a result of the impact, the child may be thrown into the air before landing on the road. This may result in a combination of injuries including a fractured femur, intra-abdominal or intra-thoracic injuries and a head injury ("Waddell's triad"). Rosenberg *et al.*[13] demonstrated that the risk of developing shock was significantly higher for those patients with a combination of femoral fracture, associated fractures and injuries. Of the five patients who sustained injuries in addition to their femoral fracture, there was no documented evidence of shock at any stage nor did any of these patients require transfusion. However, should hypotension develop, the child should be evaluated for an additional source of blood loss other than the femoral fracture.

Options for the treatment of femoral fractures in children include traction, casting, external fixation, open reduction and plating, and flexible or locked intramedullary nailing. The choice of treatment is dependent on a number of factors including age, the child's size and bone age, the mechanism of injury and the presence of other injuries, the region of the femur affected, and the advantages and disadvantages of operative intervention.

On reviewing the initial fracture management of the patients in this study, it was deemed appropriate in all of the cases admitted to the unit. The majority of patients were treated definitively in a hip spica cast following an average of 9.8 days in traction, the aim of which is to minimise femoral shortening and allow the formation of early callus, thus providing some fracture stability prior to the application of hip spica. This time spent in traction accounts for a substantial portion of the overall duration of inpatient stay.

On reviewing the data collected for the patients treated in hip spica who returned to theatre, there was no obvious reason to account for this problem. Despite requiring revision of hip spica, all of the cases proceeded to uneventful fracture union. A successful outcome was also achieved in those treated by operative intervention with no complications relating to their overall surgical management.

Although femoral fractures are dramatic and disabling injuries, both to the patient and their family, most unite without significant complications or sequelae. On evaluating fracture union in this series, the time to fracture union was rapid and age-dependent with the average time to union being 3 months. Delayed union, which is uncommon in children, was evident in only one case. There were no cases of non-union, which is in keeping with the fact that this complication is rare in paediatric femoral fractures.[18,19]

In summary, femoral fractures represent a small but significant workload for the RBHSC fracture service. Whilst we accept that this study is retrospective and the limitations that this implies, much of the epidemiological data collected concurs with other reports in the literature regarding these injuries. Furthermore, conservative and operative treatment of these fractures, where appropriate, provided a satisfactory outcome in terms of successful fracture union with minimal complications. Reducing the inpatient duration of stay and time to hip spica application are controversial issues and require further evaluation in a more prospective manner.

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PET-CT in the diagnosis of recurrent rectal cancer complicated by left thigh abscess

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Recurrent rectal cancer presents a difficult problem for both patient and surgeon. One of the main factors influencing recurrence includes involved circumferential resection margins.[1] In the diagnosis of pelvic recurrence, the most common symptom is pain, which may be perineal and/or radiate to the lower limbs. Usually computed tomography (CT) and magnetic resonance scanning are the imaging modalities of choice. More recently, the introduction of PET (Positron Emission Tomography) and PET-CT, have shown accuracy in the detection of pelvic recurrence following colorectal cancer.[2] We present an unusual case, in which use of PET-CT identified a perforated pelvic recurrence of a rectal cancer, which was complicated by a left thigh abscess.

CASE REPORT

A 57-year old man, who 2 years previously had undergone an anterior resection for a locally advanced rectal adenocarcinoma, with adjuvant chemo-radiotherapy was referred to our unit. At initial surgery, his liver was clear and there was no tumour spillage. Gross pathology revealed a large cancer invading the mesorectum. Histology demonstrated a moderately differentiated Dukes' C (pT4,N2) adenocarcinoma, with features predisposing to a high likelihood of recurrence including tumour to within <1mm of the circumferential resection margin (CRM) as well as lymphovascular invasion.

When referred, he complained of symptoms suggestive of pelvic recurrence including anorexia, weight loss, diarrhoea and most ominously bilateral buttock pain. Clinical examination revealed signs of cancer cachexia. On digital rectal examination there was no evidence of a pelvic mass, although the anastomosis felt rigid.

When admitted, in addition to the symptoms and signs described, he also complained of left hip pain and was pyrexial (38°C), with tenderness overlying the left hip. Blood investigations revealed; Hb 6.7g/dl, WCC 11.1 x 10^9/l, Albumin 27g/l and CRP 289 mg/l (Normal <7mg/l). PET-CT scanning revealed a pre-sacral mass with soft tissue density and increased uptake of [F^{18}]2'-fluoro-2-deoxy-D-glucose (FDG) within the pelvis (*Figure 1*). The first image is a mid-sagittal CT, the middle image is the FDG-PET and the third image is the fused data.

In addition an abnormal area was noted to extend laterally through the sciatic notch (*Figure 2*).

He underwent laparotomy, pelvic drainage and formation of an end colostomy. At operation, no attempt was made to excise the recurrent tumour within the pelvis. Histopathology of a tissue biopsy confirmed tumour recurrence. Following surgery he complained of increasing pain in the left hip and thigh with clinical evidence of cellulitus. A CT scan (Figure 3) showed evidence of gas formation along the lateral aspect of the left thigh deep to tensor fascia lata, extending to the knee. He underwent incision and drainage of the left leg. Following this a further smaller abscess developed over the left fibular region requiring further incision and drainage. From this he made a slow but steady recovery and subsequently had his left leg wound closed prior to

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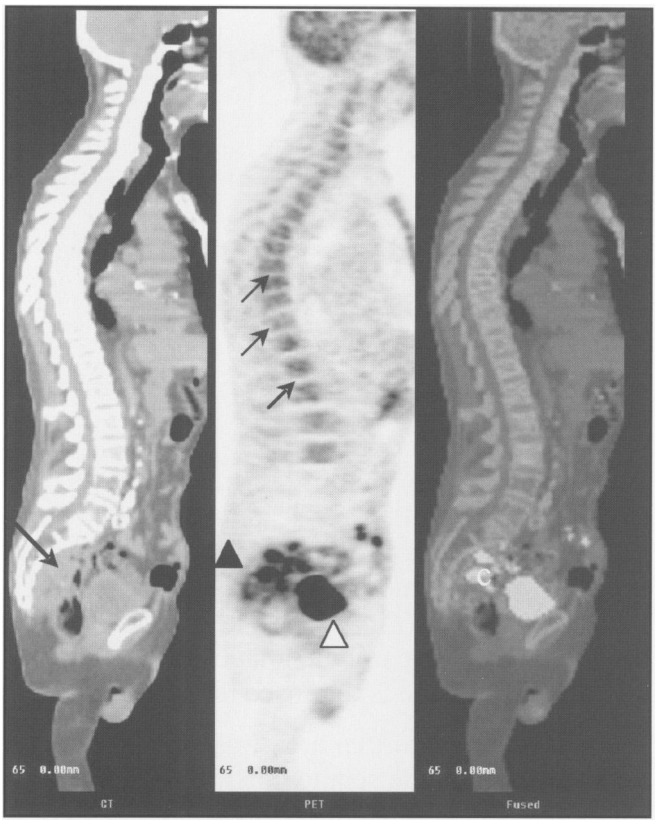

Fig 1. PET-CT (sagittal section) demonstrating a pre-sacral mass with soft tissue density (long black arrow) and abnormal FDG uptake within the pelvis (black arrow head). Note the normal FDG excreted in the bladder (white arrow head). The fused (PET-CT) image shows abnormal activity within the pelvis (c). Also note the increased activity in the spinal bone marrow due to pyrexia and marrow stimulation (short black arrows). Note the absence of marrow in the lumbar spine due to prior radiotherapy.

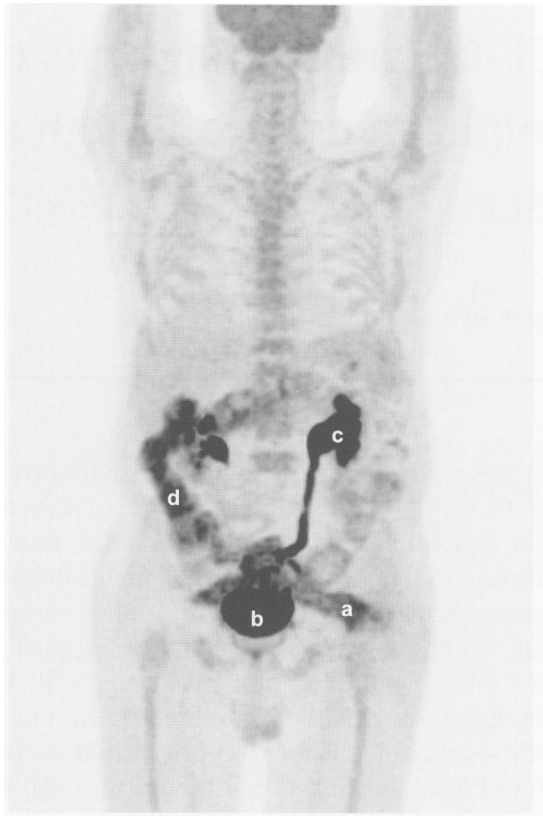

Fig 2. Maximum Intensity Projection (MIP) of the FDG-PET data (coronal section) demonstrating enhanced activity extending laterally to the left from the pelvis (a). Normal FDG activity is seen in the bladder (b), left kidney and ureter (c) and colon (d).

discharge 2 months after admission. On discharge, he was referred to oncology to be considered for further adjuvant treatment.

DISCUSSION

Local recurrence of rectal cancer after "curative" surgery is a major clinical problem, with a low resectability rate and a dismal prognosis. As a consequence of Total Mesorectal Excision (TME), 5 year survival figures for rectal cancer have risen from 45-50% to 75%, with a decrease in local recurrence rates from 30% to 5-8%.[3] However in spite of better surgery and improved neoadjuvant and adjuvant therapies, recurrence remains a problem. This case demonstrates the typical presentation of recurrence: that is, buttock pain as a consequence of pelvic nerve infiltration by tumour.

Positron emission tomography with [F^{18}]2'-fluoro-2-deoxy-D-glucose (FDG) is being increasingly

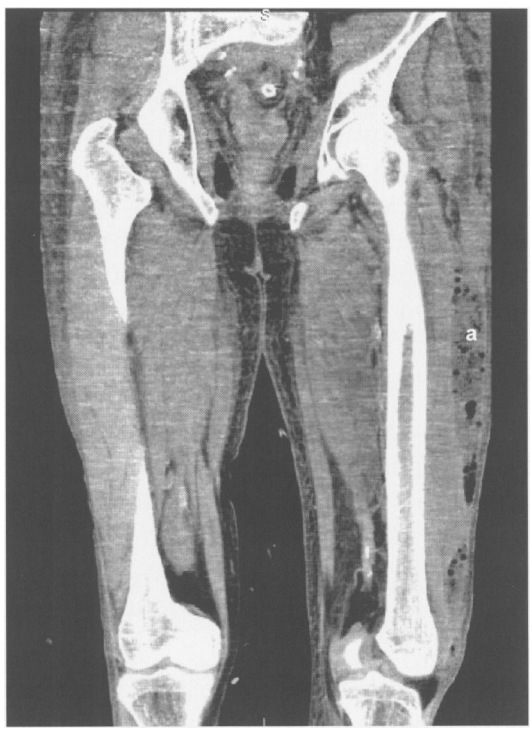

Fig 3. Coronal section, demonstrating gas formation (a) along the lateral aspect of the left upper leg.

used in the management of cancer and is helpful in discriminating recurrent tumour from post-intervention scar tissue. PET-CT has a clear role to play in the diagnosis of any potential local recurrence of rectal cancer, with the literature reporting an accuracy of 96%.[4] In this case, there was a pre-sacral mass and increased FDG uptake, features typical of recurrence with in addition extra-pelvic FDG activity.

Colorectal perforations causing gluteal/thigh abscesses are reported, in association with both diverticular disease[5] and colorectal malignancy.[6] Appropriate management of such sepsis usually involves a laparotomy with a defunctioning end stoma, plus or minus pelvic drainage and appropriate antibiotic therapy. Progression of sepsis, as happened in this case was the result of spreading infection into the lateral fascial compartment of the leg, giving rise to the tenderness, cellulitus and gas forming infection that required incision and drainage.

Primary abscesses of the thigh are uncommon and although readily diagnosed, their aetiology may often be obscure.[7] Routes of extension of infection into the thigh can be either direct, through the subcutaneous tissues, or through naturally occurring defects in the abdominal wall.[5] Whilst percutaneous drainage of localised collections may be performed,[7] more extensive abscesses require formal surgical drainage.

In conclusion, we describe the unusual and uncommon complication of a recurrent rectal cancer, which was complicated by a left thigh abscess, and demonstrate the role of PET-CT in this case.

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Natural history of Asymptomatic Bile Duct stones at time of cholecystectomy

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STRUCTURED ABSTRACT

Objectives: **There is little data on the natural history of asymptomatic bile duct stones and hence there is uncertainty on the management of asymptomatic bile duct stones discovered incidentally at the time of laparoscopic cholecystectomy. We retrospectively reviewed a group of patients who had previously underwent laparoscopic cholecystectomy, but who did not have a pre-operative suspicion of intra-ductal stones, to determine if any biliary complications had subsequently developed. A group of patients who had no pre-operative suspicion of intra-ductal stones, but routinely underwent intra-operative cholangiogram (IOC) at time of cholecystectomy, served as the control group.**

Methods: **A telephone questionnaire was completed by each patient's family practitioner in 59 of 79 (75%) patients who underwent laparoscopic cholecystectomy. In the remaining 20 patients additional information was obtained from hospital records and from the central services agency (CSA). These patients had no pre-operative suspicion of bile duct stones and therefore did not undergo an IOC or ERCP. The control group (73 patients) had no pre-operative suspicion of bile duct stones but had a routine IOC performed to define the biliary anatomy.**

Results: **59 patients were followed up for an average of 57 months (range 30 – 78 months) after laparoscopic cholecystectomy. None of these patients developed pancreatitis, jaundice, deranged liver function tests (LFT's), or required ERCP or other biliary intervention. In the additional 20 patients where no information was available from the family practitioner, 11 patients had follow up appointments with no documentation of biliary complications or abnormal LFT's. 19 of 20 patients were traceable through the CSA and were all alive. Only 1 patient was untraceable and therefore unknown if biliary complications had developed. In the control group, 4 of 73 (6%) patients had intraductal stones detected and extracted. Thus the prevalence of asymptomatic bile duct stones during the time of cholecystectomy in our population was 6%.**

Conclusions: **Asymptomatic bile duct stones discovered at the time of cholecystectomy do not appear to cause any biliary complications over a 5-year follow up. Incidental bile duct stones found in patients undergoing laparoscopic cholecystectomy may not need to be removed.**

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INTRODUCTION

Common bile duct stones are commonly found in patients undergoing cholecystectomy. The probability of co-existing ductal stones increases with age, being 6% in younger patients (less than 80 years old) and 33% in patients over 80years.[1] Studies have estimated the prevalence of asymptomatic bile duct stones in Western populations to be between 5.2% - 12%.[2-5] It is accepted practice to extract symptomatic ductal stones due to the risk of recurrent biliary obstruction, cholangitis and pancreatitis.[6] It is recommended that common duct stones, even if incidental should be removed, as these patients will characteristically develop complications such as cholangitis, pancreatitis, biliary pain or jaundice.[7] However these recommendations are based on little data, except on historical studies.[8]

The clinical relevance and management of asymptomatic bile duct stones remain controversial. Few studies have directly looked at the management of truly asymptomatic bile duct stones because if ductal stones were detected they were subsequently removed. Other studies, in which ductal stones were left in situ, did not directly look at asymptomatic bile duct stones.

AIM

In our unit, the use of intraoperative cholangiogram (IOC) varies according to surgeon preference. The aim of this study was to retrospectively examine a group of patients who underwent laparoscopic cholecystectomy, but who did not have a pre-operative suspicion of ductal stones (and therefore did not undergo routine IOC or pre-operative ERCP), to determine if they had developed any biliary complications over a 5-year follow up period. This study was based on the assumption that this group of patients would have included a number of patients with asymptomatic bile duct stones.

METHODS

Consecutive patients who underwent laparoscopic cholecystectomy between April 1993 and March 1997 were identified from recognised hospital codes during retrospective case note review. These operations were performed on 2 sites (UHD and AH) within the Trust. Only cholecystectomies performed at a single site (UHD) were examined and the rest excluded. Patients who had a pre-operative suspicion of choledocholithiasis (i.e. liver function tests (LFT's) were within normal range, no evidence of pancreatitis, jaundice or cholangitis, and no biliary dilatation on ultrasound examination) were also excluded from analysis. The study group comprised those patients without a pre-operative suspicion of choledocholithiasis and in whom no IOC or (pre or post operative) ERCP was performed. The control group was those patients with no pre-operative suspicion of choledocholithiasis but whom had IOC performed routinely. The control group had similar demographics to the study group but were not specifically age and sex matched.

Follow up of the study group was in the form of a telephone questionnaire to the patients respective family practitioners questioning whether patients had attended with complaints consistent with biliary pain or pancreatitis, abnormal LFT's, or had required any further biliary procedure including abdominal ultrasound or ERCP. If family practitioners were not contactable by telephone, follow up was obtained by reviewing hospital notes and/or by contacting the Central Services Agency (CSA) to determine if any patients had died.

RESULTS

A total of 423 consecutive patients were considered for review. Of these 423 patients, 190 patients had their procedure carried out in a separate centre and were not included in the analysis. From the remaining 233 patients, 81 (35%) patients had a pre-operative suspicion of concomitant bile duct stones based on raised LFT's, or duct dilatation on imaging and were also excluded from the analysis. In the remaining group of 152 patients, 79 patients had no pre-operative suspicion of ductal stones and no IOC or pre-operative ERCP was performed (study group). The other 73 patients also had no pre-operative suspicion of ductal stones but routinely had an IOC performed at time of laparoscopic cholecystectomy due to the surgeon's preference to determine the biliary anatomy (control group). Five (6%) patients in the study group had their operation converted to an open cholecystectomy compared to 7 (10%) patients in the control group.

A 75% response rate was achieved from telephone questionnaires. The majority of the remaining 25% (20/79) of patients were no longer with their indexed family practitioners. In these patients where no information was available from the family practitioner, 11 patients had follow up hospital appointments prior to and after the 5-year follow up period with no documentation of biliary complications or abnormal LFT's. 19 of 20 patients were traceable through the CSA and were all alive. Only 1 patient was untraceable and therefore unknown if biliary complications had developed.

The control group consisted of 73 patients (64 females: 9 males). Mean age of patient was 53.5y. In this control group, 4 out of the 73 patients i.e. 6% of patients had intra-ductal stones detected at time of surgery by IOC. These were removed either endoscopically post surgery or underwent open bile duct exploration at the index operation. Therefore the prevalence of asymptomatic bile duct stones in our population was 6%.

Family practitioner data was available for 59 of 79 patients in the study group (n=59. 53 females: 6 males). Mean follow up period following cholecystectomy was 57 months (range 30 - 78 months). Mean age of patient was 52y (range 31y-84y). Some of the study group patients had attended their family practitioners since cholecystectomy:- 4 patients with symptoms of gastro-oesophageal reflux disease, 2 patients diagnosed with duodenitis following OGD, 1 patient diagnosed with diverticulitis following barium enema for lower abdominal pain. 1 patient had ongoing nausea and 1 patient was diagnosed with neuropathic pain and referred to a pain clinic. However, none of the patients in the study group had any episodes of pancreatitis, jaundice, deranged LFT's or required ERCP or other biliary investigations in the 5-year period following laparoscopic cholecystectomy.

DISCUSSION

There is consensus that symptomatic bile duct stones should be removed. In an early series in 1941,[8] 38 patients who refused surgery or were considered unfit for surgery were followed for 6 months to 13 years. 45% remained asymptomatic and 55% developed complications such as biliary colic, jaundice and cholangitis. Johnson and Hosking reported similar outcomes with over 50% of patients with retained duct stones developing symptoms with 25% developing resultant serious complications.[1] The natural history of symptomatic bile duct stones appears to be less benign than that of asymptomatic gallstones.[9] However, many common bile duct stones pass spontaneously without any symptoms.[10,11] Acosta *et al* demonstrated gallstones in the faeces in 11.8% of patients with known gallstones but without symptoms of bile duct stones.[2] In a randomised study by Murison, patients who were undergoing cholecystectomy, but without symptoms of common duct stones, were randomized to IOC or no IOC. Bile duct stones were discovered in 12% of patients in the cholangiography group. It was assumed that a similar percentage of patients in the group without cholangiography had stones but none developed symptoms in over 3 years of follow-up.[3]

The likelihood of stones passing spontaneously and the risk of bile duct stones causing symptoms may be dependent on size but data supporting this is limited.[12] Stones up to 8 mm may pass without problems; a study where bile duct stones were left deliberately were shown to pass spontaneously when ERCP was later performed.[13]

Selective cholangiography for those patients with predictors of common bile duct stones appears to stratify patients in detecting a higher proportion of patients with ductal stones and thereby reducing costs.[14-22] This approach reduces the number of ductal explorations but will result in missed stones. Importantly, these missed stones seem not cause any morbidity in follow up of these patients.

In our study, the prevalence of incidental ductal stones detected at time of cholecystectomy was 6%. We would expect a similar prevalence in our study group of patients who underwent cholecystectomy but without cholangiogram ie. 4 or 5 patients. Follow up of these patients over a 5-year period, revealed no complications related to bile duct stones. Other studies have indicated that if retained ductal stones become symptomatic, they do so prior to discharge following cholecystectomy, or within 3 years of cholecystectomy.[23,24] This study confirms data from a previous study by Murison who randomised 285 patients requiring cholecystectomy, but without suspicion of bile duct stones, into 2 groups. Group 1 underwent perioperative cholangiogram and group 2 did not. Bile duct stones were detected in 12% of patients in group 1. Follow up of the patients in group 2 over a 3-year period revealed no symptoms or complications related to retained bile duct stones.[3] Our study supports the conclusions of Murison *et al*.

There are several potential weaknesses of this study. The prevalence of asymptomatic bile duct stones in our population was low (6%) but consistent with other published studies.[1] A consequence of this low prevalence rate is the small number of patients in the study group who would be expected to have had intra-ductal stones at the time of cholecystectomy. As information was not available from patients' family practitioners in 25% of our study group, we obtained information on these patients from hospital records and computerised laboratory systems to ensure no biliary complications had occurred. The CSA was also contacted to ensure these patients had not died

as a result of biliary complications. In addition, the retrospective design of this study may have inherent recall bias. The telephone questionnaire relied on family practitioners to recall patient visits with biliary complications and some patients may have been missed due to lack of documentation or incorrect coding. Although not specifically age or sex matched, the control group had similar demographics to the study group and therefore we feel the prevalence of intra-ductal stones in the control group would also be valid for the study patients.

We believe that routine intra-operative cholangiography in order to detect coincidental bile duct stones is not required in patients without clinical, biochemical or radiological evidence of ductal stones. This may result in missed ductal stones, but importantly these did not cause any morbidity during a 5-year follow up.

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Periods of low atmospheric pressure are associated with high abdominal aortic aneurysm rupture rates in Northern Ireland

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ABSTRACT

Seasonal and circadian variation in the incidence of ruptured abdominal aortic aneurysm (RAAA) has been reported. We explored the role of atmospheric pressure changes on rupture incidence and its relationship to cardiovascular risk factors. During a three year-period, 1st April 1998 and 31st March 2001, data was prospectively acquired on 144 Ruptured Abdominal Aortic Aneurysm (RAAA) presenting to the Regional Vascular Surgery Unit at the Royal Victoria Hospital, Belfast, Northern Ireland. For each patient the chronology of acute onset of symptoms and presentation to the regional vascular unit was recorded, along with details of standard cardiovascular risk factors. During the same period meteorological data including atmospheric pressure and air temperature were recorded daily at the regional meteorological research unit, Armagh. We then analyzed the monthly mean values for daily rupture incidence in relation to the monthly values for atmospheric pressure, pressure change and temperature. Furthermore atmospheric pressure on the day of rupture, and day preceding rupture, were also analyzed in relation to days without rupture presentation and between individual ruptures for various cardiovascular risk factors. Data demonstrated a significant monthly variation in aneurysm rupture frequency, ($p<0.03$, ANOVA). There was also a significant monthly variation in mean barometric atmospheric pressure, ($p<0.0001$, ANOVA), months with high rupture frequency also exhibiting low average pressures in the months of April (0.24±0.04 ruptures per day and 1007.78±1.23 mB) and September (0.16±0.04 ruptures per day and 1007.12±1.14 mB), respectively. The average barometric pressures were found to be significantly lower on those days when ruptures occurred (n=1127) compared to days when ruptures did not occur (n=969 days), (1009.98±1.11 versus 1012.09±0.41, $p<0.05$). Full data on risk factors was available on 103 of the 144 rupture patients and was further analyzed. Interestingly, RAAA with a known history of hypertension, (n=43), presented on days with significantly lower atmospheric pressure than those without, (n=60), (1008.61±2.16 versus 1012.14±1.70, $p<0.05$). Further analysis of ruptures grouped into those occurring on days above or below mean annual atmospheric pressure 1013.25 (~1 atmosphere), by Chi-square test, revealed three cardiovascular risk factors significantly associated with low-pressure rupture, ($p<0.05$). Data represents mean ± SEM, statistical comparisons with Student t-test and ANOVA. These data demonstrate a significant association between periods of low barometric pressure and high incidence of ruptured aneurysm, especially in those patients with known hypertension. The association between rupture

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incidence and barometric pressure warrants further study as it may influence the timing of elective AAA repair.

INTRODUCTION

Ruptured abdominal aortic aneurysm (RAAA) remains a leading cause of death in elderly males, causing 2.1 per cent of all deaths in men and 0.75 per cent of all deaths in women over the age of 65 years in England and Wales.[1] Autopsy studies suggest that the numbers of RAAA are increasing annually,[2] and despite improvements in perioperative care the mortality rates have remained fairly static over the last fifty years.[3]

A clear seasonal variation has been reported in the incidence of rupture in both thoracic[4] and abdominal[5] aortic aneurysms. More recently a relationship between seasonal periods of low atmospheric pressure and aneurysm rupture has been reported.[6] A circadian variation has also been reported which mirrors the circadian variation in systolic blood pressure and thrombotic events, respectively.[7] It is known that wall stresses blood vessels are exposed to are determined by the net effect of blood pressure and extra-arterial tissue pressure, and their ability to cope depends largely on the strength of the vessel wall.[8,9] Indeed a calculated mechanical wall stress has been suggested as a better predictor of aneurysm rupture than simply aneurysm diameter alone.[10,11] A number of risk factors have been identified for abdominal aortic aneurysm (AAA) rupture including aortic size, hypertension, age, gender, smoking, chronic obstructive pulmonary disease, and family history.[12] Yet the relationship between these risk factors and atmospheric pressure with regard to aneurysm rupture is unknown.

The majority of ruptured AAA present de-novo and not in those previously under surveillance, but with the expansion of regional AAA screening programmes many more asymptomatic AAA shall come to under clinical supervision,1 making timing of repair an important consideration. Changes in atmospheric pressure may increase transmural arterial stress by transiently lowering extra-arterial pressure in respect to blood pressure, or by increasing blood pressure itself, predisposing to rupture of a weakened aneurysm wall. Alternatively altered pressure flux across the arterial wall may activate lytic factors within the aneurysm wall, which predispose to rupture. We therefore intended to explore the effects of changes in atmospheric pressure on risk of aneurysm rupture and the relationship between atmospheric pressure and known cardiovascular risk factors, as it may have immense bearing on when and how AAA are repaired in the future.

METHODS

Case identification and Data retrieval

Prospectively acquired data between, 1998 and 2002, on the incidence of RAAA presenting to the Regional Vascular Surgery Unit at the Royal Victoria Hospital, Belfast and atmospheric pressure data retrieved from the regional meteorological research unit, Armagh, were analysed. In all cases aortic rupture was diagnosed and confirmed at surgery in 144 cases (mean age 73.4 years [range 43-92]). Ruptures occurred on 127 days within this period and presented as follows: on 112 days one rupture, on 13 days two ruptures, and on 2 days three ruptures. On arrival time of onset of acute symptoms and past medical history was determined from patients or witnesses and recorded prospectively in a computerized vascular registry (Northern Ireland Vascular Registry: NIVASC). Accuracy of prospective data was confirmed by retrospective case identification from death certificate record and the admission record of the accident and emergency department, operating room, intensive care unit and high dependency unit. All patient charts were inspected manually to confirm data accuracy. Cases were only included if the analysis of rupture was confirmed by the presence of blood outside the aorta (intra- or retroperitoneally) at laparotomy for AAA repair or at autopsy. The details of patients that had a clinical or radiological diagnosis of RAAA but not fit enough for surgery were also recorded. Patients with aorto-caval or aorto-enteric fistulas were not included in the analysis. Special attention was given to the accurate identification of time of acute onset of symptoms or rupture and the pre-morbid state of the patient regarding the presence or absence of hypertension and or treated hypertension and other cardiovascular risk factors.

Meteorological Data

Belfast is located on the east coast of Northern Ireland on the western edge of Europe. The data on climate in this region were obtained from the Regional Meteorological Unit at Armagh Observatory. Daily records (high, low, and mean) of atmospheric pressure and air temperature were recorded prospectively at the regional meteorological center at Armagh Observatory, for the study period.

Statistical analysis.

Data are expressed as counts of event (rupture) by month and daily rupture frequency per month

(counts of event per month divided by days), averaged over the 3-year period. Data expressed as mean +/- standard error mean. Standard univariate analysis examined the association between demographic and clinical characteristics, meteorological data and rupture presentation. Full data on risk factors was available on 103 of the 144 patients (71.5%), as such risk factor analysis was restricted to this subgroup. In these patients events (rupture) were further subcategorized into those occurring above (n=44) and below (n=59) mean atmospheric pressure (1013.25mB~1 atmosphere), to explore the effect of common cardiovascular risk factors on rupture during periods of low atmospheric pressure. Chi-squared test was used for statistical analysis. A P value less than 0.05 indicated statistical Population characteristics including information on demographics, medical and family history, smoking, occupation and medication were collected prospectively in a computerized vascular registry (Northern Ireland Vascular Registry; NIVASC). Data was retrospectively checked for accuracy by manual search of all written case records, by one of the authors (MO'D). Cardiovascular risk factors were recorded prospectively into a computerized vascular registry (NIVASC) at time of patient presentation, these data included: no risk factors; cerebrovascular; TIA or CVA; diabetes; family history: cardiovascular; hyperlipidaemia; previous vascular surgery/ amputation; hypertension: treated/ BP>160/95; tobacco: smoker or history of smoking; cardiac: CCF; MI; CABG; ECG changes; pulmonary: chronic obstructive disease; MI; renal: serum creatinine above 150 micromol/L; AF.

RESULTS

Seasonal variation in rupture rate and meteorological data

Data demonstrated a significant monthly variation in aneurysm rupture frequency, ($p<0.03$, ANOVA). There was also a significant monthly variation in mean barometric atmospheric pressure, ($p<0.0001$, ANOVA), months with high rupture frequency also exhibiting low average pressures in the months of April (0.24±0.04 ruptures per day and 1007.78±1.23 mB) and September (0.16±0.04 ruptures per day and 1007.12±1.14 mB), respectively, (*Figure 1*). There was a significant inverse correlation between the daily barometric atmospheric pressure and the daily rupture frequency, ($r=-0.0051$, $p<0.017$). There was also a significant inverse correlation between the monthly average daily change in barometric atmospheric pressure and the average monthly rupture frequency, ($r=-0.25$, $p<0.05$). Data for mean air temperature demonstrated a significant monthly variation, peak value (15.55±0.07 0C) in July and nadir value (4.40±0.09) in January, ($p<0.0001$), ANOVA, however there was no significant correlation between temperature and number of ruptures ($p<0.68$).

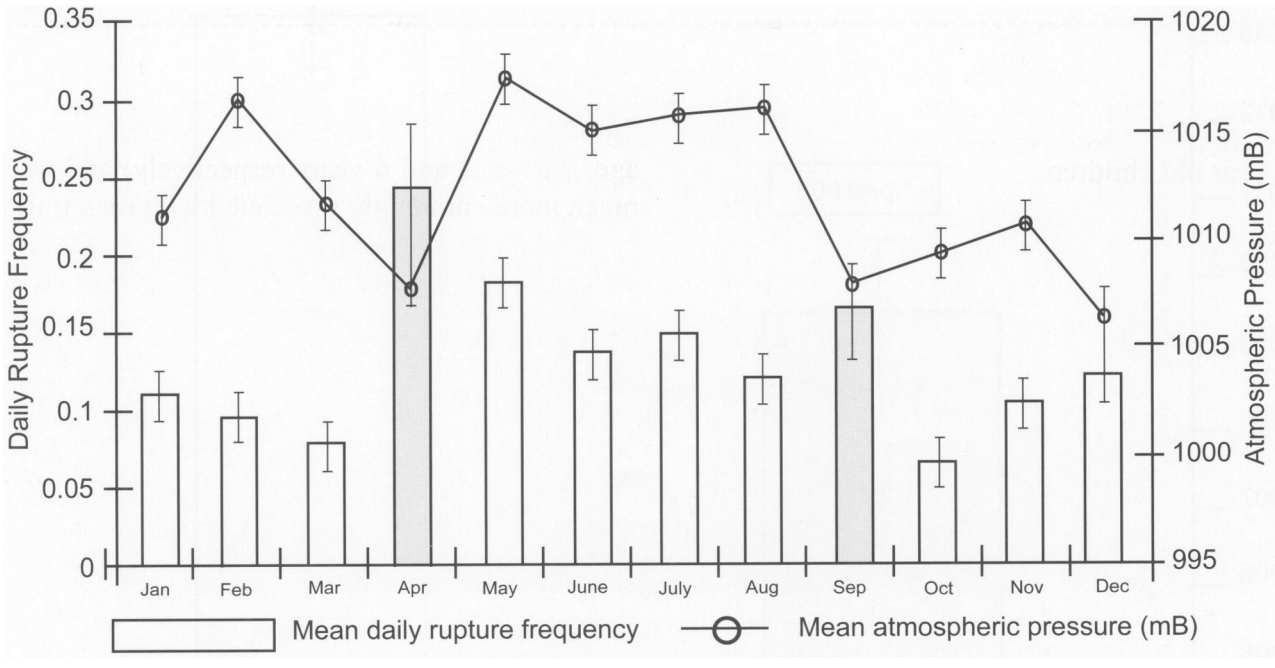

Fig 1. Monthly average of daily frequency of ruptured abdominal aortic aneurysm (bar) and monthly average of daily atmospheric pressure, shown for comparison, Mean (±SEM). Significant variation in monthly rupture frequency, ($p<0.029$), and atmospheric pressure, ($p<0.0001$), ANOVA.

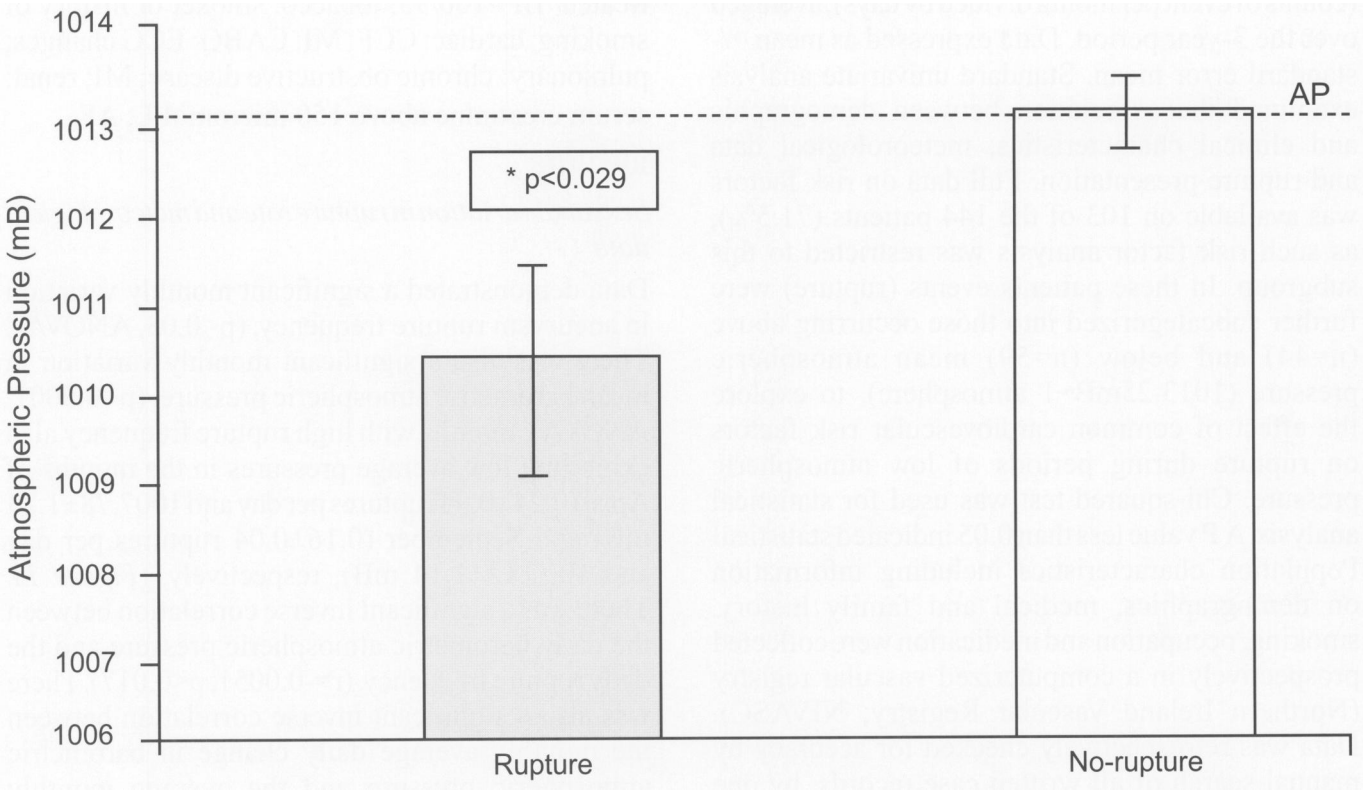

Fig 2. Histogram of average atmospheric pressure on days when ruptures occur compared to those when no ruptures occur, Mean (±SEM), ($p<0.029$), Students T Test. *AP (1 Atmosphere pressure 1013.25 mB).*

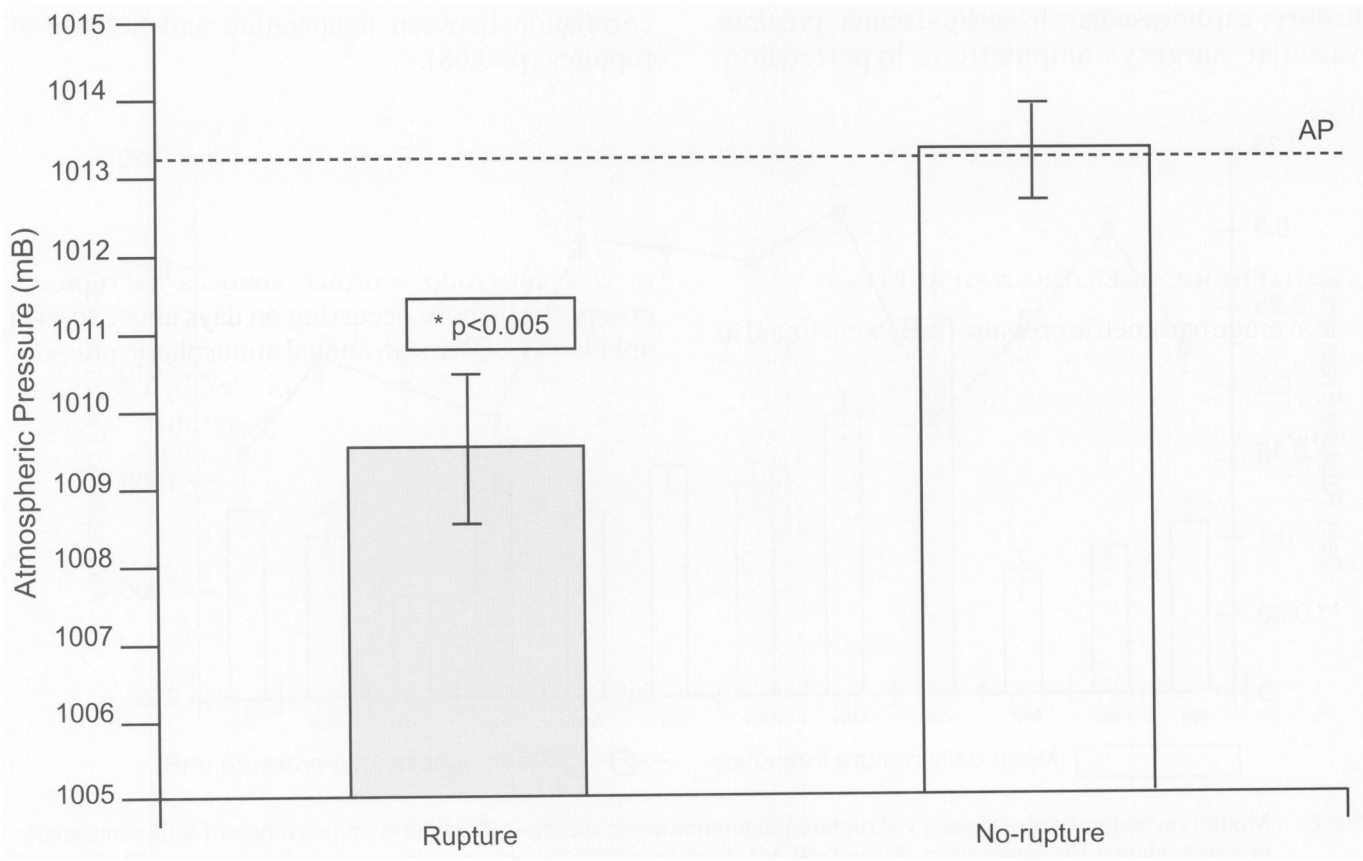

Fig 3. Histogram of average atmospheric pressure on day before rupture compared to those when no ruptures occur, Mean (±SEM), ($p<0.005$), Students T Test. *AP (1 Atmosphere pressure 1013.25 mB).*

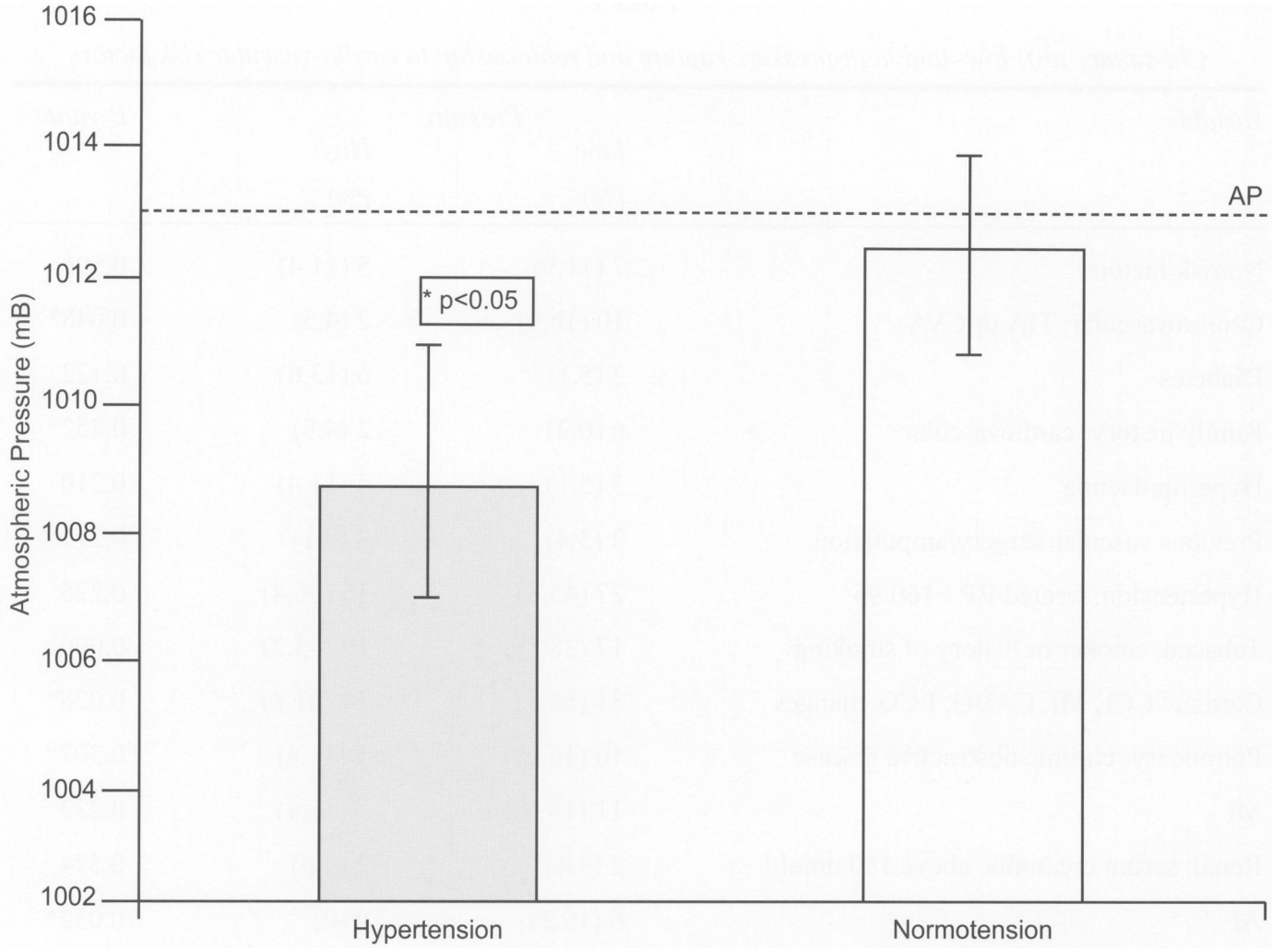

Fig 4. Histogram of average atmospheric pressure on days when ruptures with known hypertension compared to those without occur, Mean (±SEM), ($p<0.05$), Students T Test. *AP (1 Atmosphere pressure ~1013.25 mB).*

ATMOSPHERIC PRESSURE AND RUPTURE

The average barometric pressure (mB) were found to be significantly lower on those days when ruptures occurred (n=127) compared to days when ruptures did not occur (n=1096 days), (1010.35±1.26 versus 1013.24±0.35, $p<0.029$), (*Figure 2*). Interestingly, when analyzing the preceding 24-hour period atmospheric pressure was highly significantly lower the day before rupture presentation as when not, (1009.58±1.25 versus 1013.30±0.35, $p<0.005$), (*Figure 3*). Furthermore, the pressure change was significantly greater on days preceding rupture than days not preceding rupture, (7.36±0.61 versus 5.95±0.15, $p<0.028$).

RISK FACTORS AND RUPTURE AT LOW-ATMOSPHERIC PRESSURE.

Full data was available on 103 of the 144 patients (71.5%), as such risk factor analysis was restricted to this subgroup. Further analysis of ruptures grouped into those occurring on days above (n=44) or below (n=59) mean annual atmospheric pressure 1013.25±0.35mB (~1 atmosphere), by Chi-square test revealed three risk factors significantly associated with low pressure rupture, ($p<0.05$), (*Table 1*).

RUPTURE AND HYPERTENSION

Interestingly, RAAA with a known history of hypertension (treated hypertension or known hypertension defined as BP>160/95), (n=43), presented on days with significantly lower atmospheric pressure than those without, (n=60), (1008.61±2.16 versus 1012.14±1.70, $p<0.05$), (*Figure 4*).

DISCUSSION

Ruptured abdominal aortic aneurysm rupture (RAAA) remains a major cause of death especially

TABLE I

Chi-square test: low- and high-pressure rupture and relationship to cardio-vascular risk factors

Variable	*Pressure*		*P-value*
	Low (%)	*High* (%)	
No risk factors	7 (11.9)	5 (11.4)	0.596
Cerebrovascular: TIA or CVA	10 (16.9)	2 (4.5)	0.048*
Diabetes	3 (5.1)	6 (13.6)	0.122
Family history: cardiovascular	6 (0.2)	2 (4.5)	0.252
Hyperlipidaemia	3 (5.1)	5 (11.4)	0.210
Previous vascular surgery/amputation	2 (3.4)	4 (9.1)	0.212
Hypertension: treated/BP >160/95	27 (45.8)	16 (36.4)	0.225
Tobacco: smoker or history of smoking	17 (28.8)	19 (43.2)	0.096
Cardiac: CCF, MI, CABG, ECG changes	31 (52.5)	14 (31.8)	0.028*
Pulmonary: chronic obstructive disease	10 (16.9)	5 (11.4)	0.307
MI	11 (18.6)	5 (11.4)	0.233
Renal: serum creatinine above 150 umol/l	2 (3.4)	2 (4.5)	0.574
AF	6 (10.2)	0 (0)	0.032*

among elderly men. The majority of RAAA present de-novo and not in those previously under surveillance, but with the expansion of regional AAA screening programs many more asymptomatic AAA shall come to under clinical supervision.[1] Repair by elective open technique represents a successful treatment strategy that has a very acceptable mortality rate of 2-5 per cent in specialist units.[3,13] With the widespread adoption of endovascular repair it may be that treatment for those deemed inoperable by open means due to co-morbid disease will also increasingly be offered treatment. The timing of elective repair in the United Kingdom has been guided by the UK small aneurysm trial[14,15] and a variety of studies suggesting predictive risk factors for rupture.[3] *Bown et al*, have recently reported an association between low atmospheric pressure and aneurysm rupture,[6] although in that study they made no attempt to look at other risk factors predisposing to rupture. Our study supports the role of atmospheric pressure in the seasonal variation in rupture incidence and would suggest the timing may be critical in those awaiting elective repair, especially if they have co-existent hypertension. Unfortunately in this study, as in others, information on aneurysm size was not available in the vast majority of patients as they presented *de-novo* and were too unstable to undergo pre-operative computerized tomogram (CT) scanning. Furthermore, due to the expedient presentation of these individuals full pre-morbid health data could only be verified in 103 of the 144 patients and as such analysis was restricted to this group. The study has certain limitations inherent in the population studied, it is known that many deaths due to RAAA occur in the community and are undiagnosed, the low community post-mortem rate in our own region and the British Isles in general would make any attempt to include these deaths in the analysis unachievable at present. However, this study may stimulate such analysis in Scandinavian Countries where population post-mortem rates are considerably higher. Further study is required to assess the influence of aneurysm size and periodicity of rupture, to assess whether the larger aneurysms are

more at risk from atmospheric pressure effects.

Several studies have shown a seasonal variation in the presentation of AAAR with peak incidence in spring and autumn as in our series.[16-20] *Bown et al*, found high rupture peak incidence in the winter associated with low atmospheric pressure, which is most likely due to a regional difference in climatic condition and patient cohort.[6] We have also found a more direct relationship between the low atmospheric pressure on the day of and the day preceding aneurysm rupture, which would seem more relevant to a critically stressed aneurysmal arterial wall. It has been suggested that seasonal variation is related to temperature,[20] smoking habits,[16] or seasonal variation in hypertension.[16] *Ballaro et al*, reported a seasonal variation in the incidence of recorded deaths from abdominal aortic aneurysm in England and Wales, with a peak of deaths in the cold winter months. Winter peak of blood pressure, an independent risk factor for AAAR, in hypertensive patients was suggested as one possible cause.[16] In this study we have shown that those patients suffering RAAA with a known history of hypertension present on days with significantly lower atmospheric pressure than those without. Hypertension is an established risk-factor for RAAA,[12,15] and has also been linked to increased aneurysm growth rate.[21] Indeed a retrospective study has suggested that the treatment of hypertension with beta-blockade can inhibit aneurysm growth.[22] A circadian variation in aneurysm rupture has been reported which mirrors the circadian variation in systolic blood pressure and thrombotic events, respectively.[7] It is known that wall stresses that blood vessels are exposed to are determined by the net effect of blood pressure and extra-arterial tissue pressure, and their ability to cope depends largely on the strength of the vessel wall.[8,9] Indeed a calculated mechanical wall stress has been suggested as a better predictor of aneurysm rupture than simply aneurysm diameter alone.[10,11] Abdominal aortic aneurysm (AAA) rupture is believed to occur when the mechanical stress acting on the wall exceeds the strength of the wall tissue.[23] Changes in atmospheric pressure may increase transmural arterial stress by transiently lowering tissue pressure in respect to blood pressure creating a net expansive force, predisposing to rupture of a weakened aneurysmal wall. Alternatively atmospheric pressure may act by increasing blood pressure itself, causing increased stress across the weakened aneurysm wall. These same effects could also influence endotension and the integrity of endovascular aortic repair.

It is of interest that periodic changes in pressure in the 24-hour period preceding rupture have been shown in our study. This may suggest that pressure related changes within the aneurysm wall induce certain factors, which subsequently predispose to aneurysm rupture. Mechanical stress has recently been reported to up-regulate genes controlling cyclooxygenase-1, tenascin-C, and plasminogen activator inhibitor-1, in human aortic smooth muscle cells by DNA microarray techniques.[24] Elevated barometric pressure has been shown to increase human endothelial cell secretion of pro-inflammatory cytokine interleukin-1 beta and aortic smooth muscle cell osteoprotinin, respectively.[25,26] The development of aortic aneurysms is associated with inflammation, tissue-remodelling, and upregulation of Matrix Metalloproteinases (MMP)'s. MMP's can degrade a variety of extracellular proteins such as elastin, collagen, or proteoglycans. Increased levels of MMP-2, -3, -9, and –12 have been found in the aneurysm wall.[27,28] Recently gene disruption of MMP-9 has been found to suppress the development of experimental abdominal aortic aneurysms.[27] Conversely, a decreased level of Tissue Inhibitor of MMP (TIMP) has been found in the aneurysmal wall, moreover it has been recently reported that local expression of TIMP-1 may prevent aortic aneurysm degeneration and rupture in a rat model.[27,29] Furthermore inactivation of TIMP-1, in a KO mice enhances aneurysm formation.[29] Taken together these data suggest that the proteolytic balance in the vascular wall is a key determinant of aneurysmal development and perhaps rupture. Polymorphisms in the promoter region of MMP-3 genes have recently been linked to the development of coronary artery aneurysms in humans, suggesting a genetic susceptibility to proteolysis in some patients predisposes them to aneurysmal vessel change, creating an identifiable population at risk.[27] The role of atmospheric pressure alone and transmural pressure changes on gene up-regulation and in particular MMP secretion remains unknown and warrants further study.

CONCLUSION

Once again we have shown a seasonal variation in the incidence of abdominal aortic aneurysm rupture, with peak incidence in the spring and autumn months. We have shown that the barometric atmospheric pressure was significantly lower on those days when ruptures occurred compared to those days when they did not. We have shown a significant correlation between months with high rupture incidence and low barometric atmospheric pressure. The relationship between variations in

atmospheric pressure and abdominal aortic aneurysm rupture certainly warrants further evaluation, and may need to be considered in the future planning for those patients awaiting elective abdominal aortic aneurysm repair especially those with hypertension. The effects of changes in atmospheric pressure on risk of aneurysm rupture may have immense bearing on when and how AAA are repaired in the future.

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Medical History

Epidemic Jaundice:

Harvard's 5th General Hospital at Musgrave Park in World War II

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U.S. DEPLOYMENT TO ULSTER AND EIRE

On September 2, 1939, Winston Churchill joined Chamberlain's cabinet. Nine days later Franklin D Roosevelt wrote as follows:

> "My dear Churchill:
>
> It is because you and I occupied similar positions in the World War that I want you to know how glad I am that you are back again in the Admiralty. Your problems are, I realize, complicated by new factors but the essential is not very different. What I want you and the Prime Minister to know is that I shall at all times welcome it if you will keep me in touch personally with anything you want me to know about. You can always send sealed letters through your pouch or my pouch.
>
> I am glad you did the Marlboro [sic] volumes before this thing started – and I much enjoyed reading them.
>
> "With my sincere regards, Faithfully yours, [Franklin D Roosevelt]" [1]

On November 16, 1939, the US Surgeon General wrote to Dean C Sidney Burwell (MD, 1919) of the Harvard Medical School about responsibility for reactivating Harvard's Hospital No. 5, "Thus perpetuating the fine traditions of World War I of (Harvard's) United States Base Hospital No. 5." [2]

On June 13, 1940, Churchill had suggested in a letter to Roosevelt that US forces be moved to Ulster and Eire. On February 20, 1941, the 5th General Hospital met at the Harvard Club, 320 Commonwealth Avenue, Boston, with Elliott Cutler, Moseley Professor of Surgery and Chief at the Peter Bent Brigham, as Acting Director. Cutler had served in the same designated Harvard Hospital No. 5 in World War I, which had been under the directorship of Harvey Cushing, his predecessor as Moseley Professor. Plans were being made in the United States and the United Kingdom for the still neutral US forces to be stationed in Ulster. In April 1941, the US War Department issued RAINBOW-5 which detailed the deployment of thirty thousand US troops in Ulster.[3] On June 12, 1941, the British Government signed a contract with GA Fuller-RR Merritt Chapman Corporation to begin constructing US bases in Ulster. My father, now commanding officer of the 31st British Military General Hospital at Musgrave Park outside Belfast, was told that the 31st was to be taken over by the Harvard-affiliated 5th US General Hospital, the first unit of its kind scheduled for deployment under Operation MAGNET planned by RAINBOW. The activation of Operation MAGNET was agreed by President Roosevelt and Churchill and the Joint Chiefs at the Arcadia Conference held in late December 1941 through early January in Washington, DC, shortly after the US entry into World War II in early December 1941.[4]

CUNARD LINER SUNK

My father was commander of the British Hospital, because although a Territorial, he had distinguished himself in France. A senior surgeon at the Royal Victoria Infirmary at Newcastle-upon-Tyne, from June 3 through June 17, 1940, while in command of the rear guard of the 8th British General Hospital at Rennes, he did much war surgery. When the enemy attacked with high explosive bombs and machine guns on June 15th, he obtained trucks and ambulances

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and the patients and staff headed south. On Monday, June 17, 1940, the Cunard Liner, the *Lancastria*, was at anchor a few miles off St. Nazaire. According to *The New York Times* of July 26, 1940, one officer declared "We were so tightly packed on board that we could not move when the planes came over, so the men just jeered." Then came the bombing and the sinking and "At what seemed a prearranged signal the bomber started releasing incendiaries which set fire to the oil. Within a few minutes some of the rescue craft were in flames." In St. Nazaire harbor on June 17, 1940 my father evacuated the remains of his hospital and 52 survivors of the *Lancastria* sinking, on board the SS *Glenaffric* (launched 1920, 4,900 tons, maximum speed 11 knots) and they later made Plymouth. When he heard of the sinking of the *Lancastria*, Churchill burst into tears and slapped a D (secrecy) order on the news. Nevertheless, *The New York Times* learned of the disaster and the loss of five to nine thousand lives.

My father would never speak of the voyage on the *Glenaffric*. On landing, he received an immediate award of the Distinguished Service Order (DSO). The evidence for the Prime Minister's tears comes from a junior secretary of Churchill, who was recently interviewed about her experiences on a United States Public Broadcasting Service program. She said it was the only time she saw him cry.

Churchill, during the years 1940-1956, held an annual dinner party limited to himself and the twelve Harrow Monitors (School Prefects) in the headmaster's dining room and library, after which he used to indulge in hours of post-prandial conversation. He would try out punch lines and anecdotes for his future speeches and answer questions. On Friday, December 7, 1951, again Prime Minister, he was asked if he had ever thought the Allies would lose World War II. "No," he replied, "Because from September 1939 I trusted the American President and people in seeing to victory." Then we heard of the Jeromes' relationships to the Roosevelt kin. He said it had improved with his birth at Blenheim. The tears in his eyes after my question about the *Lancastria* were when his brandy bottle was half full – the cigar was never smoked, but gestured like a conductor's baton.

5TH HARVARD AND 31ST BRITISH

The 5th Harvard US General Hospital arrived in unscheduled installments at Musgrave Park without intended equipment. On January 26, 1942, about 4,000 members of the US 34th Infantry Division landed in Northern Ireland. Seven physicians of the Harvard 5th General Hospital, 26 nurses and 14 enlisted men, arrived at Musgrave Park the first week in March, but the rest of the 5th Harvard Hospital having initially embarked from New York on February 19, 1942, did not arrive. Their USAT, *American Legion* had to turn back to Halifax on February 21, due to engine trouble.

The March arrivals were put to work at the 31st General Hospital and entertained by my parents nearby at our house, "Windyridge", which they had rented from the Toppings. The majority of the 5th General Hospital reembarked on 30th April 1942 and reached Belfast on the 12th of May. The 5th General Hospital started operation on 21st of May at Musgrave Park. Tom Lanman, the Chief of Surgery of the 5th, arrived with the delayed main body and his War Diary entry for May 12, 1942, describes his first walk that day down "a beautiful Irish lane". He joined Ted Badger, the Chief of Medicine who had arrived in March.

Fig 1. Colonel Thomas Lanman, Chief of Surgery, Harvard's 5th General Hospital, with Colonel Angus Hedley-Whyte, commanding officer of the British 31st General Hospital, walking the grounds of Musgrave Park, May 1942. Colonel Lanman was appointed Clinical Professor of Surgery, Harvard Medical School, in 1947 and was Director of Harvard Medical School Alumni Relations from 1951 until his death on March 25, 1961. *Photo courtesy of Col Magnus Smedal, Head of Radiology, 5th General Hospital, gift to author.*

Thomas Hinckley Lanman (*Figure 1*) was the son of Charles B Lanman, Wales Professor of Sanskrit at Harvard, and Mary Hinckley Lanman. Thomas' sniffling at least once upset Henry James.[5]

During May 1942, a serum hepatitis outbreak was traced to contaminated yellow fever vaccine. The British 31st General, with my father still as commanding officer, worked together with the 5th Harvard Hospital (*Figure 2*). In late May, 1942, the hepatitis in US troops became epidemic. In June 1942, the 5th General hospital opened a 900-bed annex in Waringfield and in August the combined patient occupancy of Musgrave Park and Waringfield exceeded 1,500. In late July, 1,950 soldiers were jaundiced but only two died, although about one hundred[4] suffered permanent liver damage. This excellent overall result was achieved with help from the US 2nd General Hospital staff expeditiously transferred from Oxford, and continued cooperation from the 31st General Hospital's staff which had been delayed in their move to Hatfield House.

At the British to U.S., command handover ceremony, on May 20, 1942, my mother was amused when I saluted the raising of Old Glory and not the lowering of the Union Jack. Most of the 31st General was then moved from Musgrave Park to Hatfield House.

The 800-bed 5th General (Harvard) hospital was four times extended to a fully occupied 1,500 beds. First, in Ulster because of the epidemic, secondly in Carentan, Normandy to treat battle casualties before and during the breakout. The hospital had landed over Omaha beach on the 6th of July. Thirdly, after the Battle of the Bulge in Toul, in Meurthe-et-Moselle province, northeastern France, where it moved on the 22nd of November 1944, and lastly, to treat civilian victims of the concentration camps and Allied bombing. There it ended World War II with Col Robert Zollinger[6] as commanding officer, Col Zollinger having succeeded Colonel Maxwell G Keeler.[4] The hospital treated 35,400 casualties and patients in the period May 20, 1942, until its disbandment on August 26, 1945.

After World War II the Harvard Medical School faculty who had been at Musgrave Park would frequently ask when I was coming to Harvard. So after I qualified from the University of Cambridge Medical School and was engaged to a University of Durham medical student the move seemed opportune. My fianceé was transferred to medical school at St. George's Hospital, London – the Assistant Dean, Donald Teare, had been a guest at my parents-in-law's wedding. Charles Percy Pinckney, Pediatrician-in-Chief of St. George's Hospital,

Fig 2. The staff of the combined Harvard 5th General Hospital and British 31st General hospital in front of Musgrave Park, the former boys reformatory outside Belfast, May 1942. Note the relatively few British officer nurses and the bereted US officer nurses who fought the yellow fever vaccine-associated hepatitis epidemic which sickened 1,950 US soldiers, in Ulster.
Photo courtesy of Col Magnus Smedal, Head of Radiology, 5th General Hospital, gift to author.

arranged for Charles A. Janeway who had been Head of Laboratories in the 5th Harvard General Hospital and was now Chief of Medicine and Thomas M Rotch Professor at Boston's Children's Hospital, to give a Hunterian Lecture. "No dinner after your lecture," said Pinckney, unless you promise an internship." Tessa, now my medical student wife, was seated next to Professor Janeway at the dinner and they seemed to get on well. Subsequently, Tessa failed to get the Brackenbury Prize as the top medical student only because of her low marks in Pathology. This ignorance is still being corrected in her position as Head of Neuropathology at the Massachusetts General Hospital and Professor at Harvard where she is a close colleague of Ulsterman Robert (Robin) Young, Director of Anatomic Pathology.

In 1971, my father's obituary in *The Lancet*, written by Sir Ian Fraser, DSO,[7] stated "Outwardly he gave the impression of being an easygoing country gentleman. Very few surgeons over 70 years of age are out on horseback two or three times a week, as he was until recently." *The British Journal of Surgery* concluded its *In Memoriam*, "Harvard gave Angus an excuse to visit America whenever possible."

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Case Report

Migration of Filshie clips – report of two cases and review of the literature

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CASE 1 – MIGRATION OF A FILSHIE CLIP TO THE BLADDER

A 46 year old woman presented with a four month history of vague suprapubic discomfort. This became worse prior to her menstrual period and eased following menstruation. Her periods were regular with a 4/28 day cycle. She had no intermenstrual or post coital bleeding and no dyspareunia. She also complained of irritative bladder symptoms consisting of frequency, nocturia and urgency. There was no dysuria or haematuria. There were no gastrointestinal symptoms. In her past medical history she had had an ovarian cystectomy and had undergone a laparoscopic sterilisation in 1994 using Filshie clips. During this procedure there was good vision of the pelvic organs which were normal and the clips were applied without difficulty to each fallopian tube.

On examination there was mild suprapubic tenderness but nil else of note. Vaginal and bimanual examination revealed marked bladder tenderness, but otherwise was normal. Transvaginal ultrasound scan was also normal. Urine culture and routine bloods including inflammatory markers were unremarkable. At cystoscopy a 2cm round nodule on the dome of the bladder covered with normal mucosa was identified, the remainder of the bladder being normal. The nodule was resected and submitted for histological examination. This demonstrated normal urothelium with early changes of cystitis cystica with mild inflammation of the submucosa with a scattered lymphoid aggregate. There were no granulomata or amyloid deposition and no dysplasia or malignancy. Overall appearances were of nonspecific active chronic inflammation. At review six weeks later she continued to complain of irritative bladder symptoms. Abdominal and bimanual examination revealed bladder tenderness, but no mass was palpable. On the following day she passed a Filshie clip per urethra. Following this her symptoms slowly improved and follow up cystoscopy three months later showed a small scar on the dome of the bladder with a tiny speck of calcification, but with otherwise normal mucosa.

CASE 2 – MIGRATION OF A FILSHIE CLIP TO THE CAECUM MIMICKING APPENDICITIS

A 45 year old woman presented with a two day history of right iliac fossa pain. This started as a sharp constant pain with no radiation, associated with nausea but no vomiting. There were no precipitating factors and she had no lower gastrointestinal, urinary or gynaecological symptoms. Her past history included a ventrosuspension in 1991, excision of benign breast lump in 1992 and laparoscopic sterilisation using Filshie clips in 1994 when omental adhesions in the right pelvis were divided with scissors. Both tubes were visualised and clips applied without difficulty.

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On examination she was apyrexic with a soft abdomen but had focal right iliac fossa tenderness with guarding. There were no palpable masses. Rectal examination revealed tenderness on the right side. Vaginal and bimanual examination were unremarkable and transvaginal ultrasound was normal. Urinalysis was unremarkable and a pregnancy test was negative. Routine blood results including white cell count and inflammatory markers were normal. She was treated expectantly, however as her pain failed to settle she had a laparotomy, where it was noted that a Filshie clip had become detached from the right fallopian tube and was eroding into the caecum causing surrounding induration. The clip was removed and a routine appendicectomy performed. The patient made an uncomplicated recovery and was discharged on the second post-operative day. Histology demonstrated that she had a normal appendix and a hysterosalpingogram performed six weeks later confirmed that the right Fallopian tube remained occluded (*Figure 1*).

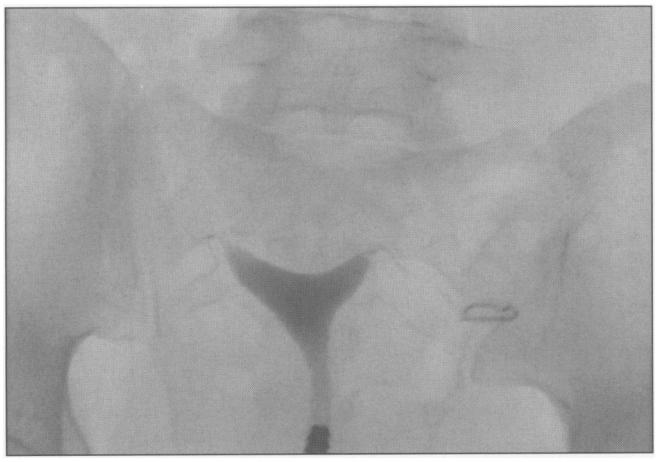

Fig 1. Hysterosalpingogram showing a closed Filshie clip on the left with an absent clip on the right. The right tube remains occluded.

DISCUSSION

Tubal occlusion is the most common method of contraception accounting for over one third of contraceptive use worldwide.[1] In 2002, 21% of women aged 45–49 in Great Britain used female sterilisation as their chosen method of contraception.[2] There were an estimated 47,268 tubal occlusions performed in England in 1999.[3]

The use of Filshie clips for laparoscopic tubal occlusion has become more popular since the 1980s and is the most widely used method in the United Kingdom being used by 82% of gynaecologists.[4] The Royal College of Obstetricians and Gynaecologists have recommended mechanical occlusion of the fallopian tubes by Filshie clips (or rings) as the method of choice for laparoscopic tubal occlusion as they are safe and technically straightforward with a failure rate of 2 - 3 per 1000 women at ten years.[5] They also destroy a shorter length of the tube and therefore potential reversal is more likely to be successful.[5]

Filshie clips are made from titanium with a silicone rubber lining between the jaws.[6] It achieves sterilisation by being placed across the whole width of the isthmic portion of the tube 1 - 2cm from the cornu.[5] This causes occlusion of the lumen and eventual avascular necrosis. The tube divides leaving two healed but occluded ends. The Filshie clip usually remains attached to the site of tubal separation and becomes peritonealised, causing few further problems. If there is a delay in peritonealisation, the clip may become detached and settle in other areas of the abdominal cavity.[7]

A number of cases of migration of Filshie clips have previously been described. These episodes have happened between ten months and seven years following sterilisation.[7-13] In these cases, clips have either been passed with few symptoms via the urethra, vagina or rectum[7,8] or caused symptoms due to a local inflammatory process or abscess formation.[10-13] One case presented as appendicitis due to obstruction of the appendix lumen with a Filshie clip.[9] The women in both cases presented here were symptomatic. One presented with irritative bladder symptoms and the other with right iliac fossa pain.

In the first case, the symptoms were due to inflammation of the bladder. These started four months prior to presentation and seven months before bladder resection. The histology showed cystitis cystica with a chronic inflammatory infiltrate in the submucosa. This confirms the hypothesis that clip migration is likely to be due to a low grade inflammatory process.[7] Given that there was likely to be an asymptomatic period of clip erosion and that resection of the bladder nodule would have hastened clip erosion, the total time of migration through the bladder wall is likely to be over one year, clearly a chronic process. It is unlikely that clip misapplication plays a significant role, as in these and previous cases,

there is little documented difficulty at laparoscopy, there have been no reported sterilisation failures in association with clip migration and when tests of tubal patency have been performed, these confirm tubal occlusion (*Figure 1*).

In the second case, the symptoms were short lived and due to inflammation of the caecum. This suggests that the erosion into the caecum was a recent event and this was confirmed at surgery as there was only superficial erosion of the caecal wall with surrounding inflammation. As there was no perforation or serious sequelae, the clip was simply removed without resection of the bowel wall. This was unfortunate from a scientific point of view as this could have provided information on the histological changes during the early stages of migration. The reason for surgery in this patient was the inability to exclude appendicitis. If her symptoms had not been on the right side, conservative treatment may have been appropriate. As there have been no reported cases of significant morbidity such as perforation or fistula formation in association with clip migration, the pain in her case may have settled and the clip could have passed asymptomatically via the rectum some time later as has been previously described.[8]

Laparoscopic tubal occlusion with Filshie clips remains the most common method of female sterilisation in the UK, being performed safely with few complications. This report adds to the small body of evidence regarding migration of Filshie clips. As well as demonstrating migration up to ten years following sterilisation and a case of migration to the caecum, the histological evidence of chronic inflammation indicates that this plays a role in the mechanism of clip migration.

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Ulster Med J 2005; **74 (2)** 129-131

Case Report

Cocktail Stick Injuries – the Dangers of Half a Stick

R Lindsay, J White, E Mackle

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INTRODUCTION

Cocktail sticks are widely recognised items used in both oral hygiene and in food preparation. We report two cases in which injuries were sustained by ingestion of one half of a cocktail stick. We wish to highlight the dangers associated with the use of half a cocktail stick, emphasising how easily accidental ingestion can occur.

CASE 1 A 68 year old lady presented to the Accident and Emergency department with a history of coughing and vomiting after possibly choking on half a cocktail stick at a party. She was unsure whether the stick had been swallowed or not. A chest

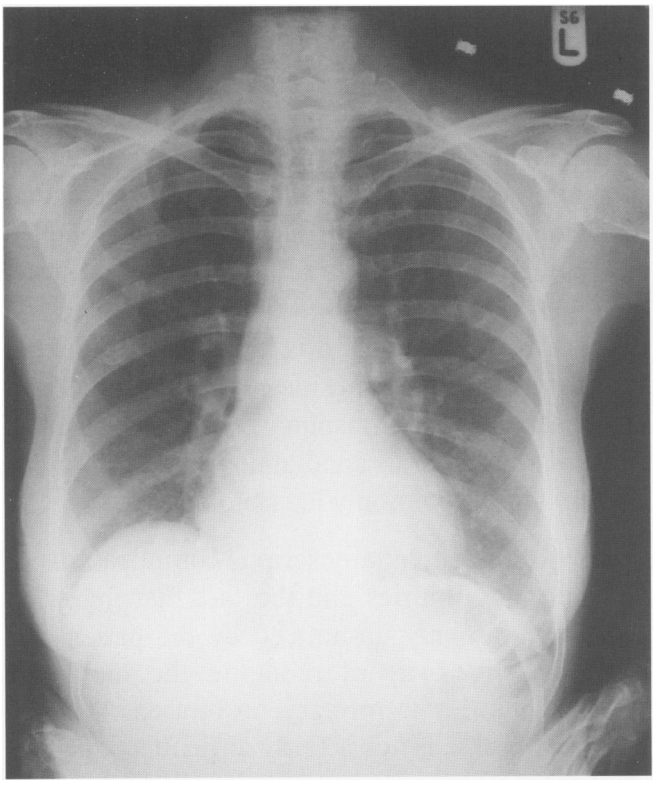

Figure 1

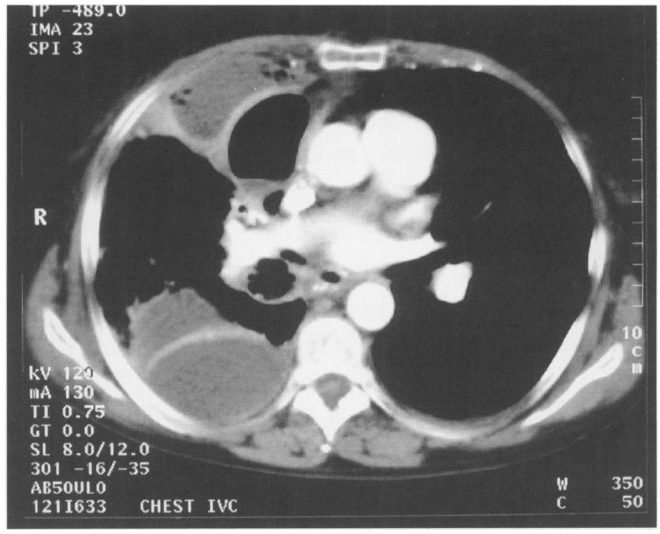

Figure 2

X-ray was performed, and proved to be normal, and she was discharged.

Three days later she developed a productive cough with dyspnoea and right-sided pleuritic chest pain. She attended Accident and Emergency once more: she was noted to be in fast atrial fibrillation and was admitted to hospital with a presumptive diagnosis of right basal pneumonia. A chest X-ray was again performed and appeared normal (*Figure 1*). Antibiotic therapy was commenced, but her condition

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did not improve. Five days after admission, another chest X-ray showed a right sided pleural effusion and pneumomediastinum suggestive of oesophageal perforation. A CT scan of the chest confirmed a distal oesophageal perforation with a right-sided empyema (Fig 2). At thoracotomy, a fragment of cocktail stick was discovered at the site of perforation. A T-tube was placed across the perforation to allow external drainage and the right lung was also decorticated. The post-operative course was slow but uneventful. The T-tube was removed after 14 days. A follow-up contrast study confirmed that the oesophageal perforation had sealed. The patient remained well 6 months after surgery.

CASE 2 A 61 year old man was referred with a 5 month history of lower abdominal pain and passage of blood and mucus per rectum. Digital rectal examination was normal. A barium enema was performed and showed a stenosing "apple core" lesion at the rectosigmoid junction typical of an adenocarcinoma (Fig 3). At laparotomy, the sigmoid colon was found to be inflamed and adherent to the caecum. The sigmoid was mobilised and one half of a cocktail stick was discovered to be penetrating through the colonic wall at the site of a diverticulum. A sigmoid colectomy was performed and the patient's post-operative recovery was uneventful; histopathology confirmed the presence of an inflammatory mass associated with a localised perforation in an area of diverticular disease, with no evidence of dysplasia or malignancy. The patient had no recollection of ingesting the cocktail stick. He remains well 6 months after surgery.

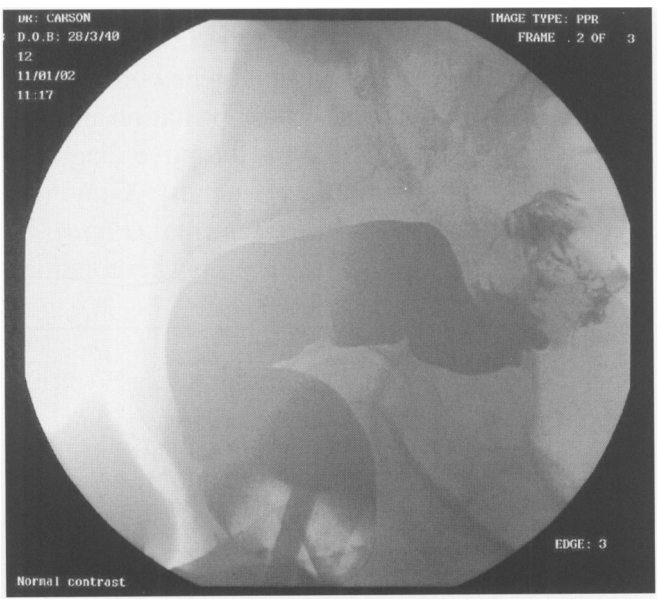

Figure 3

DISCUSSION

The dangers of ingestion of these items have been described in the international literature before, with North American authors preferring the term "toothpick" over the British "cocktail stick". We present the cases above to bring attention to the dangers posed by the use of the half-cocktail stick in the preparation of food. Injury from accidental cocktail stick ingestion has been described in every part of the gastrointestinal tract, including the anus,[1,2] and sites of perforation may mimic gastrointestinal malignancy or inflammatory bowel disease. Cocktail sticks have also been associated with hepatic abscess formation[3,4] and development of aortoenteric or duodeno-caval fistulae.[1,5-7]

A number of risk factors for accidental ingestion of a cocktail stick have been identified: recent alcohol ingestion, wearing dentures, ingestion of hot or cold liquids and rapid ingestion of food.[1,8] It seems likely that altered oral sensation or inattentiveness to the act of swallowing may allow accidental ingestion to occur unnoticed, and only 12% of patients who present with injuries remember swallowing them.[9] In a review of the literature Li and Ender,[9] found that the maximum reported interval between the ingestion of a cocktail stick and presentation with related symptoms was fifteen years. All these factors mean that a cocktail stick injury may not be suspected in a patient who presents with symptoms some time after an unremembered episode of accidental ingestion. This difficulty in diagnosis is compounded by the inability of plain radiology to demonstrate the ingested cocktail stick, which is typically made of wood or plastic and so is radiolucent. Cocktail sticks may be sometimes detected on CT,[10] small bowel series[11] and ultrasound,[12] but most cases of cocktail stick injuries are diagnosed at exploratory surgery, most commonly laparotomy (53%).[9]

In light of the potentially serious complications of cocktail stick injuries and the fact that ingestion is most commonly un-noticed by the patient the most effective way of reducing the incidence of these injuries is primary prevention. While a complete cocktail stick is fairly difficult to ingest by accident, half a stick may occasionally be ingested unknowingly, with serious results.

We suggest that the use of the half-cocktail stick in food preparation should either be abandoned or the consumer alerted to its presence as a first step in the primary prevention of these injuries. In the absence of such measures, it seems likely that the accidentally ingested cocktail stick will continue to provide a rare surprise finding at operation.

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Case Report

Solitary caecal diverticulitis – a rare cause of right iliac fossa pain

FA Abogunrin, N Arya, JE Somerville, S Refsum

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INTRODUCTION

Caecal diverticulitis, although relatively uncommon in the western population, presents an interesting diagnostic dilemma.[1] The clinical presentation usually is similar to acute appendicitis.[2, 3] Intra-operatively, solitary caecal diverticulitis may be difficult to distinguish from granulomatous disease or carcinoma.[1, 4] We report a case of solitary caecal diverticulitis that presented with clinical features suggestive of acute appendicitis.

CASE REPORT A 20-year-old Caucasian male presented with a 14-hour history of right lower abdominal pain associated with anorexia and low-grade pyrexia. Clinical examination revealed localised tenderness and guarding in the right iliac fossa. White cell count was slightly elevated at 12 x 10^9/L, with C-reactive protein raised to 54 mg/L (Normal 0-10 mg/L).

He was operated on with a clinical diagnosis of acute appendicitis. The appendix was retrocaecal in position, but normal. There was an indurated, thickened and raised 4 x 4cm area on the anterior wall of the caecum. Mobilisation and palpation of the caecum suggested the diagnosis of a caecal diverticulum with inflammation. Due to the proximity of the caecal diverticulum to the ileo-caecal valve, a limited ileo-caecal resection with ileo-colic anastomosis was carried out. The post-operative period was essentially uneventful, and he was discharged home on 7th post-operative day.

Histology showed a solitary caecal diverticulum lined with colonic type mucosa, which had become ulcerated and inflamed with overlying serosal exudates (*Figure*). The appendix was normal.

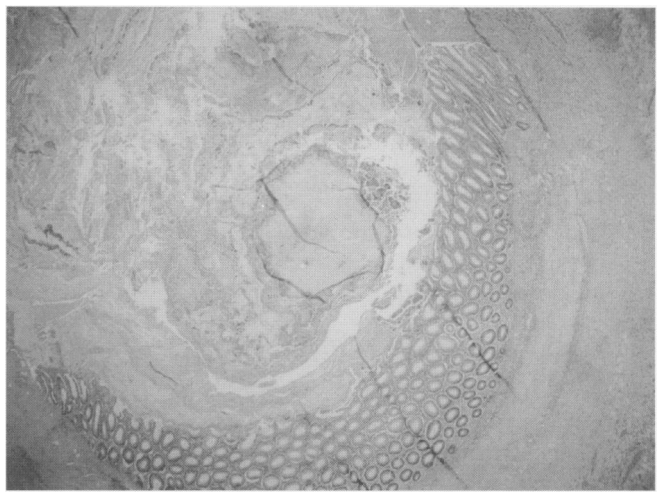

Fig. Caecal diverticulum with ulceration of the mucosa and transmural inflammation.

DISCUSSION

Caecal diverticular disease is more common in the far eastern Asian population, and usually occurs as a part of diffuse right-sided diverticular disease. Solitary caecal diverticulum is relatively uncommon and the precise aetiology is unknown.[2, 4] Most are thought to be congenital in origin and contains all the layers

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of the colonic wall.[5] However in patients presenting with caecal diverticulitis, the histological picture may be distorted because of the inflammation and necrosis affecting the wall of the diverticulum.

Eighty percent of all solitary caecal diverticulum are located about 2.5cm from the ileo-caecal junction, and about 50% are found on the anterior caecal wall.[5] The commonest clinical presentation arises from inflammation of the caecal diverticulum.[3] Other complications include perforation, haemorrhage and torsion.[2,3]

Acute appendicitis is the commonest misdiagnosis made in cases of caecal diverticulitis because of the similarity in the presenting symptoms and signs.[1,2] The average age of presentation in most series is in the early to mid forties (ranges from 20 to 51 years), about 10 to 20 years younger than the average age of presentation of left sided diverticulitis.[1] Patients usually present with right iliac fossa pain, associated with pyrexia, nausea and anorexia. Most patients have leucocytosis, but a palpable mass is uncommon.

Contrast enhanced CT scan is the most useful investigation for pre-operative diagnosis.[6] Diagnostic features include preserved enhancement pattern of the thickened caecal wall, extra-luminal mass, associated with haziness and linear stranding of the peri-caecal fat. Ultrasound scan is not very sensitive, and may show a hypo-echoic focus on a segment of the thickened caecal wall.[6] Barium enema is not a useful investigation during the acute presentation, as the caecal diverticulum is usually not visualised because of obliteration of the lumen caused by inflammation and edema.

Patients can be treated conservatively with antibiotics if a confident pre-operative diagnosis is made.[4] However, in most patients the diagnosis is made intra-operatively, when these patients are operated on with a presumptive diagnosis of acute appendicitis.

During operation, the caecum is fully mobilised for a closer inspection of the caecum. It is usually possible to palpate the ostium or faecolith after invaginating the opposite caecal wall, which helps in confirming the diagnosis .[1] If a confident intra-operative diagnosis can be made, surgery should be conservative in the form of diverticulectomy or invagination of the diverticulum and appendicectomy or a limited ileo-caecal resection.[3,4,5] Right hemicolectomy carries a higher morbidity and mortality and should be carried out only if malignancy cannot be excluded or there is extensive local inflammation associated with perforation of the caecal diverticulum.

Our case report illustrates the importance of being aware of caecal diverticulitis as a differential diagnosis. Conservative surgical treatment is usually sufficient in the management of these patients if the diagnosis is made during the operation.

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Letter to the Editor:

Hepatic Penetration of a Single Large Duodenal Ulcer

(Accepted 25th July 2005)

Sir,

We present a rare case of erosion of a duodenal ulcer into the liver in a gentleman with few risk factors for peptic ulcer disease (PUD) and on long term protium pump inhibitor (PPI).

PRESENTATION AND MANAGEMENT

An 85 year old male, who had been on omeprazole for 18 months, was admitted with sub acute small bowel obstruction of 2 weeks duration. His past medical history was Type 2 diabetes mellitus and warfarin for atrial fibrillation. Prior to commencement of omeprazole, he had been investigated for weight loss with positive faecal occult blood test positive, an oesophago-gastro-duodenoscopy (OGD) which revealed a very mild streaky gastritis and negative H. pylori test, and a complete colonoscopy that showed three histologically confirmed metaplastic polyps. He had no history of PUD, was not on NSAID's or steroids, smoked about 15 cigarettes / day and drank alcohol occasionally.

He subsequently developed acute small bowel obstruction necessitating an emergency laparotomy and was found to have an obstructing caecal tumour; a right hemicolectomy and ileocolic anastomosis was performed. Histology confirmed an adenocarcinoma. On post operative day fifteen he started passing moderate amounts of melena; there were no features suggestive of an acute abdomen. He was still haemodynamically stable and liver function tests essentially normal though haemoglobin had dropped from 10g/dl to 8g/dl by the next day when he had an OGD. A deep copiously bleeding ulcer approximately 2cm in diameter was found on the anterior wall of the first part of the duodenum.

A laparotomy was performed after unsuccessful attempts at injection with adrenaline. The ulcer was then found to have deeply eroded into the posterior surface of the medial inferior segment of the liver. This bleeding defect was adequately controlled by figure-of-eight liver stitches but he suddenly became hypotensive from a myocardial infarct, failed to respond to resuscitative measures and died intra-operatively.

DISCUSSION

Most perforations of a duodenal ulcer into the liver are 'silent' with absent or minimal abdominal pain.[1] Diagnosis may be by histological examination of endoscopic biopsies[2] but most only become only obvious at laparotomy or autopsy.[3]

PPIs are the most effective drugs for the suppression of gastric acid production;[4] in duodenal ulcers, omeprazole 20mg daily produced healing rates of 90 – 100% after 4 weeks.[5] PPIs are also efficacious in prevention of bleeding from stress ulcers.[6]

Possibilities in this unusual case are that the ulcer was missed during the initial OGD, that he developed a fresh ulcer despite PPIs, or that this was a case of a single large penetrating stress ulcer. Since in any case PPIs were meant to be effective, this may have been case of resistance to omeprazole. Claessens *et al* identified previous use of PPIs, heavy smoking and age over 60 years as factors consistently associated with non response to PPIs.[7] This patient had all three.

CONCLUSION

Resistance to PPIs is uncommon[7] but may occur in the elderly smoker post major surgery, leading to potentially serious complications.

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Abstracts

Meeting of the Ulster Society of Internal Medicine, Friday 20th May 2005

Postgraduate Centre, Craigavon Area Hospital

PROGRAMME:

2pm Welcome

2.15 to 3.10pm Presented Abstracts

3.10pm Invited abstract:

"NICAM: the flagship managed clinical network. Dr Gerard Daly, Consultant Respiratory Physician, Altnagelvin Area Hospital

3.30 Afternoon Tea

3.45pm Business Meeting

3.55pm to 4.45pm Abstracts

4.45pm Guest Lecture:

"Emerging treatments for advanced lung disease". Dr J Egan, Consultant Physician, Mater Hospital Dublin

ABSTRACTS

ACUTE PARALYSIS AND HYPOKALAEMIA IN A CAUCASIAN MAN: A CASE OF THYROTOXIC PERIODIC PARALYSIS

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A 37 year old man presented to the A+E department after he awoke unable to move his torso or limbs. There were no obvious precipitating factors and no history of viral illness.

On admission pulse was 100 bpm, blood pressure 130/84 mmHg. He had a flaccid quadraparesis with diminished reflexes, down-going plantars but no sensory deficit. ECG showed a prolonged QT interval. A blood gas sample showed hypokalaemia (1.6mmol/L) with no acid-base disturbance and normal blood gases. He had no history of recurrent vomiting or diarrhoea, and urinary biochemistry was not suggestive of excessive potassium loss.

After treatment with 80mmols of iv [K] over 5 hours his muscle weakness resolved but [K] rebounded to 5.8mmol/L. Endocrine assessment revealed a history of weight loss of 16kg in the preceding months, sweating episodes, heat intolerance, tremor and fatigue. Examination revealed a fine tremor, lid lag and a moderate goitre. Free thyroxine was >80pmol/L and TSH <0.01mU/L. A diagnosis of thyrotoxic periodic hypokalaemic paralysis was made. He was commenced on carbimazole and propranolol. Serum [K] remained within normal limits and he was discharged 4 days later with arrangements for radioactive iodine treatment.

Thyroid periodic paralysis (TPP) is a rare but potentially life threatening condition. Hypokalaemia results from intracellular potassium shifts. Potassium treatment should be carefully monitored as rebound hyperkalaemia is recognised. The mechanism of TPP is uncertain but hyperthyroidism is associated with activation of the sodium-potassium pump. The cornerstone of treatment is restoration of the euthyroid state.

DISSECTING AN UNUSUAL CAUSE OF AN ST SEGMENT ELEVATION INFARCTION (STEMI)

PM Donnelly, JDS Higginson, D Cochrane, S McMechan

Cardiology Department. Ulster Hospital.

A 64 year old lady presented acutely with severe central chest pain radiating to her left arm. There was no previous cardiac history, however multiple

risk factors for coronary disease were noted including hypertension, hypercholesterolaemia, positive family history and an ex-smoker of 12 years. The ECG characteristics of 2mm ST segment elevation across the antero-septal leads resulted in a diagnosis of acute myocardial infarction and the administration of thrombolytic therapy. The ECG appearance resolved with deep T wave inversion in the anterolateral leads. A maximum CK-MB rise of 114 U/L was recorded. Her in-patient course was complicated by further chest pain and a catheter angiogram was performed. This revealed a dissection of the left anterior descending coronary artery (LAD). As follow on intervention was thought inappropriate, a conservative management strategy was adopted. Within the next eight weeks this patient was re-admitted twice with ongoing troponin negative exertional chest pain. A repeat catheter angiogram confirmed resolution of the LAD dissection and the presence of a flow limiting obstruction in the distal LAD at the site of the healed dissection exit point.

Spontaneous coronary artery dissection (SCAD) is a rare cause of myocardial infarction. The true incidence is unknown and most cases (>70%) are identified at post mortem. It is thought that there are three different groups of patients that present with SCAD namely those with pre-existing coronary disease, women in the third trimester of pregnancy or in the early post partum period and an idiopathic group. The presentation can range from minor chest pain to myocardial infarction or sudden cardiac death. The pathogenesis is not fully understood and the mechanisms that have been proposed have resulted in confusion as to how these patients should be treated. Effective management depends on several factors such as the site of the dissection, single or multi-vessel involvement, coronary blood flow and the haemodynamic state of the patient. Conservative treatment, namely low molecular weight heparin, aspirin, beta blockade and time are effective for most patients. For patients with multi-vessel or left main stem dissection, impaired coronary blood flow or haemodynamic instability, percutaneous coronary intervention or coronary artery bypass surgery is considered the treatment of choice.

SCAD is an unusual cause of an STEMI. This case demonstrates the difficulties encountered in the diagnosis and management of coronary artery dissection. A greater awareness of its existence, particularly in young females, coupled with an early catheterisation strategy would optimise the management of this condition.

ASSOCIATION OF BACE WITH LATE ONSET ALZHEIMER'S DISEASE

A Keown, S Todd, S McIlroy, P Passmore

Department of Geriatric Medicine, The Queen's University of Belfast.

Background: ß-site Amyloid Precursor Protein (APP) Cleaving Enzyme (BACE) is the rate-limiting step in ß-amyloid (Aß) formation generating the N-terminal of the Aß peptide by cleavage of APP. Utilising a case-control study design we investigated if a polymorphism in the gene coding for BACE was associated with risk for late-onset Alzheimer's disease (AD).

Methods: DNA was extracted from a total of 263 cases and 217 age and sex matched controls from Northern Ireland (NI). Primers were designed to amplify a single nucleotide polymorphism (SNP) corresponding to NCBI cluster ID rs638405. This is a synonymous change coding for valine with either polymorphic allele. Polymerase chain reaction (PCR) products were subjected to restriction enzyme digestion by MboI and separated by polyacrylamide gel electrophoresis and visualised by silver staining.

Results: The CC genotype was present at a higher frequency in AD patients compared to controls (OR 1.84, 95%CI 0.99-2.72, χ_=4.17, p=0.041). The presence of the C allele was associated with an increased AD risk (OR 1.32, 95%CI 1.01-1.73, χ_=4.46, p=0.035).

Conclusions: This SNP is associated with increased risk for AD in the NI population.

PREDICTORS OF EXCESS MORTALITY AFTER MYOCARDIAL INFARCTION IN FEMALES.

J Neill, CG Owens, AAJ Adgey

Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, United Kingdom.

Background: Research suggests that women have higher mortality after acute myocardial infarction

(AMI) than men. Potential factors to explain this disparity include delay to presentation, less aggressive interventional strategies, and more severe disease at coronary angiography in women.

Methods: Consecutive patients (n=426) presenting to coronary care in the Royal Victoria Hospital between Jan 2002 and Jan 2004 with chest pain and AMI (troponin T >0.09ng/ml) were recruited. The following were recorded: risk factors; delay factors in presentation and treatment; infarct site and left ventricular function; coronary artery disease (CAD) extent; treatment (medical and interventional). The primary endpoint was 3 month mortality.

Results: Of the 426 patients, 30% (128/426) were female. Mean age of females was 71 (SD 11) and 63 (SD13) for males (p<0.001). Men and women had similar delay factors, risk profile, infarct site, CAD extent and frequency of LV impairment (EF <45%). Females received less clopidogrel (77%, 98/128 vs 87%, 258/296, p=0.008) despite more frequent NSTEMI presentations in women (51%, 65/128 vs 41%, 121/298, p=0.05.) Women did not undergo angiography as frequently as men (63%, 80/128 vs 75%, 225/298, p=0.006). Greater 3 month mortality in females was confirmed (15%, 19/128 vs 6%, 17/298, p=0.004.)

Predictors of 3 month mortality by logistic regression were delay in presentation, CAD extent and not receiving clopidogrel (p=0.004).

Conclusions: Females had excess three month mortality compared with males. No gender difference in delay factors or severity of disease was observed. Women were less likely to receive clopidogrel and to proceed to angiography and revascularization than men. This may be clinically appropriate given the advanced age of the females.

AN AUDIT OF COMPLIANCE OF PATIENTS ATTENDING AN OUT-PATIENT OSTEOPOROSIS SERVICE

CM McVeigh, M McQuilkin, C McNally, C Williams, SA Wright, T Beringer and MB Finch

Musgrave Park Hospital, Belfast, Northern Ireland.

Background: More than one-third of women will sustain one or more osteoporotic fractures in their lifetime. Anti-resorptive therapies have been shown to considerably decrease fracture risk, however this may be compromised by non-compliance.

Objective: Our aim was to establish levels of compliance with anti-resorptive therapy over an 18 month period in patients attending an out-patient osteoporosis service.

Methods: 126 patients were recruited from both consultant/nurse led and GP/nurse led clinics. Patients were identified as osteoporotic or osteopenic on DXA and prescribed appropriate treatment. Telephone interviews were conducted at 3, 12 and 18 months. Information recorded included knowledge of medications, adverse effects, and overall compliance with medication.

28% of total patients were non-compliant at 3 months. 64% of those who were non-compliant had experienced adverse effects and were changed to an alternative drug. Compliance in this group after a further 18months was 83%.

11% of total patients were found to be non-compliant at 12 months. 71% of these then changed treatment groups and compliance after a further 18 months was 90%.

76% of non-compliant patients cited adverse effects as the reason for non-compliance.

Conclusion: The majority of non-compliant patients were identified at 3 months with adverse effects reported as the commonest cause. Most of these patients prescribed other osteoporosis treatments at this stage then remained compliant at 18 months. As a result we propose that our nurse specialist carry out telephone reviews at 3 months to improve compliance in these patients.

IS SER9GLY POLYMORPHISM OF DOPAMINE D3 RECEPTOR RELATED TO TARDIVE DYSKINESIA?

B McGuiness

Introduction: Tardive dyskinesia (TD) is an involuntary movement disorder. It occurs in 20-30% of schizophrenic patients. Several groups have shown that a Ser9Gly DRD3 gene polymorphism is associated with risk for TD where either the G/G genotype or glycine allele has conferred elevated risk. Other studies, however, have not replicated this finding.

Aim: To determine if the presence of the Ser9Gly DRD3 gene polymorphism was associated with increased risk of TD in schizophrenic patients.

Methodology: From 580 cases a subsample of 87 individuals were analysed, including 79 trios, 6 quads and 2 quins. Blood was genotyped for the presence of allele 1 (Ser-9) and allele 2 (Gly-9) of the polymorphism. The transmission disequilibrium test was applied to look for preferential transmission. A logistic regression analysis was then carried out on 338 singletons.

Results: 29% of patients were TD positive, 71% TD negative. We found no significant genotypic association of the Gly/Gly genotype with TD (P=0.51, Fisher's exact test) nor any significant allelic association (χ_=1.39, d.f.=2, P=0.50). The transmission disequilibrium test was not significant (P=0.84).

With regard to singletons, only age contributed significantly to presence of TD. (p=0.05).

Conclusion: We found no significant association between DRD3 genotype and presence of dyskinesia. Age was the only positive predictor of presence of TD.

A CHALLENGING CASE OF SYSTEMIC SCLEROSIS

LJ Shiels, GK Meenagh, MB Finch

Musgrave Park Hospital.

We report a 57 year old woman who presented with a 4 month history of arthralgia, myalgia, an erythematous rash over the inner thighs and symptoms suggestive of Raynaud's phenomenon. Past medical history included well controlled hypertension (on atenolol and bendrofluazide).

Clinically she had waxen skin on the peripheries and dilated digital capillary loops together with a livedo-like rash. Haematological and biochemical profiles were initially normal. Auto-immune screen was also entirely normal. Punch skin biopsy revealed appearances consistent with scleroderma. Oesophageal manometry, pulmonary function testing and echocardiography were all normal. There was rapid progression of skin tethering. Due to the acute nature of this presentation of scleroderma investigations were performed to exclude underlying malignancy including chest x-ray, CT scan of chest, abdomen and pelvis and breast mammography. No abnormalities were discovered.

Two months following diagnosis this patient was found to be profoundly anaemic (Hb 6.5g/dL) and a subsequent OGD showed gastric antral vascular ectasia (GAVE syndrome) which is associated with scleroderma. During an admission for elective repeat OGD acute uraemia was discovered accompanied by marked hypertension and pruritis. Acute sclerodermal renal crisis ensued shortly thereafter necessitating emergency haemodialysis together with regular haemodialysis. Immunosuppression therapy was initiated with caution (cyclophosphamide orally). This was discontinued within 5 weeks due to marked neutropenia which was felt to be drug induced and both captopril and cyclophosphamide were discontinued. Captopril was replaced with alternative anti-hypertensives. Shortly afterwards acute hypertensive crisis arose with focal neurology and widespread ischaemic changes on CT brain.

This case highlights the clinical spectrum of scleroderma and the dilemma of medical management in the face of specific complications.

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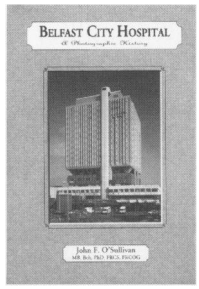
Book Reviews



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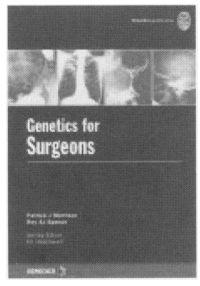

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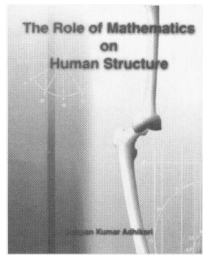

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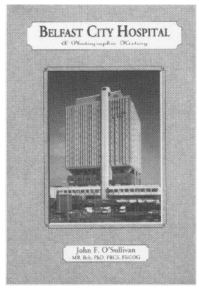

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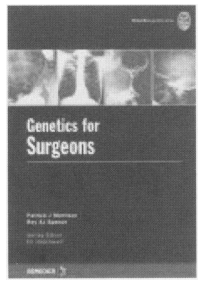

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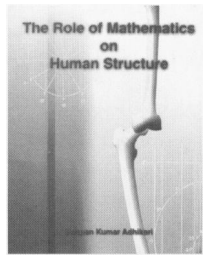

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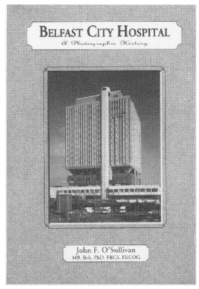

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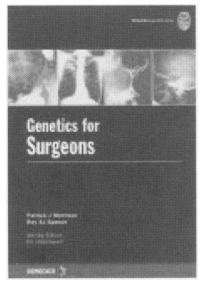

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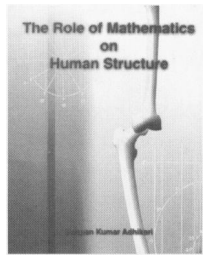

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Adhikari's book is entitled: "The Role of Mathematics on [sic] Human Structure". This might lead the reader to expect a review of the history of mathematical treatment of the human form, and, indeed, a brief flick through the pages will turn up such luminaries as Descartes and da Vinci. However, hopeful expectation is not fulfilled. Adhikari presents a series of papers (preceded by very brief abstracts) apparently intended to demonstrate how some pure mathematical principles may be applied to the human organism. The first paper is essentially a brief distillation of the life of Leonardo da Vinci, with allusion to his work on the mathematics of anatomy. I was surprised to find no mention of Leonardo's most iconic anatomical work: the Vitruvian Man (penned in around 1490). This is surely the supreme example of the mathematicisation of anatomy, although it is more a depiction of Leonardo's mathematical "ideal", rather than evidence of any fundamental insight into real human biology. Leonardo derived his picture from the canon of proportions set down by the Roman architect Vitruvius in the 1st century BCE. The "perfect man" stands in two superimposed poses, enclosed in a square, defined by the equality of his height and armspan. In the first pose, his legs are straight, and arms outstretched. In the second pose, he stands in a circle, centred on his navel, with a radius defined by the distance from the navel to the end of his spread-out legs. The arms in this pose are shown elevated to the same height as the top of the head, and the middle finger meets the circumference of the circle. All fits neatly within a clearly-defined mathematical structure. I don't know if I've ever met anyone who would actually fit precisely into such a scheme, but its power as an image is undiminished.

Adhikari correctly identifies some of the key engineering aspects of the human skeleton, and presents a host of complex equations to describe them. These do not, however, help to explain things (other than in a very general and purely post-hoc sense), nor do they elucidate any non-obvious "role" mathematics might play in treating their pathology. Where the lid really flips is in discussion of the pineal gland - favoured organ of Descartes. Adhikari garners numerous equations in an apparent attempt to explain something about this enigmatic little brain structure, but nowhere tells us what it is, or what it does. Its location is described, but in highly technical neuroanatomical terms lifted straight from an old 1989 edition of Gray's Anatomy. Adhikari bemoans the fact that modern neuroanatomy has demolished Descartes' claim that the pineal is the "origin" of the brain, while it has apparently failed to declare an alternative location. However, the need for such an "origin" in the first place is not clear; the brain is a complex system, and does not have one single controlling centre. There is no "seat of the soul".

The chapter on the heart is no more uplifting. Various equations are again pressed into service and littered with diagrams lifted from Gray's, and of debatable relevance to the text. Chemical explanations of myoglobin and haemoglobin are impenetrable, and (in several cases) factually inaccurate. In one section, the term "neoplastic" is defined as "repairing by plastic surgery or infectious disorders or Latrogenic [sic], Neurosis or Physical disorders"! And so it continues, with little in the way of a thematic thread to bind the whole confused mess together. The text is crammed with spelling and grammatical errors, and is poorly and inconsistently referenced. It is often difficult to tell where quotes end and the author's interpretation begins. The readability of the text is further hampered by inappropriate capitalisation, as well as lengthy parenthesisations, where footnotes would have been more appropriate.

But what of mathematics itself? It seems odd that a book which purports to exalt the role of mathematics in medicine and anatomy should miss some of its most beautiful and elegant applications. There is no mention of that most iconic mathematico-molecular image in medicine - the double-helix of DNA. Similarly, the discipline of bioinformatics is not mentioned, nor is the burgeoning field of the application of supercomputing resources to medical problems. The whole area of medical statistics is ignored. For a book published in 2003, this is puzzling to say the least.

Adhikari is right about one thing: the understanding of human biology can be dramatically enhanced by the application of mathematical knowledge. Having said that, people are not simply equations (or if they are, they're very complex ones). Our mathematical descriptions are approximations to the real situation at best. But, given that we have all these mathematical insights into the function of the human organism, it would, presumably, be appropriate to enquire as to the source of this supreme mathematical order. The discovery of the mechanism of evolution is arguably the most important biological discovery in history. Evolution is alluded to, but largely glossed over. This is a pity, because it offers an extremely rich vein of mathematical application. Theodosius Dobzhansky famously remarked that "nothing in biology makes sense, except in the light of evolution". Unfortunately, very little in Adhikari's book makes sense at all.

SHANE McKEE

Erratum

There were two errors in the article: Hood JM. If I can see so far. *Ulster Med J* 2005; **74(1):** 33-42.

1. Page 41, para 8, the penultimate line "eg PPOSUM" should have read
   "e.g. P-POSSUM"

2. Page 42, para 1 line 14, 'retirement of Professor AAB Barros D'Sa in the year 2000' should have read:

   "retirement of Professor AAB Barros D'Sa in the year 2002"

   We thank Prof Aires Barros D'Sa for drawing these errors to the attention of the journal.