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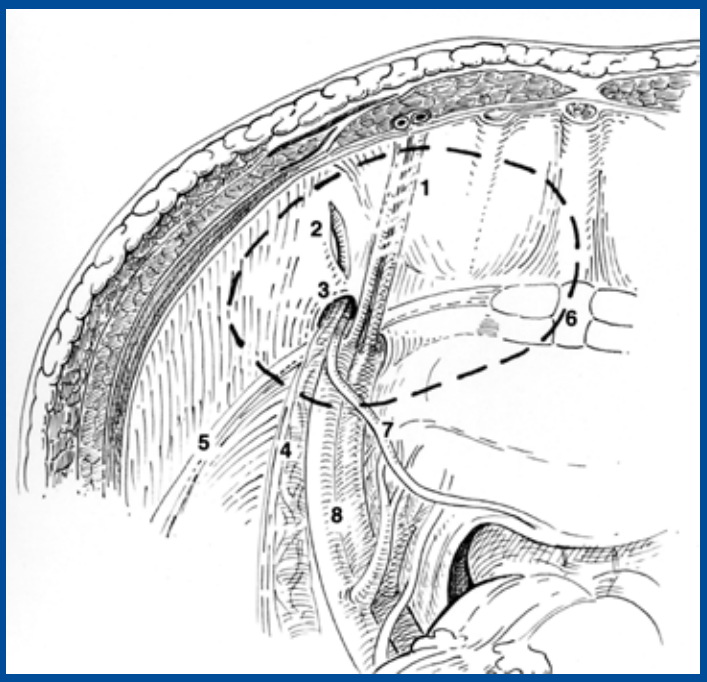

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Editorial

Treatment of bacterial infections

This issue of the journal has again a theme - that of diagnosis and treatment of infection in its various guises. It is not that long since a simple cut or abrasion could result in overwhelming septicaemia and death due to lack of suitable treatment by antibiotics – which today we all take for granted. Hedley-Whyte and Milamed nicely illustrate the progression of treatment of pneumonia over the years with the development of sulpha drugs and later penicillin. Several of the key players involved in pioneering the treatments were linked to Belfast medicine in various ways[1]. Pneumonitis is not always bacterial and may rarely be caused by viral infections such as Epstein Barr virus[2] or by tuberculosis (TB). Tuberculosis is again on the increase most recently with the arrival of immigrant workers, so the picture of lung disease changes steadily from decade to decade. In the 2008 Annual oration, Dr Rory Corbett discusses the downside of some dermatology treatments with reactivation of TB and other skin manifestations of systemic disease[3] Two more recent scourges, however, are the rising incidence of drug induced pneumonia, and of antimicrobial resistance to drugs (fig 1)[4]. Cocaine users are increasingly presenting at our emergency departments with characteristic lung findings, and the use of cocaine and other drugs and recent trends show a steady rise in use[5]. Similarly with resistance, Moore and others describe increasing antibiotic resistance to campylobacter gastroenteritis in Northern Ireland and suggest a need for General Practitioners and other medical professionals to be aware of the correct treatments[6]. Perhaps this is one area that will increasingly feature in the reorganised quality and outcomes framework (QOF) as topics are selected in the four countries of the United Kingdom by a new mechanism[7].

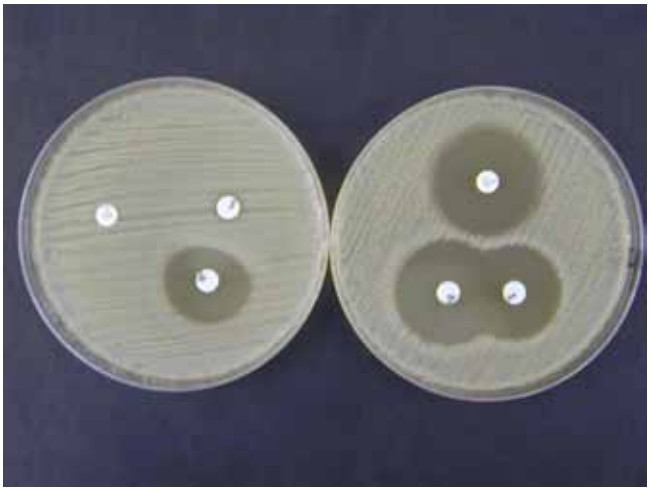

Fig 1. Resistance (left plate) and sensitivity (right plate) to MRSA. Photo reproduced from the Ulster Medical Journal[4]

For one scourge – MRSA – hope is in sight as researchers at Queens University Belfast have identified that ionic liquids possess potent broad spectrum antibiofilm activity so our hospitals may be much cleaner in the near future if a commercial application of such liquids can be developed[8].

Patrick J Morrison, Honorary Editor.

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Ulster Med J 2009;**78(2):**80-81

Commentary

My hero

Andrew CG Uprichard

Accepted 31 March 2009

For the past 28 years I have talked about him, usually when people asked about the patients I treated as a hospital doctor or when asked about heroes. He was an inauspicious man, wrinkled by the years and with lungs which bore witness to decades of smoking. Late one night and after a long weekend on-call, I received a message from admissions telling me of his chest infection and asking where I wanted to send him. Wanting to reserve my acute beds for the more diagnostically challenging cases, I had him admitted to the geriatric ward at the rear of the Lagan Valley Hospital where I was doing my pre-registration house officer rotation in 1981.

When I got around to seeing him, he was sequestered in the corner of a four-bedded side ward with hospital pyjamas and nebuliser in place. I confirmed the bronchopneumonia and continued with my examination. When I got to his legs I was greeted with one gnarled limb that reminded me more of an old and disfigured oak tree. His left tibia had obviously been subjected to devastating trauma and threatened at any point to again poke back through the stretched and shiny skin.

"What's this?" I asked.

"I got that at the Dardanelles," he replied. "On them beaches. Our boys were blown to pieces."

I immediately wished I had listened more during history lessons, but I recalled tales of the western Allies in 1915 sending a massive invasion force of troops to attempt to open up the Dardanelles strait. And how Turkish troops trapped the Allies on the beaches of the Gallipoli peninsula. And how this Battle of Gallipoli had severely damaged the career of a young Winston Churchill, then the First Lord of the Admiralty, who had eagerly promoted the use of Royal Navy sea power to force open the strait, and who had lost his job as a result. Losses had exceeded 25% of the troops sent, including over 4000 Irishmen dead.

The old man went on to describe how the bullets and shrapnel pierced his legs, but how he nevertheless made his way up to the armaments and managed to overcome one of the group of Turks who were decimating his colleagues. He looked down at the bed covers, almost embarrassed.

"Won the VC for that, I did. Sure an' I'm the last surviving Irish World War I VC."

First awarded in 1856 by Queen Victoria to reward acts of valour "in the face of the enemy" during the Crimean war, the Victoria Cross (VC) is the highest award for gallantry for enlisted service people fighting under the Crown (fig 1). The medals are cast from the bronze of the Russian cannons captured in the siege of Sevastopol. A total of 1356 VCs have been awarded to 1353 individuals, too many of which were posthumous. The last awarded was to an Australian for deliberately drawing enemy fire to allow comrades to escape and then rescuing a wounded interpreter during the Afghanistan War in 2008.

"The Victoria Cross?" I asked, "Where is it?"

"The wife has it. At home"

I asked if she could bring it in. He agreed and I walked away, feeling I had just treated a giant of a man. A man who, as a teenager (I had calculated he must have been 16 at the time) had marched up a beach and secured a safe haven for his colleagues in the middle of a bloodbath and despite horrific injuries. My fatigue cleared. I felt larger myself for having met this figure. He lifted me.

The following day when I went to see him, an elderly woman sat by his bed. Her coat was worn and her stockings laddered. Her shoes had seen better days and her hands were the hands of someone who had fought for the right to reach her eighties.

"Show it to the doctor," he said.

She reached into her pocket, pulled out a box and handed it to me. I opened the box and there was the medal. Unassuming. Even dirty. With a purple ribbon and inscribed simply "For Valour". I held it, transfixed, and returned it to the wife.

"Thank you," was all I could say.

My patient eventually recovered enough to go home and I wished him well. Life at the time was taken up with young family, postgraduate exams and plans some day to go to the USA. I forgot his name, but never his scarred legs nor his proud medal.

Years later, when I had moved to the United States and secured a career in the Pharmaceutical industry, when the kids were older and my World War II veteran father had died, I began to think more about my hero. I deeply regretted not remembering his name, for I would have liked to know what happened to him. About a year ago, I heard of a book "Irish winners of the Victoria Cross". At last! My wife managed to secure a copy from some obscure source and I excitedly sat down

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Fig 1. The Victoria Cross. Reproduced with permission from The British Broadcasting Corporation (www.bbc.co.uk/london/content/image_galleries/victoria_cross_gallery.shtml)

and leafed to the section on medals won during the Gallipoli campaign. Of the 36 VCs awarded to Irishmen during World War I, four came out of the Dardanelles, and although all four survived the incident for which they were decorated, one did not survive the campaign and two were killed later in the war.

William Cosgrove was the only Irishman who was awarded a VC in the Dardanelles and survived the war to talk about it. I had my man! But wait – he died in 1936 in London. My search expanded to all Irish World War I VCs, Dardanelles or otherwise: none was alive in 1981. Since my patient was an Ulsterman, I expanded my search to all world war I VC winners. Perhaps he was listed not as Irish but as English. Again, none had survived to 1981. I wrote to the author of the book, hoping that there was a simple explanation. He provided one – there are con artists throughout history who have used the story of war and heroic deeds to gain everything from a free bus ride to a seat at a restaurant table.

So where does this leave me? I still hope for a simple explanation, but it is almost impossible. I contacted the hospital in an effort to get his name, but although National Health staff have better things to do than search records for a list of 83-year olds admitted some time in 1981, they too drew a blank. I later heard that all VCs have the name of the recipient on the back: had I only thought to turn the medal over, I might have caught his game. But why would he have taken the risk? I can only think that the story and this medal (either fake or someone else's) was his way of holding captive the imaginations of those he shared his story with. When he sat at the bar every Friday evening and one of the lads said,

"C'mon, Tommy, tell us the story of how you won yon medal."

And they'd sit transfixed as he described how he won the gun turret single-handed, as he did with me. And I assume his wife loved him enough to play along. He may well have been a World War I veteran, and perhaps even a brave and dashing one who was indeed injured while wearing the uniform. Perhaps his country abandoned him as we do so often the men who come back from war to face an ambivalent population. We may never know the true answer.

I no longer bring him up in conversation when asked "who is the most significant person you have met in your career?", but part of me still wants to believe he was the hero I believed in a long time ago, so I can again glow in remembering when an old man with a bad leg lifted the spirits and imagination of a tired young doctor.

The author has no conflict of interest.

Ulster Med J 2009;**78(2):**82-83

Commentary

Helping to Provide High Quality Care in Primary Care

Michael Rawlins, Val Moore

Accepted 30 March 2009

THE QOF

On 1 April 2009, the National Institute of Health and Clinical Excellence (NICE) took over a new role in advising on new indicators for the NHS Quality and Outcomes Framework (QOF) in the United Kingdom. Confirmation of this change came at the end of a Department of Health consultation with patients, carers, NHS professionals and commissioners on how the process should work. The move is a strong endorsement of NICE's expertise, gained over 10 years of producing evidence-based guidance.

TABLE I:

NICE guidance is a primary source of advice on effective clinical and public health practice in the United Kingdom. It forms part of the healthcare standards in England and Wales and is generally adopted in Northern Ireland but selectively applied in Scotland.

	England	Wales	Northern Ireland	Scotland
Technology Appraisals	✓	✓	NICE guidance is generally disseminated after local review	NICE guidance is generally disseminated after local review
Interventional Procedures	✓	✓	✓	✓
Clinical Guidelines	✓	✓	NICE guidance is generally disseminated after local review	-
Public Health	✓		NICE guidance is generally disseminated after local review	NICE guidance is generally disseminated after local review

A crucial part of the new process is the creation, by NICE, of an independent Primary Care Quality and Outcomes Framework Indicator Advisory Committee, which will review existing indicators and recommend new ones. [The committee will be chaired by Dr Colin Hunter who has worked as a General Practitioner in Aberdeenshire for over 20 years. Dr Hunter takes up his post having already held a number of high profile positions, including Chairman of the Scottish Council of the RCGP (1996 – 2000) and as National Co-ordinator of Primary Care for NHS Education Scotland (1995 – 2005). Dr Hunter was also heavily involved in the original version of the QOF, helping to draw up the original outline scheme for the framework which was then proposed to the profession in 2003.] The membership of the committee, finalised in May 2009, includes individuals with experience of primary care, (including GPs and nurses) as well as patients, carers and social care professionals drawn from Northern Ireland, Scotland and Wales as well as England (table I). The process is outlined in table II. Involvement of the devolved administrations in the new process is very important for the changes proposed for the QOF to have the optimal impact throughout the UK. NICE is currently discussing how this might best be achieved in relation, for example, to piloting the indicators in a Northern Ireland context.

While QOF indicators have served to improve the quality of primary and community care, and encouraged patients to make health changes in their lifestyles, the QOF needed to change. The Next Stage (Darzi) Review highlighted a need for a more open, transparent process for reviewing and developing the indicators it uses. A recent National Audit Office report on GP contract modernisation recommended that indicators should be based more on outcomes and cost effectiveness than they are at present.

THE NEW PROCESS

Decisions on QOF indicators have not up to now been informed by systematic information on the cost effectiveness of the interventions under consideration. There is evidence that some QOF indicators may not always reflect the value of the indicators in terms of health benefit. This is why NICE is to oversee a new, independent, objective system for the development of new indicators and the review of existing ones. The system will be based on evidence of clinical and cost effectiveness using the same methodological approach that informs our other guidance products.

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Because NICE is independent, patients, carers, professionals and other stakeholders can have confidence in the new process, which separates the assessment of the evidence for reviewing and developing potential new QOF indicators from the negotiation and approval of changes to the QOF. Moreover, the new committee will meet in public so that anyone with an interest in the process can both see, and hear, how the indicators emerge. It is important to emphasise, however, that NICE's role is an advisory one. The final decision on which new indicators should be retained, which should be removed, and which new ones should be included, will still be made by NHS Employers, on behalf of the Department of Health, and the British Medical Association (BMA). NICE will therefore produce an annual 'menu' of evidence-based, cost-effective indicators. Evidence of clinical effectiveness will be looked at initially using NICE guidance, but will also in time draw upon a range of accredited sources of evidence through the new NHS Evidence service. Where cost effectiveness information it is not readily available, a method for drawing some basic conclusions will be used to assess the indicator.

AN OPEN AND TRANSPARENT PROCESS

It is important to ensure that the process is informed by stakeholders with experience of primary care. As part of the open and transparent process, consultation documents containing the proposals – ranging from proposed topics for indicators to how they have been developed – will be available to all stakeholders (including patients). Anyone can submit possible clinical and public health indicator topics on the NICE website. The Advisory Committee will then use agreed criteria to prioritise topics based on evidence of clinical and cost effectiveness. An external organisation, appointed by NICE, will then develop potential new indicators to be considered by the independent Advisory Committee and with the results of piloting and consultation. The total review cycle will take around two years but a rolling programme will ensure there are new indicators available each year. At the moment there are 88 indicators. These will be reviewed over the next three to four years, so NICE will be reviewing 20 to 30 a year, in addition to a commitment to develop around 10 new indicators over each QOF review cycle.

High-quality care depends on making decisions based on the best available evidence. Placing NICE at the heart of the process will ensure that QOF continues to help ensure patients get the healthcare that is among the best in the world.

The authors have no conflict of interest

TABLE II:

the QOF indicators process

QOF indicators process flowchart

Stakeholders submit potential clinical and public health priority topics via the NICE website

↓

NICE collates information to prioritise new indicators based on evidence of clinical and cost-effectiveness

↓

Independent Advisory Committee considers topics for inclusion in the QOF

↓

NICE consults on developed indicators

↓

Advisory Committee validates the final proposals

↓

Recommendations published on the NICE website

↓

NHS Employers, on behalf of the Department of Health, and the British Medical Association (BMA) decide on final indicators to include in the QOF

Ulster Med J 2009;**78(2):**84-89

Annual Oration

What is Beauty?

Royal Victoria Hospital, Wednesday 1st October 2008

J Rory Corbett

INTRODUCTION

Let me start with Confucius who said "everything has its beauty but not everyone sees it". Beauty is... We all remember sayings such as beauty is skin deep, is only skin deep, is not only skin deep, is in the eye of the beholder, comes from within and so forth. The American writer Jean Kerr said "I'm tired of all this nonsense about beauty being only skin deep. That's deep enough. What do you want - an adorable pancreas?" And for those of you who believe in the new saying that beauty is in a jab and have come to hear about Botox, peels and fillers, they will not get a mention, so do leave now if you wish. But before you go, let me draw your attention to a poem of Thomas Campion a Renaissance English poet, of whom it was said "he had the generous illusions of youth; devoted to the studies of poetry, music, and medicine, clothed with that finer tact and sympathy which comes to a good physician", surely still applicable to today's students, but in his poem he said:

"Beauty is but a painted hell;
shee wounds them that admire it,
shee kils them that desire it.
Give her pride but fuell,
no fire is more cruell."

But beauty is not just a visual experience; it is a characteristic that provides a perceptual experience to the eye, the ear, the intellect, the aesthetic faculty, or the moral sense. It is the qualities that give pleasure, meaning or satisfaction to the senses, but in this talk I wish to concentrate on the eye, the intellect and the moral sense.

It was the late CP Snow, a true polymath, who gave the Rede lecture in 1959 and subsequently wrote a book, both under the title The Two Cultures, in which he bemoaned the split that had taken place between the scientists and the literary intellectuals. In education, when I was at school and to a large degree it remains, even today, there is a division as to whether one follows a scientific or an arts direction, to the detriment of the other. His theory was boosted when the critic FR Leavis published his attack on the Two Cultures. He wrote of Snow's "complete ignorance of history, literature and the history of civilization… his incapacity as a novelist is … total… not only is he not a genius he is intellectually as undistinguished as it is possible to be." For those of you who have come expecting a little gentle admonition, I am afraid you are going to be either relieved or disappointed; as there is no way that I could match that. But it is one of history's ironies that nearly eighty years earlier, Matthew Arnold in giving the same lecture had made the opposite point. Written in response to an argument that literature should and inevitably would be supplanted by science, he argued, "so long as human nature is what it is, culture would continue to provide mankind with its fulcrum of moral understanding". I would suggest that there is still a role for science and art in modern medicine and I wish to show that they should be interlinked in the training for and practice of medicine.

BEAUTY

So what is beauty? First let me perhaps surprise you by stating that beauty can be defined numerically:- 1.6180339887. That is beauty - that is the golden ratio (fig 1). It was described by the Pythagorean mathematicians, as they kept seeing this ratio in things regarded as beautiful, and it was first written down by Euclid, and can be expressed either as a linear relationship or as a shape, in either case the ratio is (a+b) is to a as a is to b and is behind the pattern of many shapes we find pleasing, be it architecture, form, people - all tend to this ratio when regarded as beautiful, and with that ratio we also expect to find balance and symmetry. The Parthenon has these ratios, and balance. People also and if we look at those regarded today as beautiful, then again the ratio applies, as does symmetry, both to the face and body. The head forms a golden rectangle and the mouth and nose are placed at golden sections of the distance between the eyes and the chin, and there are many others present and when we look at the human body then the

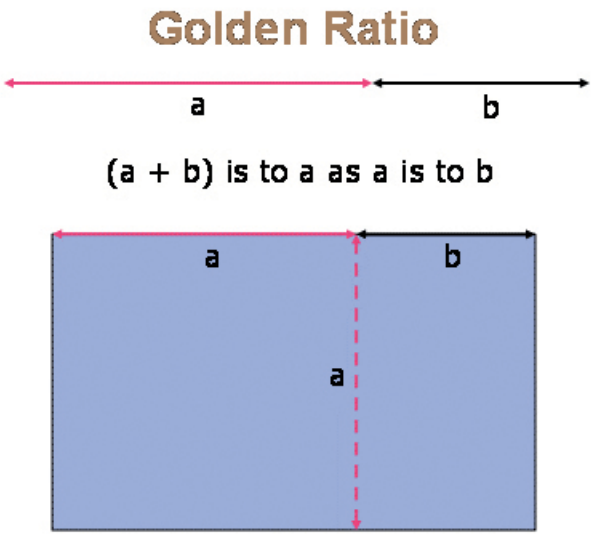

Fig 1. The golden ratio

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ratio in the average human body of the distance between the navel and the foot to the height and the ratio of the distance from the top of the head to the fingers to the height is the golden ratio, and again there are many others present. And we find these proportions in art for instance in the Sutherland tapestry of Christ in Glory in Coventry cathedral.

And not to leave out other specialities, for instance my respiratory colleagues - the divisions of the bronchi follow the rule and for our dental colleagues, the arrangement of the central incisors also. And the result of being perceived as beautiful is the person is thought more intelligent, more trustworthy, more likely to be employed and at better salary. These perceptions are important to us all but perhaps more so is the reverse perception of people with skin disease and the perception of those around them of the nature of skin disease. We are aware of the entries in the Bible, with its descriptions of what it called leprosy and the need to make others aware that you are unclean, you are dirty, and you are contagious. It has produced the leper complex for both the sufferer and the observer, still present today.

The descriptions given in the Bible covered many diseases other than leprosy, many of which were not contagious, such as psoriasis. However they were not too far off the mark with their anxiety and worry over so-called leprosy of clothes and buildings. My late colleague Dr Martin Beare showed that the fungus that causes cattle ringworm can survive in a sealed glass test tube for over a year and be successfully recultured. So also the fungus can survive on buildings, fencing and hedging, and continue to cause skin problems not only to host animals with a financial and user implication if the hide is seen as imperfect, but also to humans.

In all our dealings with patients with rashes there is constantly the "leper complex", and overlaid on that is the social importance of the skin. Look at the glossy magazines and the pages given to appearance. Appearance is everything. It is the first thing seen by others in social situations. The skin is one of the most important components of an individual's physical appearance. The skin on the face is under almost constant scrutiny in our daily interactions, though often unconsciously. If a person's form or colour is damaged then beauty maybe lost, and in modern society, individuals with an atypical facial appearance are often prejudiced against, and may experience severe social handicap, and the same applies to hand rashes.

Let me take psoriasis as an example of a chronic non-contagious dermatological disorder associated with cosmetically disfiguring skin lesions, often with severe social impact on the patient. The majority of patients feel they are stared at because of their psoriasis and regarded as contagious. They may experience outright rejection; asked to leave places such as a swimming pool, a gym or hairdresser. And because they anticipate rejection, they avoid these public places or interpersonal situations and thus reduce the quality of their life and social opportunities. It is always salutary to hear patients talking about their real problems, when they are talking casually together, then issues such as scaling in patients with psoriasis come to the forefront. The person who takes a vacuum cleaner on holiday, or the civil servant with a dustpan and brush in his briefcase to brush up around his chair before leaving work.

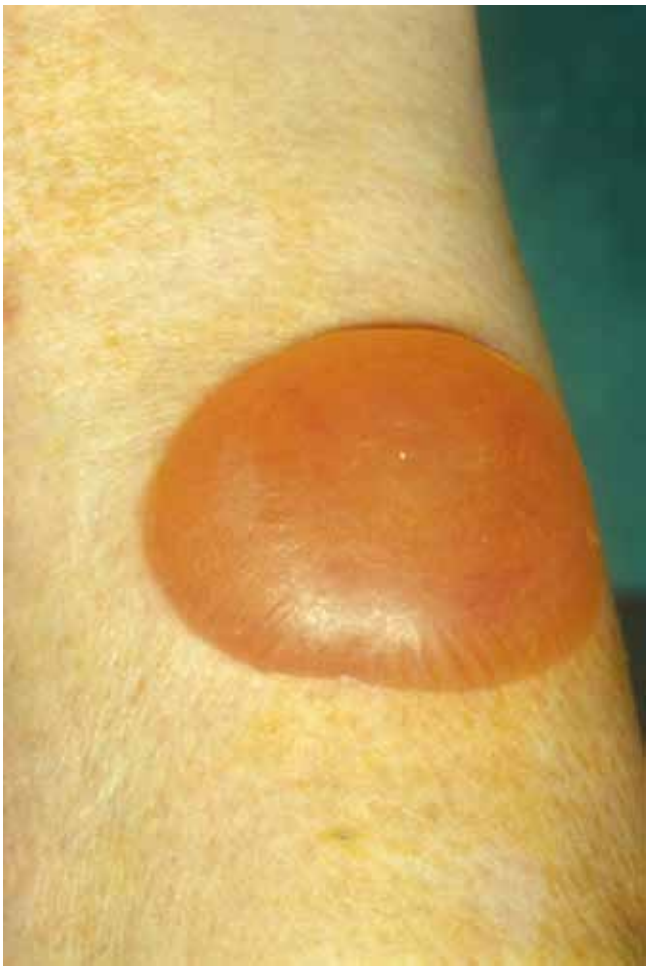

Fig 2. A blister,

The other skin condition particularly associated with social stigma is acne to which many of today's intended audience can relate, and which may lead to depression. The severity of acne can determine participation or rather lack of it in daily social activities, and adds to all the other pressures of adolescence. Individuals growing up in western society learn to believe that attributes such as clear skin, strong nails and clean hair are what are needed if one is to achieve that elusive quality of beauty. Therefore, if one lacks these features, because of a skin disorder then one is no longer seen as attractive or beautiful.

So from that how can I discuss skin disease as beautiful? So where is there beauty in skin disease. Might I suggest that it is there in colour, in form, and in pattern? I am not aiming to make you dermatologists, but let me suggest with a few slides that there is beauty in the appreciation as well as the physical appearance of some conditions. For instance colour. Like paint colour cards, a spectrum from pink to many shades of red, and yet all from the same condition, orangeybrown, or black. Or shape round with a ripple effect in tinea corporis, or with a target like appearance in erythema multiforme, or a non-anatomical patterned shape in dermatitis artefacta, a square, psoriasis in a donor graft site, or typical pattern of contact dermatitis from Elastoplast, or serpiginous from a larva of a worm. Do be wary of sitting on the sand on your next exotic holiday. I recently had a young patient who wasn't. And what about a blister? The intellectual reward of making a

Fig 3. Fungal culture plates

diagnosis purely from its appearance (fig 2). The thickness of the roof, the contents, the background, and also the mystery, why is there no surrounding inflammation? And what about the beauty of histology, staining for immunoglobulins in a blister, and routine histology surely beauty if only in colour, and metachromatic staining with purple of the mast cells using a blue dye**,** part of the fun of my intercalated degree. Enjoy the general picture of pathology, and then you will start recognising changes. Stay friends with your pathologist, who is still the last port of call for a tissue diagnosis, and as it seems a prerequisite of these lectures that Osler should have at least one quotation, then I would agree with his "As is your pathology, so is your practice". Clinical and pathological is the complete package. And while we are in the laboratory, what about fungal cultures (fig 3)? Surely there is a beauty in these? And what about the wee beasties; the flea and the adult head louse. Surely more than just their mothers love them. But as Confucius said ".. not everyone sees it". So there is beauty to be seen, the visual.

Secondly beauty and the intellect, beauty as knowledge. The more we know about a disease process the better we can manage it. For those considering research; advice I heard from Farrington Daniels junior, a photodermatologist and US government advisor in the 70's, that he gave his residents, was to read the standard textbook, find the most dogmatic statement and then look. It was often wrong. It has been written; "every fact of science was once damned. Every discovery was a nervous shock to some orthodoxy. We would own no more, know no more, and be no more if it were not for the rebellious, the recalcitrant, and the intransigent." Or Oscar Wilde put it more succinctly, "disobedience was man's original virtue" - my apologies to the chaplains.

So how has improved knowledge helped with psoriasis? How has it and how should it influence management? As we are nowhere near competing with those looking for the Higg's boson at CERN, the only comments I wish to make at the subcellular level is that the accepted wisdom that psoriasis was a condition of rapidly increased cell turnover of a few basal epidermal cells has changed to a normal rate turnover of increased numbers of cells, support for looking at accepted wisdom, and secondly that increased knowledge regarding inflammatory mediators, present in large quantities, has led to the introduction of a whole new class of therapeutic agents, the biologics. At the genetic level, although nine chromosomal loci have so far been described, even a major gene only determines 35-50% of the heritability, and that only in certain phenotypes.

We are however advancing enough to have a significant effect on therapy, where the emphasis has changed from one of reducing epidermal cell turnover, to dealing with the abnormalities of the inflammatory process. However for many years treatment has been anything but beautiful - creams and ointments. Imagine covering all your skin in an application, even just a moisturiser, at least twice per day. Then think if you had to apply a tar based product, the colour and the aroma, or one that stains; no wonder compliance was and is low. So you can imagine the joy of patients exposed to modern light treatment, slightly offset when they realised they still had to moisturise, and then the delayed findings of an increased risk of skin cancer. Systemic drugs were also much appreciated as generally easy to take, but still moisturisers were needed and there were side effects, the liver, kidneys, immunosuppression and fetal abnormalities.

And now the biological drugs. But of course there is a downside such as re-activation of TB and increased rates of infection. When they work it seems miraculous to the patient, as they add a further weapon to our therapeutic armamentarium, but they do cost, though the NHS Economic Evaluation Database has accepted a German paper[1] showing an economic advantage of etanercept, a biologic, over conventional therapy for certain groups of patients. So for each treatment there is a balance of gains and loss.

Therefore can we make topical agents easier to use, retain their apparent better safety profile, and at low cost? A major direction at present seems to be in the field of nanotechnology. A nanometer one billionth of a metre; the ratio of a marble to the earth; the length a hair in the beard grows in the time it takes to lift a razor to the face. I suspect that if you remember nothing else from this lecture you will about beard growth.

As so often it is the cosmetic companies, who are leading the research especially with sunscreens, and of course everyone who has to apply topical agents wants cosmetically acceptable ones. But there seems a long way to go. We do not know how many chemicals act when at the nano size. One cannot simply transpose the behaviour of large molecules, with which we are familiar. I am also very wary of technology in which military agencies are interested. If we are concerned by the spread of CCTV then think if a nanoparticle could be applied to you, without your knowledge, giving a constant readout of where and what you were about. As usual the balanced debate is being led by the newspapers. For instance, "if your suntan lotion can change the sex of fish, what can it do to you?", "The stuff is not only on your skin - it's in your tap water and lunches, too". "They can penetrate the brain", but companies are saying that the zinc oxide nanoparticles are fixed in the lotions, and are inert, while others suggest that none are inert at this size. So there is still a way to go.

There remain many holes in our knowledge. We have no explanation for distribution - psoriatic plaques are normally over the knees and elbows; but then why is guttate psoriasis predominantly on the trunk? Again little is known about the natural history, predictors of disease severity or remission. There are no biomarkers estimating activity. And if cleared by treatment, is it really clear? There remain many mysteries.

I am sure we all expect new knowledge at the subcellular level, but there is much new knowledge available at the patient and

societal level, which is probably more important to the patient, and this reflects a theme that is common to many specialities who deal with chronic inflammatory disease. Many years ago the late Professor Pantridge asked me how and why did patients with psoriasis die. I did not have an answer, but in my defence they so rarely died under our direct care that we had no idea of the causes of death. Now a major advance is the increasing realisation of comorbidities, associated with chronically increased levels of pro-inflammatory mediators as seen in psoriasis[2].

Psoriasis is associated with metabolic syndrome (obesity, impaired glucose tolerance, abnormal levels of fat in the circulation, arterial hypertension and is twice as common in forty to sixty year-old patients with psoriasis as among healthy people. In addition significant coronary plaques are twice as common in patients with psoriasis compared to controls and a thirty year-old patient with moderate to severe psoriasis has a threefold increased risk of myocardial infarction with mortality due to myocardial infarction or stroke two and a half times higher in patients characterised by early or frequent hospitalisation. Psoriasis is not just a skin disease or joint disease after all. The other major improvement in knowledge is the ability to measure the burden, especially psychological, both for patients and for their helpers and give them numbers that are robust and reproducible. Better than the simple " how are you feeling". The SF36 short form, with its 36 questions, is used to compare the impact of different diseases. The lower the score the bigger the impact. Psoriasis with diabetes and worse than cancer[3]. There are specific survey forms for psoriasis, the PASI - a physician determined score based on erythema, or redness, degree of scaling, induration and area of skin surface involved, and Quality of Life issues such as the dermatology life quality index[4], a patient determined index, consisting of 10 questions related to symptoms and feelings, daily activities, leisure, work and school, personal relationships and trouble with psoriasis treatment. Both score from 0 - 30, with lower scores corresponding to a better quality of life. Moderate to severe disease is with a PASI >10 either alone or with a DLQI >10.

HOW DO SCORES TRANSLATE TO MANAGEMENT?

In over 1500 patients attending dermatologists[5], there was a mean PASI of 12.0 with mean disease duration of 17.6 years. Over a quarter had been hospitalised; virtually all had had topical therapy and two-thirds had UV-phototherapy, but only one third systemic therapy. There was a severe sub-group of ~20% of patients with a PASI > 20, in whom 12 workdays had been lost in the previous 12 months per patient. Virtually one fifth were unable to work (mean = 133 days), half had been hospitalised in the last 5 years, almost 60% had a DLQI > 10 and yet less than 50% had had systemic therapy. That does not seem to read very well.

But it is not just the patient who is affected. In another study[6] looking at the effect on others in the household, there were 63 subjects questioned of whom 28 were relatives and 35 partners. The Patients themselves had a mean DLQI of 10, and mean PASI 5.2, and 40 aspects of quality of life were identified in 6 categories. The results showed that 70% complained of extra time on housework, laundry and vacuuming, 57% of psychological pressures (mainly anxiety and worries about the future), 55% of social disruption (such as meeting people), 44% of holiday plans (including sport and leisure), 37% of daily activities, shopping, work and dealing with other members of family, and the same figure for effects on personal relationships.

The subjects' Quality of Life was related to the patients Quality of Life and not disease severity scores. There certainly appears to be room for improvement, but I wonder how figures would look in other specialities.

WASHING AND SUNTANS

Having said at the beginning that I was not going to discuss Botox etc. I am going to discuss two activities that related to beauty have had a singular effect on dermatology services in recent times.

The first of these is washing and the associated beauty/ cosmetic business and the use of water. In 1961 water used per head for bathing was 11 l/day, rising to 51 litres in 1997. For 2008 around 80 litres per day is necessary. This is out of a total daily usage in England of 145-150 litres per person, per day. UK sales of bubble baths have risen from £76 million in 1981 to £173 million in 2001. Total UK sales in 2006 were £4 billion for personal wash products. With all the skin washing we are seeing an increase in the amount of dry skin and eczema, especially in the vulnerable skin of the young and the old, who then need to apply moisturisers. There are so many complaints of reactions to topicals that manufacturers seem to list more of what is not present than is.

The second major activity, that was pre-eminent in the last century as an aid to beauty, was that of acquiring a suntan. People went on holiday to get a tan, and if you came back pale it had been a failure; and what has been the result? Let us look at the pin-up girl to a certain generation - Brigitte Bardot. If one compares pictures of her in her prime in the late 1960's to those, even in the early 1990's, one can see enormous changes in terms of wrinkling and elasticity, showing the effects principally of the sun. If symmetry and balance are beauty look how easy it is to destabilise just by attaining a tan.

If aging changes are not enough to frighten you, what about the development of skin cancer? There is a problem when we come to look at the figures. Nationally, if figures are collected at all for non-melanoma skin cancer, then only the first episode is recorded and the Northern Ireland Cancer Registry has followed this practice. A registry audit suggested that 50% more skin cancers are removed than patients registered. We do have patients who have had up to 50 and more primary basal cell carcinomas removed. Using the 2007 pathology figures for the Belfast trust, which included some material from the Ulster hospital, then of 52,000 biopsies reported that year approximately a third of all, just under 14,000, were for skin lesions of which 2097 were for basal cell carcinoma, and 489 for squamous cell carcinoma.

Unless you have been living totally in your own world, then you must be aware of the issues surrounding malignant melanoma; the increases that have occurred in the latter part of last century. In a recent paper[7], between 1984 and 2005 in the province there has been a 288% overall increase, with males at 340% and females 260% but again this does not reflect the true work implications. Virtually every MM has two surgical procedures the first being to excise the lesion, which

allows histological staging, and a wider second excision. In addition the best centres in the UK would suggest that around 20-25 moles are removed for every malignant melanoma, and there are no figures available for the number of pigmented lesions that are referred, that do not require biopsy or surgery.

In 2007 there were 291 malignant melanomas reported in the Belfast trust (Dr Maureen Walsh, personal communication) with a further 1797 benign naevi, which at a figure of 8 to 1 benign to malignant gives us a much better figure than elsewhere, but raises a question are we not removing enough? And that does not include other pigmented lesions. Our figures suggest that we see three patients for every one who has a procedure. For the trust that means about 5,400 cases a year have to be red flagged, that is seen within two weeks of referral for query malignant melanoma, or changing mole, and does not include other red flag items. If all this work is the result of recent efforts to achieve a desired appearance what does the future hold for my successors from some of the present techniques that the public willingly undergoes seeking beauty, and delaying aging?

Having mentioned the beauty that lies in symmetry and balance, we can see this even when we look at skin cancer. A basal cell carcinoma relatively banal, in this type is balanced and symmetrical. Benign moles again are symmetrical and balanced, but when malignant, asymmetrical and unbalanced. There is no beauty. This is the price of achieving beauty.

It has had a distorting effect on our work balance of skin cancers and pre-cancers vs. rashes, new and review. A recent Edinburgh study[8] reported that 46% of their new referrals were for tumours, benign and malignant and 24% for psoriasis and eczema, but only 20% of reviews were for cancer with 40% for the big three rashes, eczema, psoriasis and acne. Their new referral rate has risen by 67% between 1980 and 2005, from 12.6 per 1000 population to 21. And interestingly over the same period internal referrals had almost quadrupled to 11% of total in 2005.

Andrew Finlay[9], in the 2000 Dowling Oration, (the big annual set piece of British Dermatology), made a particular plea for medical dermatology, which he saw being threatened politically by the emphasis on seeing skin "lumps and bumps". He asked the question "Are we meeting patient's needs?" I have already largely answered that question. I have discussed the shortfall in medical management and patient desires for clean and easy to use treatments. Skin tumours are usually simply cured by surgical techniques, but this is not the same for the chronic inflammatory skin conditions. We do not have cures, treatments are messy, compliance is poor, 36% of parents of children with atopic eczema admit to non-compliance. Knowledge and education outside secondary care is inadequate. Research has shown that the disability suffered by those seen in primary care and not referred on was just as marked as those sent to secondary care, and in a Welsh study[10] looking at Quality of Life scores after attendance at a dermatology clinic, the greatest benefit was perceived by those with psoriasis, eczema and acne ahead of those with cancer. There is a great untapped need. This suggests that patients with severe inflammatory skin disease deserve priority in the organisation of skin clinics, which seems to have been lost in the drive to deal with skin malignancies.

I was therefore delighted to read the consultation document from the board of the Belfast Trust entitled 'New Directions', with its particular emphasis on patient choice. Ours will be very expectant, and also the need for centres of excellence to provide the knowledge, skills and critical mass to provide these desired treatments. A chronic inflammation diseases emporium to match the cancer centre. One can but dream.

This lecture by tradition has been directed at the new clinical medical students, so if mathematicians, engineers, architects strive for beauty as the right solution to a problem, then even more that should be your aspiration as you draw a picture of medical care that you give and it does not matter what the condition is, nor what speciality you are in. However one of your biggest challenges will be to draw the same standard of picture for everyone you deal with. You will be challenged by the so-called heart sink patient, the alcoholic, the drug addict, and the prisoner. It is a real challenge to provide the same service to a prisoner who has killed, as it is to the widow. A recent anonymous personal view column in the BMJ said "we all meet patients who make our hearts sink. We will all meet patients who challenge our personal values and beliefs. We will all meet patients who will fill us with a sense of disapproval". How will you treat them? At the same time do not be seduced to provide a better service for those who might be perceived as important. Do not cut corners "being nice" when caring for colleagues.

But if you are to be enabled to produce the best picture of care there are two major parts of the picture missing from what I have already discussed, and to an extent outside your control and that is your medical education, which has been such an important tradition of this hospital, from its inception, and secondly the politico- managerial influences on health care. When I left the academic staff of this medical school we had amongst the worst staff - student ratios of the old medical schools in the UK. Since then the student numbers have risen from 864 in 2000 to 1160 in 2007, whilst there has been minimal change in the numbers of clinical academic teaching staff. The result is large numbers of students going through many clinical attachments, each in a very short time, often only for one week and this at the same time as the pressures are on medical staff to increase patient throughput. For you in your clinical studies it is even more important then, that you remember that you are in a process of adult learning, not passive teaching. There is the well known aphorism "see one, do one, teach one"

But that had been anticipated by Confucius (you can see how I reckon the balance of political and economic power is going to develop) who said "I hear and I forget. I see and I remember. I do and I understand."

Keep looking; do not be happy with ticking the box; I have seen my case of whatever in this attachment. It is repetitive seeing that leads to remembering and if you get the chance then do and doing includes proper examination. Corrigan, of his pulse, the 19th century Dublin physician, said "The trouble with doctors is not that they don't know enough, but that they don't see enough". Changes in junior doctors training due to European Working Time Directive and in the programmes themselves, have the trainees themselves complaining about lack of exposure.

So how do these parts, education and management, look in the picture that is medical care? It was earlier this year sitting in a dive boat looking across a bay at all the yachts at anchor that I saw the answer. I was conscious of two styles of design. The first was an older design, of flowing lines, above and below water. It was well finished; there were cabins for the crew. The sail area was such that most of the time even when racing it was only at 95% of its performance and safety limits, so it did have a slight degree of slack to meet an emergency, that inevitably happens at sea. The other style is that of the modern extreme racing machine. It is absolutely stripped out, bunks for only half the crew, on a Cox and Box principle, no doors for privacy and the crew living in their oilskins. Underwater the keel and rudder are hung from narrow supports. It is driven at 100% or slightly over the safety margins of the rigging and sails, and with a minimal number of crew. The problem is there is no reserve and when parts break, or there is an injury, then at great expense parts or a temporary crewman is helicoptered in, things put right, and helicoptered out but only to leave the boat in the pre-existing state.

So how is education and management being painted in? Over the years the sections have been frequently overpainted. At present it looks like the extreme model. I am reminded of the law propounded by Patrick Hutber, city editor of the Sunday Telegraph which states "improvement means deterioration". So for all involved in health care, and not just those in the medical profession, for everyone who works in or has influence in an institution such as this and that includes the porters, the administrators and even the politicians, as well as the doctors, nurses and allied professions there should be the same end picture.

We are all aware of how we react to our surroundings, our environment, our treatment on holiday, the lift we get or depression. If that is how we feel when well how much more important it is when ill. But whatever is present in the outer parts of the picture, and making up the background, in the centre is a patient and not just a client. Isn't it interesting how these less personal terms seem to slip in? But who is that patient? Is he a case or a real person? He has experiences, he has worries. So who is that patient? We were always taught to practice with the same care as you would wish if that patient was your parent, your sibling, your child, not just a bed, not just the twentieth psoriasis of the afternoon.

There are those here, who are under intense pressure to produce good-looking figures, for waiting lists, for throughputs, whatever their constituency, but to you can I also ask that you too consider the service provided. It is to an individual, a member of your family, your partner, your child, your parent. I pray that there is not a need to remember John Donne[11] who said "I observe the physician with the same diligence as the disease." He obviously in the 17th century had a different agenda, but we do have patients asking if decisions are finance or time based. To all who deliver care, and to all who plan, give time to the patients. That great philosopher Winnie the Pooh had the right approach when he said "Sometimes I sits and thinks and sometimes I just sits". It is remarkable what solutions can be found, decisions made, and more importantly, ill considered decisions avoided.

I started with Confucius, but let me finish with two others coming from different directions. The first is John Wesley, whose rule includes "do all the good you can, in all the ways you can, to all the people you can" and secondly one of the greatest thinkers of the last century Einstein. And though what he said was not to a medical audience it still applies: "The most beautiful thing we can experience is the mysterious. It is the source of all true art and all science". (Note he says both all true art and all science. Not one or the other). And he continues "He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead: his eyes are closed"

Put those words of Wesley and Einstein together and it is not a bad way to practise medicine and the picture you paint will bring pleasure to the eye, to the intellect and to the moral sense.

That is Beauty.

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Paper

Prevalence of palmaris longus absence – a study in the Yoruba population

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ABSTRACT

Background: Palmaris longus (PL) has received a growing interest for its role in constructive surgery. Since the agenesis of PL shows a strong racial variation, it is conceivable that its prevalence on the Yoruba ethnic population in Nigeria will further confirm this phenomenon.

Methods: A total of 600 subjects comprising 335 males and 265 females aged 8-60years were used to assess the prevalence of agenesis of the PL in Yoruba tribe.

Results: The overall prevalence of absence both unilaterally and bilaterally in the two sexes was 6.7%. In males, unilateral absence was 5.4%. The distribution on the right and left were 2.4% and 3.0% respectively. The bilateral absence was 1.5%. In females, unilateral absence was 6.0%. The distribution on the right and left were 2.6% and 3.4% respectively. Bilaterally, it was 0.4%. In one subject unilaterally, PL was observed to have differentiated from flexor carpi radialis.

Conclusion: Results of this finding suggested that the prevalence of PL agenesis as reported in standard anatomy texts is significantly different from our observation in this Yoruba population. The differentiation of PL tendon from flexor carpi radialis is indicative that both muscles may develop from the same muscle group as previously suggested.

Key Words: Palmaris longus; Agenesis; Yoruba tribe; Males; Females; Abnormal origin.

INTRODUCTION

PL is a small vestigial muscle that is phylogenetically degenerating. It is a slender muscle that arises from the medial epicondyle by a common flexor tendon and from adjacent intermuscular septa. The characteristic of this muscle is shown by its short belly and long tendon[1]. The belly soon gives way to a long slender tendon of variable length[2] that inserts adherent across the front of the flexor retinaculum to the palmar aponeurosis[1,3,4].

This muscle is one of the most variable muscles in humans. The variations include duplication (digastrics) and the presence of accessory palmaris longus[5]. The origin of this variation as illustrated by Humphrey[6], suggested the presence of radial, intermediate and ulnar sectors in the superficial layers of the forearm flexor muscular angulus. Thus PL usually differentiates from the intermediate sector but differentiation from the other two sectors may also be possible. It is also reported to develop independently from the palmar aponeurosis and is associated only by anatomic proximity[7].

PL, a weak flexor of the wrist is considered functionally negligible. However, there is a growing interest in the existence of the muscle because its tendon is reported to be most frequently harvested for reconstructive plastic and hand surgery[8]. Furthermore, PL tendon in various combinations is used to repair oncologic defects of head and neck, arthritis of the thumb and ptosis in children[9]. Besides, it had earlier been noted as a stabilizer of superficial structures in the palm in preparation for the abduction of the thumb[10, 11].

The agenesis of PL has been reported in anatomy texts[1,3,4]. The prevalence of the agenesis of this muscle as reported in most standard anatomy texts is about 15%. A higher prevalence (24%) was reported in North American Caucasians[12]. A survey in Pennsylvania, USA, showed 23% prevalence of absence[13]. Ceyhan and Mavt[14], reported a much higher prevalence of agenesis (63.9%) in the Gaziantep population in Turkey. Studies among the Asian population showed that the incidence is 3.4% in Japanese[15] and 4.6% in Chinese[16] respectively. Within Africa, studies have equally been conducted. Available information showed that the incidence is 1.02% in a Ugandan population[17].

The Yoruba tribe located in southwestern part of Nigeria extends through Benin republic to Togo. It is the second largest ethnic group in Nigeria constituting about 30% of her entire population. Their lives are structured around agriculture being the largest producer of cocoa in Nigeria, a major cash crop. They equally engage in trading and handicrafts and enjoy lots of social activities like burial and birthday ceremonies that have become part of their socio-cultural lifestyle[18].

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TABLE I:

The distribution of palmaris longus absence on both sexes

Number of subjects assessed	Total absence in both sexes	Total absence in males	Total absence in females
600	40 (6.7%)	23 (6.9%)	17 (6.4%)

Since the incidence of PL agenesis is highly variable and the figures used in most anatomy texts represent Caucasian populations, we thought it would be informative to report on the prevalence of this muscle in a non-Caucasian African Yoruba population, the second largest ethnic group in Nigeria.

MATERIALS AND METHODS

A total of 600 subjects comprising 335 males and 265 females aged 8-60 years were used to assess the prevalence of agenesis of PL. Systematic random sampling was used to select subjects from amongst members of the university community, primary and secondary schools and business community. The exercise was conducted with four different methods of assessment; standard test (Schaeffer's test), Thompson's test, Mishra's test I and Pushpakumar's "two-finger sign" method[19]. Each subject was initially asked to do the standard test. Where palmaris longus tendon was not sufficiently visualized due to inability to manoeuvre the technique, Thompson's, Mishra's and Pushpakumar's "two-finger sign" tests were used to confirm its absence.

In Schaeffer's test, volunteers were made to steady their forearm at 90° before opposing the thumb to the little finger

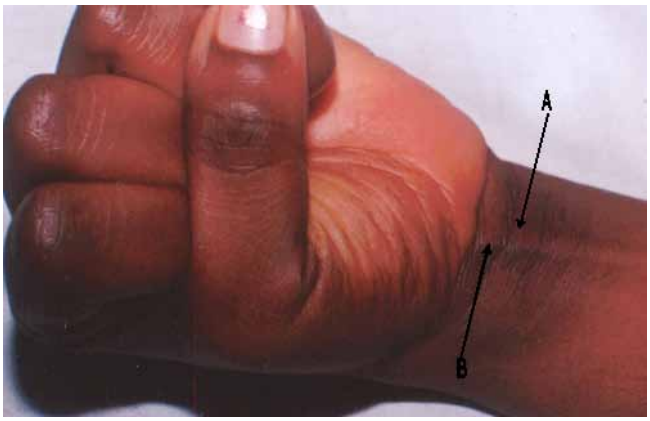

Fig 1. Thompson's test; (A) palmaris tendon and (B) flexor carpi radialis tendon

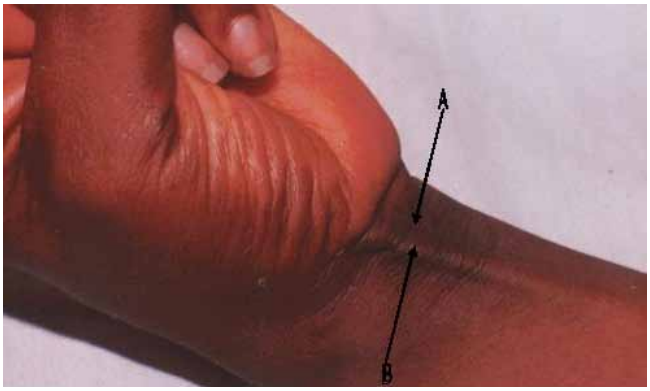

Fig 2. Pushpakumar's "two-finger sign" method showing (A) palmaris tendon and (B) flexor carpi radialis tendon.

TABLE II:

The distribution of palmaris longus absence on both limbs

Absence of palmaris longus	Right	Left	Bilaterally
Male	8 (2.4%)	10 (3.0%)	5 (1.5%)
Female	7 (2.6%)	9 (3.4%)	1 (0.4%)
Both sexes	15 (2.5%)	19 (3.2%)	6 (1%)

with the wrist partially flexed. In Thompson's test, a fist was made followed by flexing the wrist against resistance with the thumb flexed over the fingers. In Mishra's test I, the subjects were asked to abduct the thumb against resistance with the wrist partially flexed. In Pushpakumar's "two-finger sign" method, the subjects were made to fully extend the index and middle finger while the wrist and other fingers were fully flexed with the thumb opposed and flexed.

The incidence of agenesis of this muscle in both sexes and on the two sides of upper limbs was analyzed using SPSS. Correlation and percentage score were used to assess the association of its agenesis in both sexes unilaterally and bilaterally.

RESULTS

The overall prevalence of absence was 6.7% (40 subjects) (Table I). In males, PL was found to be absent unilaterally in 18 subjects (5.4%); the distribution on the right and left were 8 (2.4%) and 10 (3.0%) respectively. Bilaterally (Table II), this muscle was absent in 5 subjects (1.5%).The overall prevalence of absence in males was 6.9% (23). In females, PL was absent unilaterally in 16 subjects (6.0%); the distributions on the right and left were 7 (2.6%) and 9 (3.4%) respectively (Table II). Bilaterally, it was 1 (0.4%). The overall prevalence of absence for females was 6.4% (17) (Table I). The unilateral prevalence of absence between the males and females showed no significant difference ($p>0.05$, Table II). However, bilateral prevalence of absence in males was comparatively higher than in females.

The correlation analysis showed that the agenesis on male right was strongly correlated to male left. Likewise, female right agenesis was strongly correlated to its left side. The incidence of absence on male right and left was more strongly correlated than that of the females.

In a single subject (Figures 1 and 2) unilaterally, PL differentiated from the distal part of flexor carpi radialis tendon close to the wrist joint as could also be seen from the illustration in Fig 3.

DISCUSSION

The findings in this Yoruba ethnic population showed the overall prevalence of absence of PL to be 6.7%. This observation differs markedly from most reports in standard

Table III:

Correlation coefficient of palmaris longus absence

	Male right	Male left	Female right	Female left
Male right	1	.910	.	.
Male left	.910	1	.	.
Sig. (2-tailed)	.000	.	.	.
Female right	.	.	1	.891
Female left	.	.	.891	1
Sig.(2-tailed)	.	.	.000	.
Number	335		265	

Correlation is significant at 0.01 levels (2-tailed)

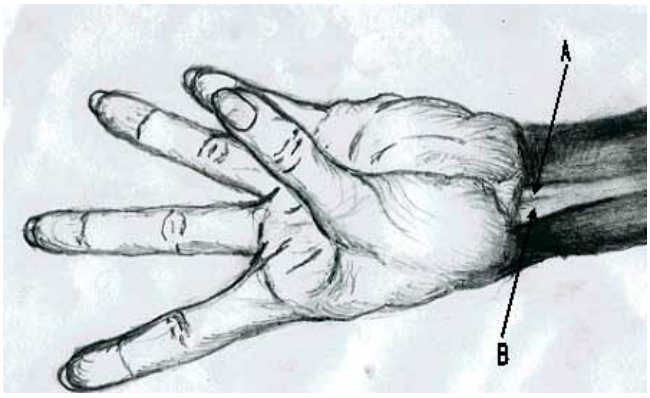

Fig 3. Illustration of the abnormal origin of palmaris longus from flexor carpi radialis. (A) Palmaris tendon and (B) flexor carpi radialis tendon.

anatomy texts (15%) believed to represent Caucasian population. The assumption is strengthened by a similar high prevalence of absence (24.4%) reported in North American Caucasians[12]; Pennsylvania (23%)[13]; Gaziantep population (63.9%)[14]; and Germans (20.4%)[20]. However, our observation tallied with the reports on Asian population which according to Adachi[15] and Sebastin *et al.*[16] were 3.4% and 4.6% for Japanese and Chinese subjects respectively. It differs from the report of 17.2% in a recent survey of an Indian population[21]. A black population report on Ugandans subjects[16] showed a much lower value of 1.02%. This is indicative of strong racial variation of agenesis of the muscle.

The unilateral absence observed to be higher in females (6.0) than in males (5.4%) correlated with most previous reports[12, 14] except for the report on Ugandans[16]. The difference between the unilateral and bilateral absence of the muscles was marked. The much lower incidence of bilateral agenesis is consistent with other accounts[22, 16] but differs markedly from Ceyhan and Mavt,[14] report on a Turkish population. There was no significant difference in the unilateral absence in both sexes. But bilaterally, the difference was marked. A strong correlation of agenesis was observed between the right and left limbs of the males and the females.

Abnormal differentiation of palmaris longus from flexor carpi radialis

In one subject unilaterally, PL was observed to have differentiated from the distal part of the flexor carpi radialis tendon. Because the flexor carpi radialis tendon was more prominently displayed, the different assessment tests for PL could not clearly demonstrate the diverging PL tendon. The obscurity was more apparent in tests (figs 1 and 2) involving the opposition of the thumb to the other fingers. Therefore, Mishra test 1 (fig 4) in which the thumb is retained in the lateral abducted position best demonstrated the tendon. This observation appears to be in consonance with the earlier report[19] that Mishra test 1 seemed the best method of clinically assessing the presence of PL. As shown in figures 1 and 2, the tendon appeared as a low ridge at the ulnar side of flexor carpi radialis tendon and together they formed a triangular shaped prominence that tapered towards the ulnar side, close to the wrist joint. PL is believed to differentiate from the intermediate sector of forearm flexor muscular angulus, but this unusual occurrence might not be unconnected with Humphry's observation that the muscle occasionally differentiates from the radial sector[6].

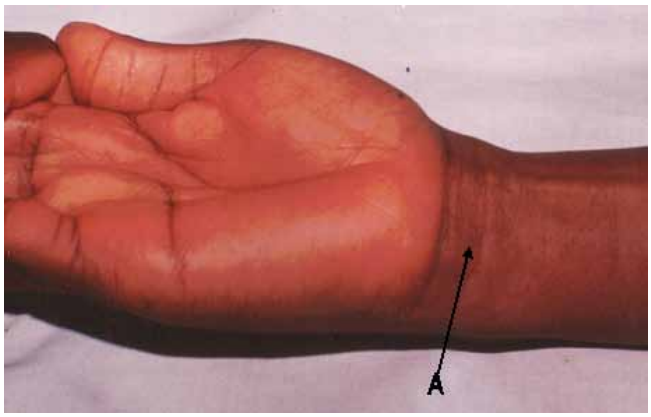

Fig 4. Mishra test I showing (A) palmaris tendon

We conclude from these results that there is a low prevalence of agenesis of PL among the Yoruba tribe in Southwest Nigeria and perhaps generally in non-Caucasian populations. The reason for this strong racial variation is not clear. It may be due to a higher prevalence of manual labour in Asian and African populations. It should therefore be necessary to investigate the prevalence of PL in other African ethnic groups and perhaps by socio-economic strata in such populations. The case of unusual differentiation of PL tendon from flexor carpi radialis observed in one of the subjects was confirmatory to Humphry's observation that the muscle could

occasionally differentiate from the radial sector of forearm flexor muscular angulus.

The authors have no conflict of interest.

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Ulster Med J 2009;**78(2):**94-98

Paper

Cocaine: Recent trends in Northern Ireland

James R Lyness

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SUMMARY

A review of autopsy reports in cases in which cocaine featured in the cause of death in Northern Ireland revealed that there were 18 deaths between 1st January 1999 and 31st December 2007. Analysis revealed an increasing incidence of these deaths during the study period and this is compared to national statistics and those published by local drug addiction services and police.

INTRODUCTION

In the autumn of 2008, cocaine made headline news following a record seizure of the drug off the coast of Ireland, with an estimated value of £403 million. This valuable cargo was destined for the streets of the United Kingdom and Ireland[1]. Just over a week following this seizure about £150,000 worth of cocaine was seized from a property in south Belfast[2]. It would appear that this drug, once thought to be the drug of choice for more affluent sections of society, has become increasingly available in Northern Ireland (figure 1).

Cocaine is a stimulant drug and has been used by the Peruvian Indians for centuries for the well-being and increased endurance it produces after sucking on the leaves of the plant *Erythroxylon coca* and related species[3]. It produces an increased euphoria and arousal with an elevation in alertness, mood and vigour, and it is these properties which have made it a drug of abuse in modern society. In the United Kingdom it is considered a Class A drug under the Misuse of Drugs Act 1971[4].

In Northern Ireland 28% of the population aged 15-64 years reported taking illegal drugs at some point in their life. Twenty five percent of the population reported the use of Cannabis, making it the most common drug of abuse. Poppers, which contain amyl nitrate, and Ecstasy, which contains methylenedioxymethamphetamine (MDMA), were the second most prevalent drugs of abuse with 8% of the population reporting their use. Despite cocaine's relatively lower rate of usage within this population (5%) it has become increasingly prevalent in Northern Ireland society in recent years[5]. This increase in cocaine use is further demonstrated by an increased referral rate of cocaine users to services for problem drug use and an increase in the annual seizure rate of cocaine by the Police Service of Northern Ireland (PSNI)[6,7]. This review compares the experience of the State Pathologist's Department for Northern Ireland with the data collected by the above agencies.

Fig 1. Line of cocaine.

METHODS

This review examined fatalities in which cocaine featured in the cause of death in Northern Ireland over a nine year period (1999 – 2007) using retrospective review of autopsy reports from the Northern Ireland State Pathologist's Department. Pathologists of this department undertake postmortem examinations in almost all cases of sudden unnatural death instructed by Coroners in the province.

The search term 'cocaine' was entered into the electronic register of the State Pathologist's Department. This allowed interrogation of cases between 1982 and 2007. Following case identification, the autopsy report for each fatality was reviewed and the relevant details recorded.

RESULTS

Eighteen cases where the cause of death was directly associated with the use of cocaine were identified in Northern Ireland between 1st January 1999 and 31st December 2007. The date of death and final cause of death of each case are shown in Table I. During the period 1999 to 2002 there were a total of five deaths associated with cocaine use. Of note however in only one of these deaths was cocaine the solitary drug detected on toxicological screening of post mortem samples. In the remaining four cases, death was attributed to multiple drug use including cocaine combined with amphetamines and/or opiates. During the period from 2005 to 2007 there were a total of thirteen deaths of which nine

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TABLE I

Date of Death and final cause of death on report of autopsy

Date of Death	Cause of Death
7/1999	1. Heroin intoxication combined with cocaine and methylenedioxymethylamphetamine.
9/2000	1. Combined heroin, cocaine, thioridazine, diazepam and alcohol intoxication.
9/2000	1. Cocaine intoxication
12/2001	1. Methylenedioxymethylamphetamine and cocaine intoxication.
11/2002	1. Heroin and cocaine intoxication combined with diazepam.
1/2005	1. Poisoning by heroin, amphetamine and cocaine.
6/2005	1. Cocaine intoxication.
12/2005	1. Poisoning by cocaine. 2. Alcohol intoxication.
12/2005	1. Carbon monoxide poisoning 2. Intoxication by alcohol and cocaine.
7/2006	1. Poisoning by cocaine and methylenedioxymethylamphetamine.
8/2006	1. Poisoning by cocaine.
10/2006	1. Poisoning by cocaine.
5/2007	1. Poisoning by cocaine.
5/2007	1. Myocardial necrosis and fibrosis due to cocaine abuse 2. Self Starvation.
7/2007	1. Poisoning by cocaine.
8/2007	1. Cocaine toxicity.
8/2007	1. Poisoning by cocaine.
8/2007	1. Poisoning by cocaine 2. Alcohol intoxication.

(69.2%) were attributed to cocaine exclusively, including cases in which alcohol was also detected.

Despite no cocaine associated deaths being recorded in 2003 and 2004, during the review period there was an overall trend of increasing annual number of deaths associated with cocaine as reported by the State Pathologist's Department for Northern Ireland. Figure 2 shows the annual number of deaths in which cocaine is included in the final cause of death following full autopsy and toxicological examination. Although a relatively low number of cases, there is a definite upward trend, particularly during the period 2005-2007. There were no cocaine associated deaths recorded prior to 1999.

The average age of the deceased at the time of death was 30.27 years (range 18-51 years). Sixteen (89%) of the 18 deaths were male and two (11%) were female. Eight of the 18 (44%) individuals were unemployed at the time of death

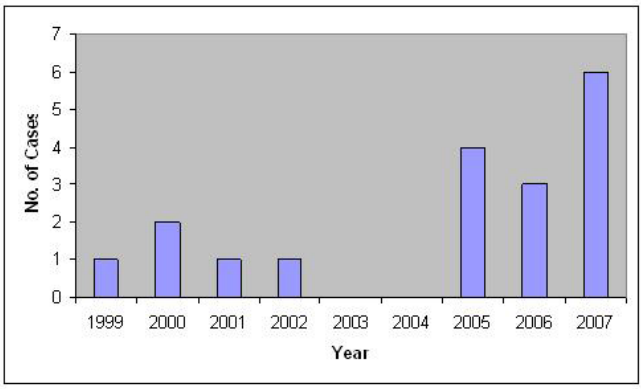

Fig. 2. Annual number of cocaine associated deaths recorded by the State Pathologist's Department for Northern Ireland.

and 10 (56%) employed. Five of the 18 (28%) individuals had no significant medical history, four (22%) had a history of previous drug abuse, five (28%) had a history of depression and two (11%) had a history of cardiovascular disease.

At autopsy there were minimal external findings and the majority of these were non specific. Two cases (11%) showed petechial haemorrhages in the conjunctival lining of the eyelids and six (33%) showed facial congestion. Two (11%) were associated with minor self inflicted or accidental trauma. In five (28%), needle puncture marks were detected, of these, three were associated with cocaine use combined with opiate use, one involved resuscitation attempts and in another, the needle mark was not thought to have been related to cocaine use.

On internal examination, eight cases (44%) showed cerebral swelling and the average brain weight was 1524g (range 1340 – 1870g). In three cases (17%) there was evidence of tongue biting, which may indicate seizure activity or simply be associated with a terminal cardio-respiratory arrest. The average heart weight was 383g (range 225 – 496g) and nine cases (50%) were over 400g in weight reflecting a degree of myocardial hypertrophy. Fourteen cases (78%) had normal coronary arteries, two (11%) demonstrated moderate narrowing, and in two cases (11%) there was severe narrowing. Two of the four cases with coronary artery disease had a previous history of cardiovascular disease. Myocardial fibrosis was detected on microscopy in five cases (28%).

Alcohol analysis of blood samples taken at post mortem revealed concurrent alcohol consumption in eight cases (44%). There was an overall average blood alcohol concentration of 61.6 mg per 100mls (range 0 – 231mg per 100mls).

Toxicological analysis of post mortem blood samples detected unmetabolised cocaine in 14 cases (78%). Of these 14 cases only 10 specified the concentration of the drug detected and the average concentration was 1.22µg per ml (range 0.03-5.9 µg per ml). The major cocaine metabolite, benzoylecgonine, was detected in 17 cases (94.4%) including the four cases in which no unmetabolised cocaine was reported. The cutting agent lignocaine was detected in nine cases (50%). Amphetamines were detected in five cases (28%) and opiates in four cases (22%). Furthermore, in three of the cases in which opiate was detected the heroin metabolite

6-monoacetylmorhine was also reported. Nasal swabs were taken in seven cases (39%) and all of these were positive for cocaine, indicating nasal insufflation. Three (17%) of the seven cases in which stomach contents were analysed showed the presence of cocaine, consistent with oral intake, however, the possibility of drug swallowed following nasal insufflation cannot be excluded.

DISCUSSION

The incidence of deaths attributed to cocaine in Northern Ireland remains low but there has been an increase in the number of cocaine related deaths during the review period, 1999 to 2007. Of particular note there was an increase in the number of deaths attributable to cocaine as the single drug of use since 2005. Prior to this cocaine was largely associated with multiple drug use. Statistics published by the Office for National Statistics for England and Wales show a similar increase in the annual numbers of deaths where cocaine was mentioned on death certification between 1998 and 2006[8,9] (figure 3).

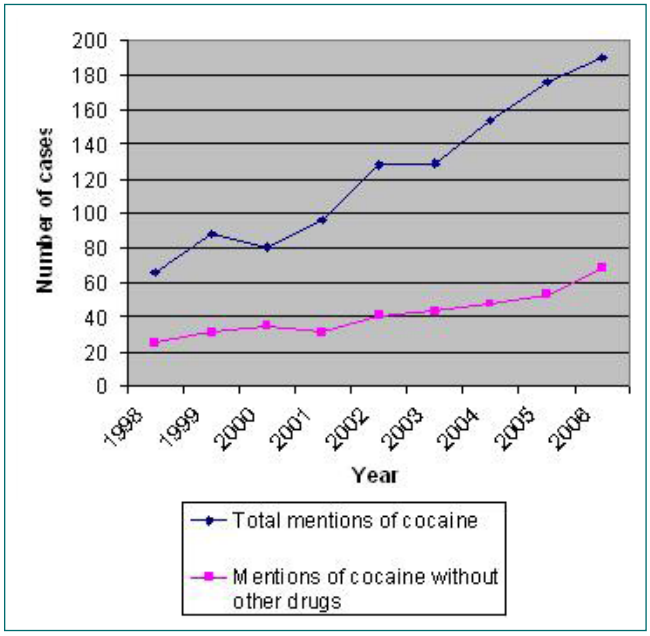

Fig. 3. Annual numbers of deaths where cocaine is mentioned on the death certificate in England and Wales, 1998 to 2006.

Drug addiction services and the PSNI have reported similar trends within Northern Ireland during this time. Figure 4 shows the breakdown of drug use in individuals presenting to drug addiction services for problem drug misuse in Northern Ireland during the 12 month period ending 31st March 2007. Only slightly more individuals reported cocaine (147) than heroin (145) as their primary problem drug, making cocaine the third most reported main problem drug of abuse. The proportion of individuals reporting cocaine use increased to 30% when all subsidiary abused drugs are included, making it the second most common drug of misuse behind cannabis. There was also an increase in the proportion of clients between the periods 2005/06 and 2006/07 who reported cocaine as their main problem drug, from 5% to 11% respectively[10]. Of note, these figures do not include alcohol which is undoubtedly the most common substance of abuse.

There has been an increase in the number of cocaine seizures

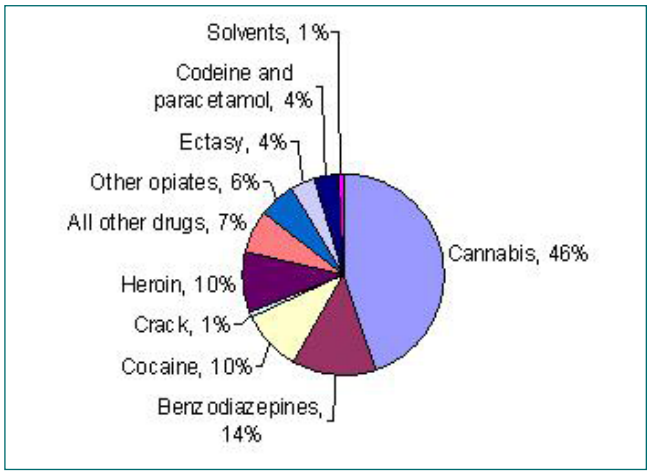

Fig. 4. Main drug of abuse reported by individuals presenting to services for problem drug misuse in Northern Ireland between March 2006 and March 2007.

recorded by the Police Service for Northern Ireland. In the year 2005/06 the PSNI recorded 168 individual seizures of cocaine - this increased to 405 individual seizures in the year 2007/08[7].

These figures may reflect increases in the supply of cocaine within Northern Ireland, changes in the demand, trends within the local drug culture, or reporting of use. As a consequence it seems probable that cocaine will become an increasing problem in Northern Ireland and as a result there will be a corresponding increase in the incidence of cocaine related health problems.

Cocaine use can affect all of the body systems and death can result from a single dose or from the chronic effects due to prolonged use. Table II shows a summary of the major cocaine related diseases. Many of the pathological changes associated with cocaine use appear to be catecholamine mediated. Cocaine use disrupts catecholamine metabolism and it has been shown that cocaine abusers have elevated circulating levels of catecholamines[11]. The most commonly involved system is the cardiovascular due to the cocaine associated elevation in blood pressure, heart rate and vascular tone. Potentially lethal myocardial alterations include hypertrophy, fibrosis and microangiopathy[12-14]. As indicated in Table II, cocaine use is also associated with accelerated atherosclerosis and an increased risk of thrombosis. The risk of sudden death is further increased if an individual has pre-existing coronary artery disease. Similarly, coronary artery spasm (which is commonly quoted by medical students in relation to cocaine use) is unlikely to cause episodes of myocardial infarction unless it occurs at the site of pre-existing coronary atheroma[11]. In this series, 22% of the cases had evidence of coronary atheroma and 28% showed evidence of chronic myocardial damage on microscopy by the detection of myocardial fibrosis. The fibrosis in each case was patchy or multi-focal, which is consistent with catecholamine toxicity rather than the typical, more confluent, pattern seen in coronary atheromatous disease. Chronic cocaine users have an increased incidence of cardiac hypertrophy, which further increases the risk of sudden cardiac death, and 50% of the hearts examined were over 400g in weight, in keeping with a degree of myocardial hypertrophy.

TABLE II.

Major Cocaine associated diseases

Cardiovascular System	• Myocardial infarction • Arrhythmia • Accelerated atherosclerosis • Thrombosis • Coronary artery spasm • Myocardial hypertrophy • Myocardial fibrosis • Aortic dissection
Central Nervous System	• Cerebral infarction • Subarachnoid haemorrhage • Intracranial haemorrhage • Seizures • Excited Delirium
Respiratory System	• Erosion and perforation of nasal septum • Bronchiolitis obliterans • Pulmonary oedema • Pulmonary hypertension
Gastrointestinal System	• Ischaemic colitis
Renal System	• Acute tubular necrosis due to Rhabdomyolysis • Accelerated arteriosclerosis • Infarction and thrombosis

The second major organ system associated with sudden death and cocaine use is the central nervous system. There were no definite cases within this series in which death was attributed to central nervous system sequelae of cocaine. However, it is well recognised that the incidence of intracerebral haemorrhage, cerebral ischaemia and subarachnoid haemorrhage following drug abuse is increasing[15]. Seventeen percent of the cases in this study showed signs of tongue biting, but this is a non specific finding and should not be taken as definitive evidence of a seizure.

Excited delirium is often associated with cocaine use and is widely reported in the literature following numerous controversial cases involving individuals, apparently suffering from this condition, who were in the custody of the police or who were being chased by the police at the time of death[16,17]. Excited delirium is characterised by hyperthermia, delirium, agitation, respiratory arrest and subsequent death. The precise mechanism of death in these cases is somewhat controversial, and a full discussion is beyond the scope of this review, but it is often associated with hyperthermia, rhabdomyolosis, hyperkalaemia and sudden cardio-respiratory arrest[18]. None of the cases in this series specifically recorded a diagnosis of excited delirium. However, there were two cases in which bizarre behaviour was noted prior to death. The first involved apparently uncontrolled physical activity, within the confines of a bedroom, which resulted in multiple injuries. The second reported that the deceased individual had forced a vacuum cleaner nozzle into his mouth, apparently to alleviate shortness of breath.

There has been considerable media attention surrounding cases of cocaine related nasal septum perforation. This is often due to celebrities using nasal insufflation of cocaine. Such is the increasing usage of cocaine worldwide that its' insufflation should be included in the differential diagnosis of destructive lesions of the mid face, along side more classical diagnoses such as Wegener's Granulomatosis[19]. In this series only 39% of cases record a nasal swab being taken at post mortem and all of these yielded a positive result for cocaine. None of these demonstrated any obvious nasal septum necrosis.

Additional common routes of administration of cocaine include intravenous injection and oral consumption. Twenty eight percent of cases recorded needle marks on external examination at post mortem. None of these are thought to have been caused by the solitary injection of cocaine and all were associated with either combined opiate use or medical intervention. Seventeen percent of the seven cases in which stomach contents were analysed were positive for cocaine. This may indicate oral consumption but it may also be accounted for by swallowing of traces cocaine following nasal insufflation or redistribution in the post mortem period. In cases of oral consumption it is recognised that dentists may encounter individuals with cocaine related oral disease[20]. Finally, crack cocaine, which is cocaine produced in its base form, can be smoked and the detection of the cocaine metabolite anhydroecgonine methyl ester, in toxicological specimens, would confirm this route of administration[21]. Routine toxicological analysis does not screen for this metabolite.

Analysis and interpretation of post-mortem toxicological specimens is complex and provides a number of very specific challenges. These include consideration of the unstable nature and degradation of the substance and redistribution of the substance from tissues containing a higher concentration than the blood during the post-mortem interval. Furthermore, with prolonged usage of some drugs, including cocaine, tolerance will undoubtedly develop to the desired effects[22]. Therefore, there is no well defined fatal range of blood levels for cocaine. Indeed, in cases in which toxicological analysis is negative for cocaine but at post mortem there is evidence of potentially fatal complications of the drug in a known user, it would not be unreasonable to include cocaine as a factor in death. Unmetabolised cocaine was detected in 14 cases (78%), indicating recent usage of the drug prior to death. The term 'recent usage' is often cited as it can be difficult, as with any drug, to give a dogmatic indication of the time prior to death following its administration The half life of cocaine is reported as being between 0.7 and 1.5 hours, depending on whether or not the individual is a chronic or naïve user. In the absence of alcohol the principle metabolite of cocaine is benzoylecgonine and this was detected in 17 of the reviewed cases, including the 4 cases in which no unmetabolised cocaine was detected. Benzoylecgonine has a much longer half-life than cocaine, approximately 4.5 hours, and is likely to be detectable in the plasma for up to 48hrs after ingestion[23]. The single case in which no benzoylecgonine was detected would indicate extremely rapid death following administration of cocaine.

CONCLUSION

The incidence of cocaine associated deaths recorded by the State Pathologist's Department has increased during the period 1999-2007. This upward trend appears to reflect similar trends in statistics published by other agencies which show increased availability and use of cocaine in Northern Ireland. As the use of cocaine continues to increase the medical profession will increasingly be exposed to cocaine related morbidity and mortality.

The author has no conflict of interest.

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Paper

The incidence and rate of rhegmatogenous retinal detachment seven years after cataract surgery in patients with high myopia.

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ABSTRACT

Background: Cataract extraction is the most commonly performed surgery in the National Health Service. Myopia increases the risk of postoperative rhegmatogenous retinal detachment (RRD). The aim of this study was to determine the incidence and rate of RRD seven years after cataract extraction in highly myopic eyes.

Methods: Retrospective review was performed of notes of all high myopes (axial length 26.0 mm or more) who underwent cataract extraction during the study period in one centre.

Results: 84 eyes met the study criteria. Follow-up time from surgery was 93 to 147 months (median 127 months). The average axial length was 28.72 mm (sd 1.37). Two eyes developed post-operative RRD; the incidence was 2.4% and the rate one RRD per 441.6 person-years. The results of 15 other studies on the incidence of RRD after cataract extraction in high myopia were pooled and combined with our estimate.

Conclusion: Both patients in our study who developed RRD had risk factors for this complication as well as high myopia. Risk factors are discussed in the light of our results and the pooled estimate.

Our follow-up time is longer than most. Future case series should calculate rates to allow meaningful comparison of case series.

Keywords: Extracapsular cataract extraction, Myopia, Phacoemulsification rate, Retinal detachment

INTRODUCTION

Cataract extraction is the most commonly performed surgery in the United Kingdom's National Health Service[1] and in the United States[2]. Features of cataract surgery such as short procedure times, day surgery and high success rates can lull patients into believing that it is a risk free procedure. However sight threatening postoperative complications exist, and the most common of these is rhegmatogenous retinal detachment (RRD)[3]. The normal lifetime risk of RRD in high myopia without surgery has been estimated to be 40 times the lifetime risk of RD in emmetropia[4], and myopia also increases the risk of postoperative RRD[5]. The aim of this retrospective study was to determine our incidence and rate of primary or recurrent RRD following cataract extraction in highly myopic eyes, and to review pertinent risk factors in the light of our and others' experiences.

METHODS

All high myopes who had undergone cataract surgery in one centre (the Royal Group of Hospitals, Belfast, Northern Ireland {RGH}) between January 1995 and December 1999 inclusive were identified. Their electronic and written medical records in two ophthalmology units were examined retrospectively. The two centres were the RGH and Altnagelvin Area Hospital, Londonderry, Northern Ireland (AAH). High myopia was defined as an axial length of 26.0mm or more as determined by A-scan biometry (Humphrey). Eyes with shorter axial lengths were not included. For patients who had cataract surgery in both eyes within the study period, only the first eye to have surgery was included. Eyes with a history of retinal detachment were excluded. The following details were recorded: sex; age; axial length; use of prophylactic laser photocoagulation; intraoperative and postoperative complications; intraocular lens (IOL) power and position and use of neodymium-doped yttrium aluminium garnet (Nd:YAG) laser capsulotomy. All patients had had a pre-operative assessment. Corneal curvatures were measured with a keratometer. A-scan biometry was performed and IOL power determined by the Sanders Retzlaff Kraff (SRK) II formula. All patients had postoperative education about the symptoms of a retinal tear or detachment. All cataract surgery was performed by consultants or experienced junior surgeons using similar techniques. There were at least two postoperative clinic visits per patient. The nature of any

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TABLE I.

Data on the cases of post-operative RRD

	Case 1	Case 2
Age at time of surgery (years)	47	59
Sex	Male	Male
Fellow eye	-3.5 D	Artificial Eye
Preoperative Myopia (D)	-7	-2.5DS / -1.0DC
Axial Length (mm)	29.02	26.92
History of previous RD	No	Yes (fellow eye)
IOL	+8D (posterior chamber)	+9D (posterior chamber)
Type of procedure	Phacoemulsification	Phacoemulsification
Intraoperative complications	None	Zonular dehiscence and vitreous prolapse
Time of RD post-cataract surgery	60 months	27 months
Nd-YAG laser for PCO	Yes	No
BCVA at final follow up	20/40	20/60

postoperative ophthalmic problems, which involved either laser or surgical procedures, was recorded. This study adhered to the guidelines of the Declaration of Helsinki.

A search was performed on Medline for studies published after 1993 on retinal detachment following cataract extraction in high myopia. Papers on clear lens extraction for refractive purposes were excluded. Information on the incidence of retinal detachment following extracapsular (ECCE: meaning extraction by nucleus expression) and phacoemulsification procedures was collated and pooled.

RESULTS

Eighty-four eyes met the study criteria. The average age at the time of cataract surgery was 69.35 years (s.d. 11.81: range 32 – 92 years). Twenty-two patients were male, 62 female. Median follow-up time from cataract surgery was 127 months (93 to 147 months). Six patients died during the follow-up period, a median of 96 months after cataract surgery (range 74 – 131 months). Two eyes had been excluded as they had a history of retinal detachment in the operated eye. Three eyes had a history of RRD in the fellow-eye: these were included. Prophylactic treatment of predisposing retinal lesions was not performed in any case. Phacoemulsification was performed in 71 cases and ECCE in 11 cases. Trabeculectomy was combined with phacoemulsification in one case, and trabeculectomy with ECCE was carried out in one case. The average axial length was 28.72mm (s.d. 1.37, range 26.50 – 32.11mm). The median power of the IOL used was +8 dioptres (D) (0.0D to +10D). (In one case, data on IOL strength was unavailable.) In two cases a capsular tear occurred intraoperatively, but no vitreous prolapse was noted and the IOL was in each case placed in the capsular bag. In one case vitreous was noted in the anterior segment intraoperatively (case two of RRD, described below). In one case iris prolapse was noted postoperatively: surgical repair was undertaken 20 days postoperatively. One eye had no lens implant at the time of surgery, but 76 months later had secondary implantation of a +10D lens in the posterior capsular bag. Due to postoperative high myopia, this lens was exchanged for a +4D lens placed in the ciliary sulcus one week later. Thirty-two eyes underwent post-operative Nd-YAG posterior capsulotomy for posterior capsular thickening. The median time from cataract surgery to laser capsulotomy was 46 months (range 5 – 134 months).

Two of the 84 eyes developed post-operative RRD (table I). This represents a rate of one RRD per 441.6 person-years, or an incidence of 2.4%. Both cases with RRD were male, aged 47 years (case one) and 59 years (case two) at the time of cataract surgery.

In case one of RRD, uncomplicated phacoemulsification was performed and a +8D IOL placed in the posterior chamber. The axial length was 29.02mm. Posterior capsular thickening developed and 57 months following cataract surgery Nd-YAG laser posterior capsulotomy was carried out. Twelve shots of 2.3mJ were used. Three months following YAG laser treatment the patient bumped his head off a pillar, and developed floaters and photopsia the same day. He presented 2 days later with RRD associated with two horseshoe shaped tears. This was treated with cryopexy and application of a scleral buckle. Seventy-six months following RRD repair, the Snellen visual acuity in the eye was 20/30 with glasses and the patient was discharged from clinic.

Case two had a history of RRD in the fellow eye 19 years prior to the pertinent cataract operation. The fellow eye RRD had presented immediately following a slip, when the eye hit a chair. Two attempts were made to surgically repair the RRD, but these were unsuccessful and the eye became phthisical. The patient wore a cosmetic shell over this fellow phthisical eye. The other eye had an axial length of 26.92mm. During the phacoemulsification procedure a strand of vitreous was noted in the anterior segment immediately after placement of a +9D IOL in the capsular bag. This was thought to be due to zonular dehiscence. Anterior vitrectomy was not necessary, and when Miochol® (acetylcholine chloride) was applied, the pupil constricted satisfactorily and vitreous was no longer evident. Twenty-seven months later the patient presented with a superior bullous RRD. A posterior and a peripheral retinal

TABLE II.

Reported incidences of RD following lens extraction.

Phaco +/- IOL			ECCE +/- IOL				
Author (yr of pub)	**N. of eyes**	**N. of RRDs**	**N. of eyes**	**N. of RRDs**	**Def. of myopia**	**Age range (years)**	**Follow-up (months)**
Alio[4] (07)	439	12(2.7%)	0	-	Ax.L. 26.0mm or more & SE -6.0D or more	21 - 90	2 - 147
Alldredge[5] (98)	80	0	0	-	-7.0D or more minus		9 – 77
Badr[6] (95)	0	-	368	6(1.6%)	Ax.L. 26.0mm or more	30 - 86	6 - 86
Fan[7] (99)	45	1(2.2%)	73	1(1.4%)	Ax.L. 26.0mm or more	29 - 84	12 - 89
Jacobi[8] (97)	0	-	253	3(1.2%)	Ax.L. 27.0mm or more	66 +/- 11.8	7 - 103
Ku[9] (02)	62	1(1.6%)	63	1(1.6%)	Ax.L. 26.0mm or more	61.6 mean +/- 12.27	6 – 82
Liang[10] (97)	0	-	90	1(1.1%)	Ax.L. 27.0mm or more	49 – 75	27 – 33
Liesenhoff[11] (94)	0	-	136	5(3.7%)	Ax.L. 26.0mm or more	33 - 92	Minimum 24
Lyle[12] (96)	109	1(0.9%)	0	-	IOL 11D or less & Ax.L. 26.0mm or more	39 - 89	3 - 79
Nissen[13] (98)	0	-	237	4(1.7%)	Ax.L. 25.5mm or more	40 - 93	14 – 32
Ravalico[14] * (03)	237	0	147	0	IOL 11D or less	21 - 90	8 – 146
Ripandelli[15] (03)	930	74(8.0%)	0	-	-15D or more	39 - 81	36
Tosi[16] (03)	73	1 (1.4%) †	0	-	Ax.L. 29.1mm or more	53 - 91	48 - 78
Tsai[17] (07)‡	36	?	16	?	Ax.L. 26.0mm or more	34 - 91	25 – 103
Williams	**72**	**2 (2.8%)**	**12**	**0**	**Ax.L. 26.0mm or more**	**32 - 92**	**93 - 147**
Zhang[18](04)	68	0	0	-	Minus 10 D to minus 20D	27 - 85	3 – 12
TOTAL / RANGE	**2115**	**92 (4.4%)**	**1379**	**21 (1.5%)**	_	**21 - 93**	**2 - 147**

* Not including four cases of post-operative retinal tears were treated with laser retinopexy. † Not including three cases of post-operative retinal tear, treated with laser retinopexy. ‡ The figures on surgery and RRD numbers of Tsai *et al* were not included in the totals, as it was unclear how many undergoing each type of surgery had RRD. In this study two eyes developed RRD postoperatively

Ax.L - axial length, D - dioptres, N- number, Ref. - refraction, SE - spherical equivalent, Yr of pub - year of publication

hole were noted. Surgery consisted of pars plana vitrectomy, gas tamponade, laser and cryo retinopexy, and placement of a scleral sponge. Twelve months later the vision in this eye was 20/50, and he was discharged from clinic.

Fifteen other studies published after 1993 were found using Medline on the incidence of RRD after cataract extraction in high myopia (table II)[6-20]. This figure does not include papers on lens extraction for primarily refractive purposes.

DISCUSSION

RRD is a well recognised complication of cataract surgery. Risk factors include refractive myopia and increased axial length[5]. The aim of the present study was to retrospectively examine our experience and to review selected factors influencing retinal detachment after cataract extraction in highly myopic eyes.

In our series 2.4% of high myopes developed RRD following cataract extraction, and the rate was one RRD per 441.6 person-years. No non-myopic control group was studied, but the incidence of RRD after cataract surgery in eyes of any axial length has been reported to be to be 0.5 to 1.0%[3]. No data on the *rate* of RRD following cataract surgery in eyes of any axial length has been published to the best of our knowledge, although the risk at certain postoperative time points has been calculated[6].

Many risk factors for RRD following cataract extraction have been identified. In summary[5], reported risk factors include male sex, younger age, ethnic origin or race[21], increased axial length, a history or family history of retinal detachment, lack of an intact posterior capsule, vitreous loss, vitreoretinal pathological features such as lattice degeneration or ocular trauma after surgery[22]. An intraocular lens implant is thought to be protective compared to aphakia[10]. The intraoperative maintenance of an intact posterior capsule is important in reducing the risk of RRD[23,24]. Anterior vitrectomy is thought to be protective by preventing vitreoretinal traction. The two patients who developed RRD (table one) had risk factors for post-cataract surgery RRD as well as high myopia. Both were male. Case one had had Nd-YAG laser posterior capsulotomy. Case two had a history of phakic RRD in the fellow eye and during cataract surgery prolapse of a strand of vitreous occurred. In both cases of RRD in our series, there was a

history of head trauma temporally related to the apparent onset of an RRD. It would be impossible to accurately determine the prevalence of post-operative trauma in our sample. However we suggest that pseudophakic high myopes should be advised to avoid contact sports and if possible, situations where there is a risk of tripping or falling. It is noteworthy that in one of the two cases, the fellow-eye had no useful vision (table one): this reaffirms the importance of high quality cataract surgery in high myopes.

In this study both rate and incidence of primary or recurrent RRD are reported. The problem with the use of incidence is said to be the dependence on the length of follow-up[25]. This is illustrated by the fact that in papers in which the incidence of RRD following phacoemulsification is less than our figure of 2.4%, the minimum follow-up is much lower than our minimum follow-up of over 7 years (93 months). In the pooled studies other than our own study, the median minimum follow-up time was 9 months (range 2 - 48 months), and the median maximum follow-up time was 80.5 months (range 12 - 147 months). Our follow-up time, of 93 to 147 months, is longer than most. Our follow-up data highlights that the risk exists for at least 5 years after surgery in high myopes, as one of the RRDs in our sample occurred 60 months after cataract surgery. It has been said that increased risk of RRD after cataract extraction remains up to two decades after surgery[23]. However RRD occurring years after cataract surgery may be related to the natural history of myopia, rather than pseudophakia *per se*.

Rate is therefore said to be a more valid measure to report than incidence in case series in which the length of follow-up for each subject varies[25]. As rate is not reported in any of the collated studies, incidence must be used to compare their results. The purpose of combining study estimates is that the resultant large number of subjects increases the likely accuracy of the estimate of incidence, at least for a minimum of two months follow-up (table II). One weakness of pooling estimates is that studies vary in several ways. Age-range and ethnicity of the sample, use of prophylactic laser, study design, surgical technique, length of follow-up and frequency of post-operative visits all vary. What is being estimated therefore becomes blurred. Conversely the action of pooling studies that vary in certain aspects may be to improve the generalisability of findings. Some studies used axial length to define myopia while others used a refractive criterion. Nevertheless, it is possible to combine the estimates of post-operative RRD incidence and define myopia simply as "high". In different studies intraocular lens implants were used in all, some or none of the subjects. Information on how many subjects received or did not receive a lens implant was not available in many of the papers. It is merely possible therefore to give a pooled estimate of RRD incidence following phacoemulsification with or without a lens implant, and for ECCE with or without a lens implant.

Jacobi *et al*[10] summarised the results of eight other studies, published from 1984 to 1993, on pseudophakic RD in high axial myopia: in these studies the incidence of RD varied from 1.7% to 7.5%. We summarised findings of studies published from 1994 onwards, a period when the use of ECCE was declining and that of phacoemulsification increasing. When these studies are pooled, including ours, the mean incidence of RRD following phacoemulsification, with or without an IOL, is 4.4% (range 0 to 8%), and following ECCE with or without an IOL the pooled mean is 1.5% (0 to 3.7%).

Both of our patients who developed retinal detachment had undergone phacoemulsification. In Northern Ireland almost all cataract operations are now done by phacoemulsification rather than by ECCE. In our study on surgery performed in the late 1990s, 84.5% of cataract operations were by phacoemulsification, the remainder being ECCEs. The collated results suggest that ECCE is associated with less risk of post-operative RRD than phacoemulsification. Future studies on surgery from more recent periods may show the reverse trend: a lower risk of RRD following phacoemulsification as ECCE is now often reserved for cataracts which are denser or more 'difficult' (for example, if there is zonular instability), and higher skill levels for phacoemulsification are established as the technique predominates. Furthermore phacoemulsification fluidics and small incisions are said to reduce forward movement of the vitreous[18].

Posterior capsule opacification (PCO) requiring Nd-YAG laser occurred in 37.6% (n = 32) of eyes in our study. One would expect patients, individual clinicians and ophthalmology centres to vary in their tolerance of PCO and their readiness to intervene, and reported rates of laser for PCO vary widely[26]. Nd-YAG laser capsulotomy is reported to increase the risk of RRD 3.9 fold [21]. The incidence of RRD following Nd-YAG posterior capsulotomy varies in the published data from 0[27] to 0.89%[28] to 10% in highly myopic eyes[29]. One (3.1%) of the eyes in our study that underwent Nd-YAG laser developed RRD three months following capsulotomy. It is not clear how much the parameters of Nd-YAG laser influence the risk of RRD. For example it is unknown whether many small acoustic shock waves or few large waves passing through the posterior chamber have a greater effect: this may be worthy of further study. It is also not known how rupture of the posterior capsule, intra- or post- operatively, increases the risk of RRD although changes in the nature of the vitreous, rupture of the anterior hyaloid face and vitreoretinal traction caused by forward movement of the vitreous are important.

Some of the studies whose results were pooled used prophylactic laser for predisposing retinal lesions and some did not. In our study prophylactic laser was not performed in any case. Complete fundal examination with scleral depression was not performed in all our cases, and therefore it is impossible to comment on the prevalence of predisposing retinal lesions. In studies by Lyle and Jin[14] and Fan[9] on retinal complications following cataract extraction in myopia, none of the patients treated prophylactically with argon laser photocoagulation developed retinal detachment. However the benefit of prophylactic treatment of any type of retinal lesion is not established. Retinal tears and subsequent detachment can occur in previously normal areas of retina or at the edge of photocoagulation scars[30,31]. Evidence for a policy of treatment only of symptomatic retinal tears was reported by Wilkinson[32], and we feel our results support this policy.

Although our estimate of the incidence of RRD following cataract surgery in highly myopic eyes is similar to the incidence in the other pooled studies, our figures are subject to several potential sources of error. The two centres where

records were examined were the RGH and AAH, chosen as the only centres in the region in which RRDs were treated during the whole study period. The majority of RRDs in the region are treated at the RGH. However from 1997 RRDs were also treated at another unit (the Mater Hospital). Furthermore it is possible that RRD cases treated elsewhere were missed, or that some patients with RRD failed to seek care or were not referred to an ophthalmologist. We believe it is likely that few, if any, cases of RRD were missed. All of the patients had addresses in Northern Ireland at the end of the follow-up time, reflecting the stability of the population. The possibility remains however that our estimate of this complication is an underestimate. Also the number and timing of follow up visits varied among our patients. More frequent visits may in theory allow identification and treatment of tears before RD develops. The retrospective nature of our study implies reliance on case notes being accurate and complete, which is not certain. Nevertheless the present study serves to highlight RRD as a complication of cataract surgery, especially in high myopes.

Future case series should follow the advice of Jabs[25] to calculate rates to allow meaningful comparison of case series. A larger sample size than ours would provide more accurate data. Furthermore the precise prevalence of and risk posed by various predisposing retinal lesions, such as lattice and cobblestone degeneration, staphylomata and the state of the posterior vitreous, would be an interesting focus for prospective study. Our retrospective study relied on case notes, which did not uniformly record such details. Risk factors for pseudophakic RRD were present in both cases in our study that developed RRD. The risk of complications and the symptoms of RRD should be explained carefully to all patients pre-operatively, particularly myopes in whom RRD is more likely despite uncomplicated surgery or prophylactic retinal treatment. Should posterior capsular rupture occur during cataract surgery the ophthalmologist should be alert to the fact that how this is managed can influence the risk of subsequent RRD. Furthermore in high myopia the need for Nd-YAG posterior capsulotomy should be carefully weighed against the risk of RRD. Patient education is crucial given the variable but potentially long duration from surgery to RRD.

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Paper

Non-epithelial malignancies and metastatic tumours of the breast

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ABSTRACT

Introduction: Non-epithelial breast malignancies include primary lymphomas, sarcomas, haematological malignancies, melanomas as well as secondary metastases to the breast. They account for less than 1% of all breast tumours. The demographics and clinical features are similar to epithelial breast cancers but the prognosis and management options are often very different. Most reported series are small with limited follow-up. The main aim of this study was to review our experience for these malignancies and to compare this with the published literature.

Methods: A 14-year retrospective review of all breast resection specimens was completed in the Antrim Area Hospital Cancer Unit. Clinical records of patients diagnosed with non-epithelial breast malignancies were then reviewed for data regarding patient demographics, clinical presentation, pre-operative investigations, operative findings and outcome. Pathology reports were examined carefully for tumour type, location and for evidence of lymphovascular spread. This data was compared with the available literature.

Results: Nineteen (F = 16) patients were found to have non-epithelial breast malignancies between April 1994 and August 2007. Mean age was 61.6 years (range 25-86). 17 patients (89.5%) presented with a palpable lump, mastalgia or skin change, while 2 (10.5%) patients' tumours were detected through screening. The histological types of non-epithelial malignancies were as follows: lymphoma (n = 8; M = 1 and F = 7, mean age: 68.5 range 52-86), sarcoma (n = 5; M = 1 and F = 4, mean age 56.4 range 29-69), malignant melanoma (n = 3; M = 1 and F = 2, mean age 54.3 range 25-70), multiple myeloma (n = 1; F, 71), metastatic renal cell carcinoma (n = 1; F, 63) and metastatic carcinoid tumour (n = 1; F, 52). The mean follow-up was 1541 days (32-4589 days). Nine patients were alive at the end of follow-up. Only 1 of 11 deaths was not directly related to the malignancy. The average time from surgery to death was 798.5 days (range 32-3248 days).

Conclusion: Non-epithelial breast malignancies are rare cancers with significant mortality rates. Correct diagnosis and avoidance of inappropriate therapies requires a comprehensive triple assessment and a multidisciplinary management approach.

Keywords: Breast, lymphoma, melanoma, myeloma, renal, neoplasm, sarcoma.

INTRODUCTION

Breast cancer is one of the most common cancers in Northern Ireland with an annual incidence of approximately 1000 newly diagnosed cases and over 300 deaths[1]. Between 1993 and 2003, the incidence of breast cancer in Northern Ireland increased by an average of 1.1% per year - equivalent to 20 cases[2]. Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for 10% of all new cancers and 23% of all female cancer cases[3].

Carcinomas such as ductal and lobular carcinoma are responsible for over 95% of all breast cancers[4]. Non-epithelial breast malignancies include haematogenous and non-epithelial tumours such as lymphoma, sarcoma and metastatic breast neoplasms of neuroendocrine, renal or skin origins[5]. Less than 1% of breast tumours are non-epithelial cancers and between 0.5% and 2% are metastatic deposits[5,6]. Much less is known about these non-epithelial malignancies of the breast compared with epithelial breast cancers. Most reported series are small with limited follow-up data. Young *et al* investigated 363,801 patients with newly diagnosed malignant breast cancers between 1994 and 1998 and found that 1401 (0.4%) were non-epithelial in origin[5]. The majority of these were sarcomas. A further 613 tumours were classified as haematopoietic cancers and were mostly lymphomas. The presentation, demographics and clinical features of non-epithelial and epithelial breast malignancies are similar. However, the prognosis and management options are often very different. Our objective was to review all patients diagnosed with non-epithelial malignancies of the breast and to compare our clinical experience with the published evidence.

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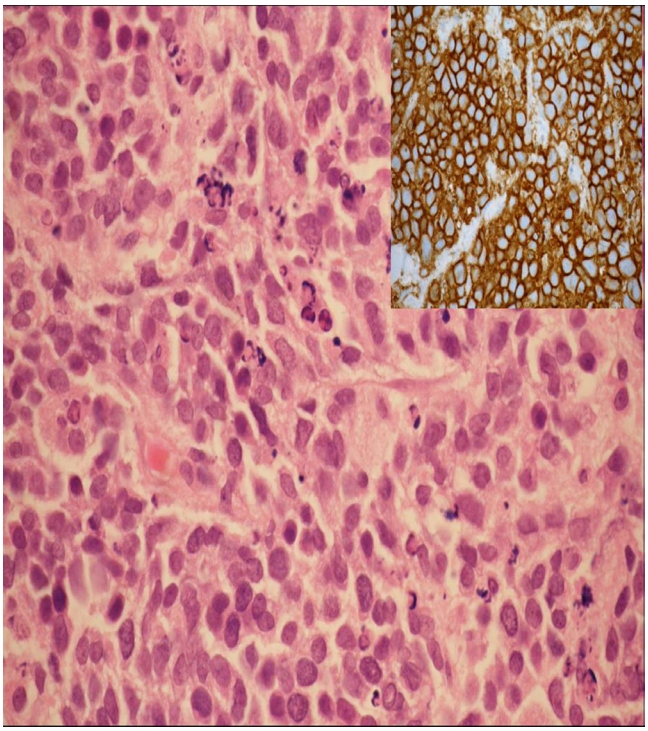

Fig 1. High-grade non-Hodgkin's breast lymphoma (haemotoxylin and eosin x 200) (Inset CD45 staining). This field shows large blast-like lymphoid cells with conspicuous background apoptosis, features in keeping with a diffuse large B-cell lymphoma.

METHODS

A 14-year retrospective histopathological review of all breast resection specimens was completed in the Antrim Area Hospital Cancer Unit. Clinical records of patients diagnosed with non-epithelial breast malignancies were then reviewed for data regarding patient demographics, clinical presentation, pre-operative investigations, operative findings, treatment and outcome. Investigative modalities were graded in a standardised manner where grade 1 corresponded to normal appearance, grade 2 benign disease, grade 3 atypical or indeterminate but probably benign, grade 4 suspicious of malignancy and grade 5 consistent with malignancy. Pathology reports were examined carefully for tumour type, location and for evidence of lymphovascular spread.

We differentiated primary breast sarcoma from cystosarcoma phyllodes[7], therefore, we excluded patients with malignant phyllodes tumours. In the absence of adequate clinical follow-up data in the hospital records, a postal questionnaire was sent to each patient's General Practitioner. All aspects of adjuvant therapies were documented.

RESULTS

Approximately 3900 patients had a pathological diagnosis of breast cancer between April 1994 and August 2007. Nineteen (F = 16) were found to have non-mammary breast malignancies (Table I). Mean age was 61.6 years (range 25-86). Seventeen patients presented to a symptomatic breast out-patient clinic with either a history of a breast lump, skin change or mastalgia. Two patients were referred to the breast clinic for further follow-up because of a screening detected abnormality on mammography.

The histological types of non-epithelial malignancies were as follows: lymphoma (n = 8, 0.21% of all breast malignancies), sarcoma (n = 5, 0.13%), malignant melanoma (n = 3, 0.07%), multiple myeloma (n = 1, 0.03%), metastatic renal cell carcinoma (n = 1, 0.03%) and metastatic carcinoid tumour (n = 1, 0.03%) (Figures 1 – 5). The mean follow-up was 1541 days (32-4589 days). Nine patients were alive at the end of follow-up. Only 1 of 11 deaths was not disease related. The mean time from surgery to death was 798.5 days (range 32-3248 days).

Lymphoma

Five female patients (patients 1-5 from table I) were diagnosed with a primary breast lymphoma (mean age 70.4 years, range 59-86 years). Four patients presented with a breast lump. An asymptomatic patient was referred from the breast screening unit. All patients had unilateral disease (left = 2, right = 3). The mean duration of symptoms was 37.3 days (range 7-93 days). Three patients had mammography performed (Grade: M3 = 1 from screening, M4 = 2). One patient had an ultrasound scan (Grade: U3). Four patients had FNA cytology performed (Grade: C1 = 1, C3 = 3). The lymphoma diagnosis was made following core biopsy in two cases and excision biopsy in three cases. Pathological analysis identified primary diffuse large B-cell non-Hodgkins lymphoma (NHL) (n = 4) (Figure 1) and a primary MALT-type lymphoma (n = 1). Four patients had chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin HCl, vincristine (Oncovin), prednisolone). There is no documentation of whether chemotherapy was administered in patients 2 and 4 who both had advanced metastatic disease from their primary breast lymphoma. Patient 3 underwent subsequent radiotherapy for metastatic axillary node disease. Three patients are currently still alive. Patient 5 has had several recurrences and has had further courses of chemotherapy for lung involvement. Patient 1 also required a further course of chemotherapy for recurrence. Patients 2 and 4 died from metastatic spread of their primary breast lymphoma where the mean time from diagnosis to death was 3248 and 32 days respectively.

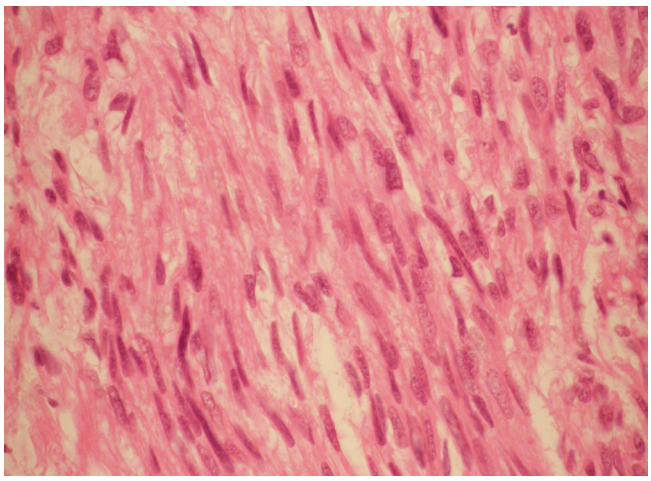

Fig 2. Breast sarcoma (H&E x 200). This field shows large spindle shaped cells with nuclear pleomorphism and eosinophilic cytoplasm. There is no differentiation which would indicate the cell of origin.

Three patients (patients 6-8 from table I, male = 1) were

diagnosed with a metastatic breast lymphoma from a remote primary lesion (mean age 65.3 years, range 52-79 years). All three patients presented with a breast lump while one complained of mastalgia. All patients had unilateral disease (left = 2, right = 1). The mean duration of symptoms was 186.0 days (range 7-365 days). One patient had mammography performed (Grade: M4). One patient had an ultrasound scan (Grade: U4). Two patients had FNA cytology performed (Grade: C2 = 1, C5 = 1). The lymphoma diagnosis was made following core biopsy in one case and excision biopsy in two cases. Pathological analysis identified the presence of metastatic B-cell NHL in all three patients. Two patients had chemotherapy with the CHOP regimen. Patient 6 underwent simple mastectomy without adjuvant therapy. Patient 8 underwent subsequent radiotherapy to treat cerebral metastases. Unfortunately all three patients have died where the mean time from diagnosis to death was 775, 1045 and 133 days for patients 6-8 respectively.

Sarcoma

Three patients (patients 9-11 from table I, male = 1) had primary breast sarcomas (fig 2) with an average age of 50.7 years (range 29-65 years). All patients presented to our symptomatic breast clinic with either a lump (n = 2) and/or mastalgia (n = 2) (left = 2, right = 1). The mean duration of symptoms was 192 days (range 31-365 days). Patients 9 and 10 had palpable masses whereas patient 11 had minimal localised thickening only. Patients 9 and 10 had positive mammograms (M4 = 2) while patients 10 (U4) and 11 (U1) had ultrasound assessments. Fine needle aspiration was positive in patient 9 (C5) but insufficient in patient 11 (C1). Patient 9 underwent simple mastectomy and axillary node clearance for a primary rhabdomyosarcoma where immunohistochemical labeling was positive for actin (smooth muscle) and negative for epithelial markers. Despite adjuvant chemo- and radiotherapy, she died 553-days post-surgery. Patient 10 had a simple mastectomy for dermatofibrosarcoma protruberans and remains well 380-days later. Although ultrasound, magnetic resonance imaging (MRI) and FNA cytology investigations were normal patient 11, further investigation was arranged due to a persistent clinical suspicion of a possible lesion. A subsequent ultrasound-guided excisional biopsy demonstrated an angiosarcoma. She proceeded to simple mastectomy with adjuvant radiotherapy followed by delayed breast reconstruction one-year later. She remains well 1415 days following her initial breast surgery.

Two female patients (patients 12-13 from table I), aged 69 and 61, were diagnosed with metastatic sarcomas from distant primary neoplasms. Patient 12 had a previous primary thigh liposarcoma resection while patient 13 had a previous excision of a primary retroperitoneal leiomyosarcoma. Both of these patients presented with painless lumps in the left breast. The mean duration of symptoms was 5 days (range 3-7 days). Patient 12 had a positive mammogram (M4) and FNA (C5) with confirmation of sarcoma following core biopsy with vimentin positive immunohistochemical labeling while other epithelial, neural (S100) and muscle (actin and desmin) markers were negative. She was treated with palliative chemo- and radiotherapy and died 679 days later. Patient 12 had a positive mammogram (M4) and FNA (C5) with confirmation of sarcoma following core biopsy. Patient 12 did not undergo surgery as staging investigations had shown widespread metastatic disease. She was treated with palliative chemo- and radiotherapy and died 679 days later. Patient 13 proceeded directly to lumpectomy. She refused adjuvant therapy and remains well 2980-days following lumpectomy and has had further surgery for abdominal wall recurrences in the interim.

Malignant melanoma

Three patients (patients 14-16 from table I, male = 1) had a malignant melanoma with an average age of 54.3 years (25-70 years). These patients presented with an enlarging naevus on the right breast (patient 14), a superficial nodule on the left breast (patient 15) and a right-sided breast lump (patient 16). The mean duration of symptoms was 699 days (range 93-1825 days). Patient 14 had palpable axillary nodes and proceeded directly to excision biopsy with ANC. A mastectomy was subsequently required due to involved breast margins from deeper infiltration of the primary melanoma. Although further adjuvant treatment was declined, the patient remains disease-free. Patient 15 had been treated 3-years earlier for metastatic melanoma with lung involvement from a separate lesion on the left arm but was thought to be in remission. In view of the history she proceeded straight to excisional biopsy of the left breast nodule and pathology showed malignant melanoma. She received adjuvant chemotherapy and immunotherapy but developed lung metastases 3-years later. Following further oncological therapy the patient has been disease free for the last 9-years. Patient 16 had been treated with chemotherapy 8-years previously for a cutaneous malignant melanoma of her left lower limb and was also thought to be in remission. She had both USS and mammogram investigations (U = 4, M = 4). Subsequent FNA and core biopsy confirmed malignant melanoma (Figure 3). Despite palliative radiotherapy, this patient died 7-weeks later from metastatic disease.

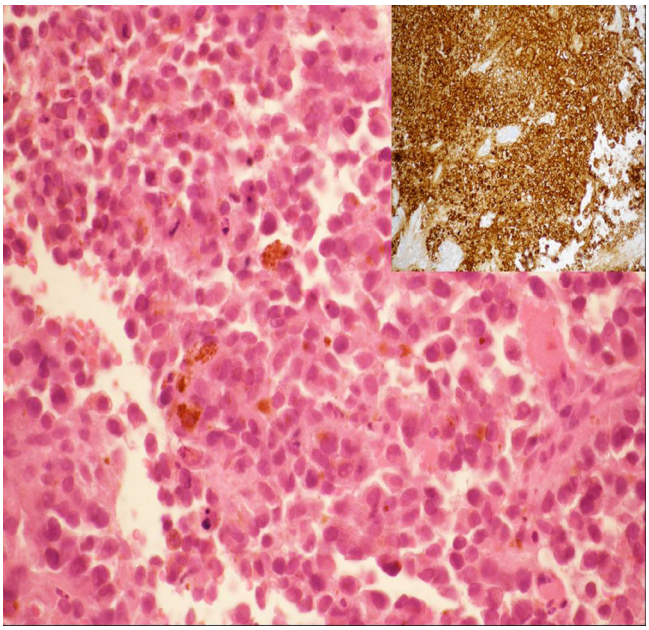

Fig 3. Breast melanoma (H&E x 200) (Inset - Hmb45 immunohistochemistry stain for melanoma). This field shows melanoma cells some of which are producing brown melanin pigment. The cells are HMB45 positive.

Metastatic multiple myeloma

Patient 17 (F, 71) presented with a 28-day history of a right-sided breast lump. She had a history of multiple myeloma and left mastectomy 4-years earlier for a metastatic myelomatous deposit. Although mammography was indeterminate (M = 3), ultrasound imaging was suspicious of malignancy (U = 4). Subsequent FNA and core biopsy investigations were indeterminate. Excisional biopsy confirmed metastatic multiple myeloma which was treated with adjuvant chemotherapy (melphalan in combination with prednisolone and allopurinol) (Figure 4). The patient died from metastatic disease 342 days later.

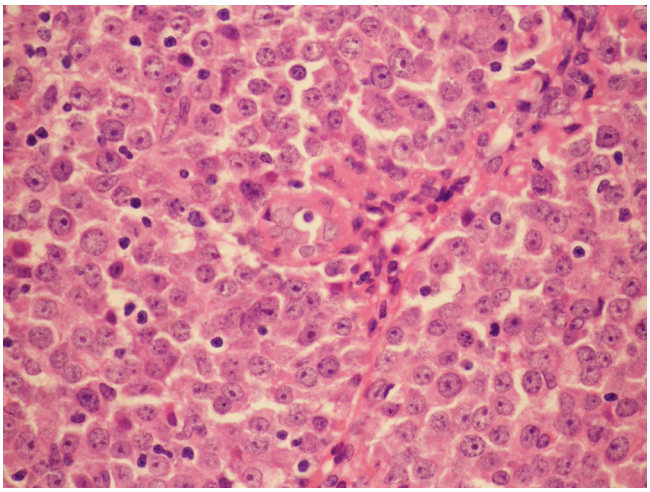

Fig 4. Multiple myeloma deposit right breast (H&E x 200). This field shows large atypical plasma cells many of which are showing immunoblastic differentiation with large central nucleoli.

Metastatic carcinoid tumour

Patient 18 (F, 52) was referred from the breast-screening department with an abnormality in the right breast. USS and FNA investigations were equivocal and suggested fibroadenosis. Core biopsy suggested invasive ductal carcinoma and she proceeded to WLE and ANC. Histopathology analysis confirmed a grade-1 carcinoid tumour without nodal involvement. She proceeded to a simple mastectomy and was subsequently referred to the regional neuroendocrine department. Although she had no clinical evidence of carcinoid syndrome, she was commenced on the somatostatin analogue lanreotide. She was subsequently referred for gastrointestinal screening where a primary carcinoid tumour was detected in the distal small bowel 9-months following her initial breast surgery. A small bowel resection was then performed and she remains well on lanreotide with no evidence of carcinoid syndrome.

Metastatic renal cell carcinoma

Patient 19 (F, 63) presented with a seven-day history of a right-sided breast lump. Past medical history included left nephrectomy for renal cell carcinoma 4-years previously and she had known bony metastases. Mammogram and USS were suspicious of malignancy (M = 4, U = 4). FNA showed malignant cells and core biopsy confirmed metastatic renal cell carcinoma (Figure 5). Wide local excision and ANC was performed and the patient received chemotherapy. A subsequent CT scan revealed widespread metastases. She died 1128 days later.

DISCUSSION

We will discuss the various types of non-epithelial breast malignancies, with particular emphasis on epidemiology, symptomatology, investigation, pathology, and current management strategies for each particular type, with reference to our own experience over the last 14-years.

Lymphoma

Epidemiology: The reported incidence of primary breast lymphoma (PBL) in the literature ranges from 0.04% to 0.5% for all breast malignancies. It is estimated that the breast is involved in less than 1% of all patients with non-Hodgkin's lymphoma and approximately 1.7% of extra-nodal non-Hodgkin lymphomas[8-9]. Secondary spread of lymphomas to the breast is reported to account for just 0.07% of all breast malignancies[8]. However, these secondary lymphomas comprise the largest group (17%) of tumours that metastasise to the breast[8,10]. Our experience was similar with an incidence of 0.13% for PBL and 0.08% for secondary breast lymphomas.

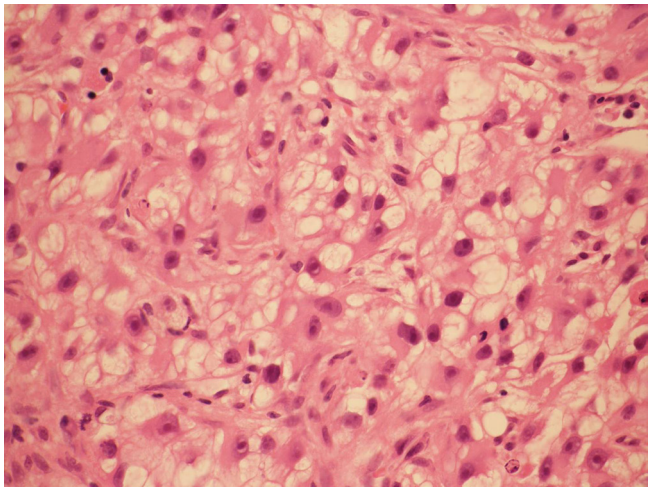

Fig 5. Metastatic renal cell carcinoma of breast (H&E x 200). This section shows the typical morphology of renal cell carcinoma with small pleomorphic nuclei, clear cytoplasm and a fine vascular background.

The reported median age for primary and secondary breast lymphoma ranges from 51 to 61 years[8,11]. The patients in our study were slightly older (mean 70.4 and 65.3 years for primary and secondary lymphomas respectively).

Symptomatology: Wiseman and Liao defined the clinical criteria for the diagnosis of PBL where; the breast is the clinical site of the first major manifestation of the lymphoma, there is no history of previous lymphoma or widespread lymphomatous disease elsewhere and that the lymphoma is demonstrated with close association to breast tissue in the pathologic specimen[12]. They also state that ipsilateral lymph nodes may be involved if they develop simultaneously with the primary breast tumour[12]. The PBL patients in our series presented in a common way with a painless unilateral breast mass. Although bilateral PBL disease has also been reported, we did not identify any such cases in our study[9]. PBL frequently appears as

TABLE I:

Clinical data for all 19 patients

NO	Age	Sex	Symptom	Investigations		Diagnostic (+/-therapeutic) procedure	Pathological Diagnosis	Treatment	Current Status	Length of follow-up (days)
				Mam	USS					
1	59	F	L	+	+	EB	PBL	C	Alive (recurrence 2003)	2741
2	83	F	L, P	n/a	n/a	WLE	PBL	Palliative	Dead	3248
3	63	F	L	+	n/a	WLE	PBL	Dx, C	Alive	4589
4	86	F	L	n/a	n/a	EB	PBL	Palliative	Dead	32
5	61	F	SC	+	n/a	WLE	PBL	C	Alive; several recurrences	3150
6	79	F	L	n/a	n/a	CB	SBL	SM	Dead	775
7	52	M	L	n/a	n/a	EB	SBL	C	Dead	1045
8	65	F	L, P	+	+	FNA/CB	SBL	Dx, C	Dead	133
9	58	F	L, P	+	n/a	FNA	PBS (rhabdomyosarcoma)	SM+ANC, Dx, C,	Dead	553
10	65	M	L	+	+	SM	PBS (dermatofibrosarcoma)	SM	Alive	380
11	29	F	P	n/a	-	FNA / US-guided EB	PBS (angiosarcoma)	SM, Dx	Alive	1415
12	69	F	L	+	n/a	FNA/CB	Metastatic liposarcoma from primary thigh lesion	Palliative C, Dx	Dead	679
13	61	F	L	n/a	n/a	L	Metastatic leiomyosarcoma from primary retroperitoneal lesion	L-	Alive, several recurrences	2980
14	59	M	S	n/a	n/a	EB	Malignant Melanoma	EB+ANC; SM later	Alive	373
15	25	F	L	n/a	n/a	EB	Metastatic malignant Melanoma,	EB, C, I	Alive	4470
16	70	F	L	+	+	FNA/CB	Metastatic malignant Melanoma	Palliative	Dead	50
17	71	F	L	+	+	EB	Metastatic multiple myeloma	EB, C	Dead	342
18	52	F	SC	+	-	WLE	Metastatic Carcinoid	WLE+ANC -	Alive	1210
19	63	F	L	+	n/a	FNA/CB	Metastatic renal cell carcinoma	WLE +ANC, Dx	Dead	1128

(symptom: L = lump, P = pain, S = skin change, SC = screening detected abnormality; investigations: Mam = mammography, US = Ultrasound, n/a = not performed or result not available, + = abnormality detected, - = abnormality not detected; diagnostic (+/- therapeutic) procedure: WLE = wide local excision, SM = simple mastectomy, ANC = axillary node clearance, EB = excisional biopsy, L = lumpectomy, CB = core biopsy; Pathological diagnosis: PBL = primary breast lymphoma, SBL = secondary breast lymphoma, PBS = primary breast sarcoma, Treatment: Dx = radiotherapy, C = chemotherapy, I = immunotherapy).

a benign or less suspicious lesion on clinical assessment even though some reports state that lymphomas are larger at diagnosis than carcinomas[11,13-14]. Skin changes or nipple discharge are uncommon[13]. Previous reports document a right-sided predominance. However, recent studies have not supported this and in our series there was equal involvement bilaterally[8,11,13]. Axillary lymph nodes are involved in 30-40% of cases.[13] Only one patient in this series had palpable nodes (patient 8). The presence of B symptoms (fever, night sweats and weight loss) is uncommon[9].

Investigation: Radiologically, Lyou *et al* described lymphomas as oval-shaped and high-density masses on mammography and as single and hypoechoic masses with circumscribed or microlobulated margins on ultrasonography[15]. The detection

of PBL by screening mammography, as occurred in the case of patient 5, is rare[14]. The reported sensitivity of FNA cytology in breast lymphoma is approximately 90% and is most sensitive when combined with immunohistocytochemistry (IHC) or flow cytometry[8]. In addition to histological analysis, further radiological staging is recommended with CT imaging of the chest, abdomen and pelvis to detect any evidence of visceral or nodal dissemination[8,9].

Pathology: The most common histological type reported in the literature when primary and secondary cases are grouped together is diffuse large B-cell lymphoma which represents 45% to 90% of all cases[8]. Burkitt-type lymphoma, and mucosa-associated lymphoid tissue–type lymphoma have also been documented[9].

Treatment: In our series, surgical biopsy was required for diagnosis in the majority of patients and excision was part of treatment in several patients treated in the earlier part of the study period. In contrast to epithelial breast neoplasms, it is now accepted that surgical resection is usually only indicated for diagnostic purposes in PBL. Jennings *et al* reported that mastectomy conferred no improvement in survival or recurrence risk[11]. They also reported that combined chemoradiotherapy improved survival and recurrence rates in both stage I (node negative) and stage II (node positive) patients[11]. CHOP is the standard chemotherapy regimen[9,11]. The addition of the monoclonal antibody rituximab is occasionally indicated and had been used in the treatment of recurrent disease in Patient 5.

Prognosis: Histological tumour grading and stage can be used to predict patient outcomes. The use of the International Prognostic Index which evaluates risk factors such as Ann Arbor stage, extranodal disease, elevated LDH levels and performance status on echocardiography is limited in PBL[9,16]. The prognosis for PBL is generally poor with improved survival in patients with low-grade disease. Reported five-year survival rates in PBL are 78-89% for stage I patients and 50% for stage II[11]. Three of the five patients (60%; 2 low-grade, 1 high-grade) with PBL in this series survived beyond five years.

Sarcoma

Epidemiology: Primary breast sarcomas (PBS) are reported to account for less than 0.1% of all breast malignancies[7]. The incidence of PBS in our series was 0.08%. Although PBS typically affects women in their forties or fifties, a wide age range has been reported (24-81 years)[7]. The average age of patients in this series was similar (mean age 50.7 years). PBS occurs very rarely in men[7]. Radiotherapy has been implicated in the aetiology of some sarcoma types especially angiosarcoma[17,18]. No cause was identified for any of the patients in our series. Angiosarcoma of the breast accounted for 0.03% of all breast malignancies in this series, which compares with the 0.04% reported in the literature[17]. Angiosarcomas also occur in younger patients with an age range between 20 and 40 years (patient 11)[17].

Symptomatology: PBS most commonly presents as a painless breast lump[7]. Sarcomas tend to spread locally or haematogenously and do not usually spread to regional lymph nodes[18]. Each of the five patients included in this series had palpable breast lumps with no evidence of axillary lymphadenopathy.

Investigation: Radiologically, PBS are generally ill-defined lesions without calcification and may be mistaken for fibroadenomas[19]. A combination of ultrasound and MRI has been recommended for investigation of angiosarcoma[20]. However, both modalities failed to detect an angiosarcoma in patient 11 from our series. Therefore, if clinical suspicion persists, the authors recommend further pathological assessment even if these modalities appear normal. Although FNA cytology permits the diagnosis of sarcomatous lesions, it does not facilitate subtyping or tumour grade. Core-needle or excisional biopsies are therefore invariably required.

Pathology: Malignant fibrous histiocytoma, fibrosarcoma, angiosarcoma, stromal sarcoma, leiomyosarcoma and liposarcoma comprise the major subtypes of breast sarcomas[7,21,22]. Proportional figures of each subtype vary between case series because of differences in classification.

Treatment: Excluding angiosarcomas, current evidence suggests that PBS have a similar course to sarcomas arising at any other site[21]. Surgical resection remains the most important treatment factor influencing outcome[23]. All patients in our series underwent surgical resection apart from patient 12 who was known to have widespread metastatic disease which was treated with palliative chemoradiotherapy. Patient 9 had ANC in addition to resection as FNA and core biopsy respectively had suggested an epithelial malignancy. McGowan *et al* showed no statistically significant cause-specific survival difference between breast-conserving surgery and mastectomy if negative margins were achieved[18]. Wide local excision should be adequate in most cases as tumour multicentricity and axillary spread is rare[18,21,22]. There is no conclusive evidence that radiotherapy is beneficial in PBS. However as radiotherapy has been shown to be beneficial in the treatment of other sarcomas, adjuvant radiotherapy may be indicated for PBS patients with questionable or positive margins, high-grade features and those that are larger in size[22]. The role of chemotherapy in the treatment of PBS is also unclear[22].

Prognosis: PBS is an aggressive tumour. Prognosis is based on tumour size and histological grade[7,21]. Other reported prognostic indicators include the age of the patient, tumour subtype and the presence of positive margins[7,23]. Zelek *et al* reported overall survival rates of 82%, 62% and 36% for patients with grades one, two and three breast sarcomas respectively[21]. Angiosarcomas have been linked with a poorer prognosis[21].

Metastatic Spread to the Breast

Epidemiology: Metastatic spread to the breast from primary tumours at other sites in the body is rare[24]. A retrospective review over a 16-year period showed that non-haematological metastases accounted for 0.2% of all breast malignancies treated[24]. There was a female predominance and the most frequent types of non-haematological tumours spreading to the breast were malignant melanoma and neuroendocrine tumours such as carcinoid[25-27]. Malignant melanoma of the breast skin, as shown in patient 14, accounts for less than 5% of all malignant melanomas whereas melanoma metastases to the breast, as demonstrated in patients 15 and 16, accounts for 1.2% of all malignant melanomas[28,29]. Carcinoid tumours

in the breast may occur as metastases from a known carcinoid primary tumour, as the first presentation of a carcinoid tumour (patient 18), or as a primary carcinoid breast malignancy. Following a review of all documented cases in the literature, Upalakalin *et al* estimated that 41% of all carcinoid tumours in the breast were metastases from elsewhere[27]. There are only isolated case reports documenting renal cell carcinoma metastasising to the breast. Although metastases were present in approximately 30% of patients with renal cell carcinoma, the breast was rarely involved[30]. As overall survival from metastatic disease improves, the incidence of secondary breast malignancies is likely to increase in number.

Symptomatology: The majority of patients have a known primary tumour. However, some patients will present with occult primary disease where the breast metastases are the first manifestation of the disease[24,31]. Patient 18 in this series presented with metastatic carcinoid of the breast and subsequent investigations identified a small bowel carcinoid. In the review of metastases from a variety of different primary sites, Vaughan *et al* reported an average time between the diagnosis of the initial primary malignancy and development of a metastasis to the breast of 60.9 months[24]. We identified a similar time interval for patients with non-haematological breast metastases (Patients 12, 13, 15, 16, 18, 19) of 49.7 months (0-102 months). Metastases to the breast are usually mobile, well-demarcated and firm[24,31]. Skin changes or mastalgia are unusual but axillary lymphadenopathy is often seen[6,32]. Clinical differentiation between metastases to the breast and primary cancers is difficult[26]. In melanoma, the patient will usually be premenopausal and have had a primary lesion on the upper body[28]. The presence of clinically significant extraosseus features in myelomatous metastases occur in less than 5% of cases and usually signifies aggressive disease[26]. Carcinoid syndrome is usually not a feature of carcinoid tumours of the breast. If a patient with a breast lump also has symptoms of carcinoid syndrome then the lump should be biopsied to exclude metastatic carcinoid from a primary elsewhere[27].

Investigation: These malignancies show a wide range of mammographic and ultrasound appearances[31]. They often appear as round, well-circumscribed lesions without the microcalcifications of primary epithelial malignancies and may be misinterpreted as benign lesions[24,31]. Ultrasound commonly shows hypoechoic masses[31]. FNA or ultrasound guided core biopsy is advised to diagnose breast lumps that either clinically or radiographically are not typical of primary breast tumours[6,33].

Pathology: Vergier *et al* reported that histological characteristics of metastases included the presence of well-circumscribed tumours with multiple satellite foci, an absence of an intraductal component or the presence of lymphatic emboli[25]. Histologically, carcinoid tumours of the breast may be misdiagnosed as epithelial malignancies even when the patient has a known history of a carcinoid tumour elsewhere[27]. An accurate diagnosis of a breast metastasis is important to avoid unnecessary mastectomy and to implement appropriate investigations for the primary lesion and to commence systemic chemotherapy if indicated [24].

Treatment: Deciding which treatment is most appropriate can be challenging in these cases as it is often difficult to predict if and when a patient will develop complications of metastatic disease. There is little information in the literature regarding best practice. In the study by Vaughan *et al*, 61% of patients underwent some form of resection but only 22% of these patients had their resection for a curative intent[24]. Surgical debulking or excision for palliative purposes may be appropriate in widely metastatic disease. In cases of melanoma of the breast without multiple deposits, WLE or quandrantectomy is acceptable[29]. For solitary multiple myeloma of the breast, a localised biopsy with radiotherapy has been recommended, with chemotherapy reserved for disseminated disease[26]. With regards to primary carcinoid tumours of the breast, modified radical mastectomy or breast conserving surgery with ANC and radiotherapy has been advised[27]. Patients with metastatic carcinoid tumours should undergo lumpectomy alone[27].

Prognosis: There is limited data in the literature regarding the prognosis of these patients but breast metastases usually indicate disseminated metastatic disease and a poor prognosis[28,34]. As new systemic treatments emerge however survival rates may improve. Vaughan *et al* reported a mean survival time of 17.8 months following the diagnosis of a breast metastasis of non-haematological origin[24]. Survival was similar regardless of primary site apart from patients with medullary thyroid cancer who survived for longer. In this study, three patients with non-haematological metastases to the breast died (patients 12, 16 and 19) with a mean survival time of 619 days (approximately 20 months). Median survival in a review of 27 cases of melanoma metastases to the breast was 12.9 months[28].

CONCLUSION

Non-epithelial malignancies of the breast include primary breast tumours such as lymphoma and sarcoma and metastatic deposits from primary tumours elsewhere in the body. They are rare cancers with a female predominance. Nineteen patients were identified in this 14-year retrospective review accounting for 0.49% of all breast malignancies treated. A thorough history and triple assessment is required to correctly identify these cancers as clinical and radiological differentiation from the more common epithelial cancers is often challenging. Primary breast sarcomas require surgical excision and adjuvant therapy whereas lymphomas can be predominantly managed with oncological therapies alone. Management of metastases to the breast depends on a number of factors including tumour type and extent of metastatic disease.

Conflict of interest - the authors have no conflict of interest.

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Paper

Telemedicine and Trauma Referrals – a Plastic Surgery Pilot Project

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ABSTRACT

A pilot study of the use of digital images as an adjunct to telephone referral was undertaken. Hand trauma represented the majority of the twenty patients included in the study, and the system was found to be an effective aid to delivering appropriate management. We have found image analysis to be a useful addition to the telephone referral process already in use in our unit, but it is unlikely to replace the need for real time clinical assessment of the patient.

INTRODUCTION

Recent papers have demonstrated the value of telemedicine in plastic surgery[1-3]. Most notably, Wallace and colleagues incorporated a three phase trial into their trauma service and found telemedicine to be a valuable method of providing preliminary information, often significantly modifying management[1]. Richard Wootton has described the success of minor injuries telemedicine, which had been applied to over twenty units in the United Kingdom in 2001. He noted that it would be more economically sensible in rural regions like the highlands and islands of Scotland than in London, for example[4].

Our unit provides a plastic surgical service to the whole of Northern Ireland, receiving daily trauma referrals from distant peripheral hospitals and minor injury units. We wished to take advantage of the potential benefits of telemedicine, and decided that the first step should test the reliability of still digital image analysis combined with verbal consultation.

METHODS

A pilot study of twenty trauma patients was undertaken. Each patient in the study was assessed at a trauma clinic by a house officer with very limited plastic surgery experience. This was in order to mirror the limited plastic surgery experience of a doctor in an Accident and Emergency department. Following the assessment, informed consent was taken for digital photography of the injured body part or X-ray. An image of the injured body part or X-ray (on a light-box) was taken using a digital camera. The same camera was used throughout the study, with resolution 3.2 mega pixels and automatic flash. The same room was used for all photography, with standard illumination. The house officer then contacted the registrar, and presented the findings from history and examination. The digital image was viewed on a ward computer. Based on the image and description, a preliminary management decision was made and documented. The registrar then assessed each patient in person. The management decision following face to face consultation was documented and implemented.

RESULTS

Twenty patients were included in the pilot study. Seventeen of these were hand injuries. The distribution is shown in Figure 1. In only one of the twenty patients did face to face consultation highlight important patient history details that were not obtained from the referral. In one of the cases a discrepancy in examination findings was identified (a house officer diagnosis of "significant skin loss" on a finger was deemed insignificant following registrar review). In one patient there was a difference between the management plan based on history / image analysis and the plan following face to face consultation. Five of the twenty patients could have been adequately managed in a casualty department. Thus for a quarter of patients, image analysis could have led to advice which would have precluded the need for transfer to our department.

DISCUSSION

Demartines wrote 'Telemedicine is believed to favour and simplify the exchange and diffusion of information, knowledge and surgical education by permitting broader access to expertise and second opinions without travel'[5]. He recognised that surgical applications of telemedicine remain limited, probably due to a lack of information and the need for more research. In the planning of research he stressed the need to consider the clinical effectiveness of the service as well as the quality of the technology.

A 2001 systematic review of telemedicine literature[6] found that only a few studies compared telemedicine application with conventional service provision (something we attempted to do, albeit on a small scale). Roine felt that more evidence is needed regarding the cost effectiveness of telemedicine, and that implementation of new services should have a sound business case, and a link to data collection and analysis.

Whitten and colleagues echoed the need for better standards of economic analysis within telemedicine studies[7]. They recognised however that 'a telemedicine service that is cost effective in the remote highlands of Scotland is unlikely to generate the same cost effectiveness in the middle of Manchester' (in agreement with Wootton[4]). Yellowlees has outlined seven core principles which underlie the development of a successful telemedicine service[8]: (Table 1)

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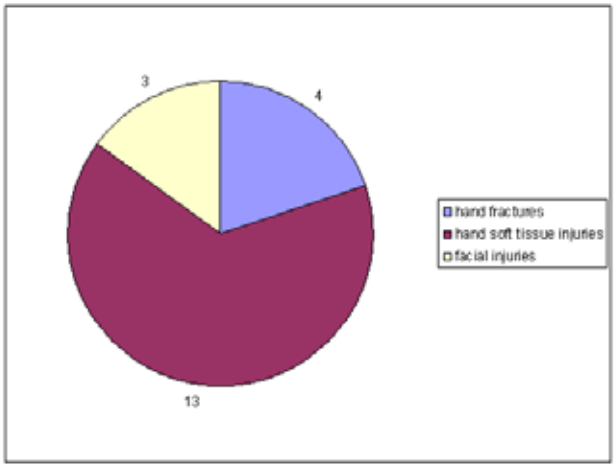

Fig 1. Distribution of trauma clinic injuries

TABLE 1:

Seven core principles

1. Telemedicine applications and sites should be selected pragmatically, rather than philosophically
2. Clinician drivers and telemedicine users must own the systems
3. Telemedicine management and support must be from the 'bottom up' rather than the 'top down'
4. The technology should be as user-friendly as possible
5. Telemedicine users must be well trained and supported, both technically and professionally
6. Telemedicine applications should be evaluated in a clinically appropriate and user-friendly manner
7. Information about the development of telemedicine must be shared

Admittedly, these principles relate more to teams who are setting up more complicated technologies, including video consultations, but they serve as useful reference points. In this study the technology was very simple, with obvious low cost implications. Digital cameras are now commonplace throughout hospitals, and photography departments are generally very facilitative. Our results were encouraging. Face to face consultation by the registrar highlighted only two discrepancies following the referral (one from history and one from examination). In only one instance was management different following face to face consultation (a wound was left to heal, rather than taken to theatre).

A larger study of telemedicine in a plastic surgery department (Wallace, 2008[1]) found that, with the technology, significantly fewer patients needed to attend the department for review, and more patients could be put directly onto a day surgery operating list. The authors felt that telemedicine improved the clarity of the communication process, and facilitated earlier and more frequent senior clinician involvement.

In terms of the size of the problem locally, the number of emergency referrals made to our department is not routinely measured. However, we recently surveyed emergency referrals to plastic surgery units throughout the United Kingdom and Ireland[9]. The 'average unit' receives between six and eight referrals each day, and between three and five each night. The 'average unit' admits between 1000 and 1500 emergency patients per year. Our emergency admissions are now close to 2000 per year, and our referral rates are almost certainly higher than the 'average' above. Most surveyed units received referrals from less than five emergency departments, whereas our unit covers all emergency departments and minor injury units in Northern Ireland. Thus there is a substantial workload and referrals often come from geographically distant locations. Telemedicine would likely be of greatest benefit for such referrals.

This system presents a simple and effective addition to routine trauma management. Due to strict guidelines relating to image storage and transfer[10], it would be advisable for images to be transferred via hospital photography departments. Out of hours, for emergency cases, images can be attached to password protected emails (with secure email accounts set up by the photography department).

It is our view that telemedicine will not (and should not) replace face to face consultation for patients who genuinely need to be seen in a plastic surgery department. It has a role in the early management of peripheral referrals, many of which do not require transfer. It seems possible from this pilot study that unnecessary transfer to the department could be reduced by up to twenty-five percent with the use of telemedicine. A robust controlled trial with larger patient numbers would be indicated to validate any significant changes to the current management system. We would hope to start this within the next year.

The authors have no conflict of interest.

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Paper

Immediate and long-term outcomes of Lichtenstein and Kugel patch operations for inguinal hernia repair.

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ABSTRACT

Aim: The aim of this retrospective study is to compare the immediate and long-term postoperative outcomes of Lichtenstein and Kugel repair of inguinal hernia.

Methods: From 1996 to 2006, 219 consecutive patients underwent inguinal hernia repair - 92 using a standard Lichtenstein repair and 127 with a Kugel patch. Patient characteristics, length of postoperative hospital stay and complication rates were assessed by retrospective review of the notes. Recurrence and chronic groin pain were assessed by postal questionnaire (with a follow up by telephone interview for non-responders). Patients with symptoms or an apparent groin swelling were reassessed by one of the authors (BD).

Results: There were 214 men and 5 women. Patients ranged from 18 to 87 years of age (mean 54 years). Seventy two percent of postal questionnaires were returned. Following telephone calls the overall response rate was 80%. The mean follow up period was 60 months (range: 9 – 132 months). Immediate complications were similar in both groups. The recurrence rates were 1.1% for Lichtenstein repair and 6.3% for Kugel patch (p= 0.09). None of the patients in the Lichtenstein group and 1.6% of patients in Kugel patch group complained of severe chronic pain in inguinal region.

Conclusion: There was no significant difference in the immediate complication rates between the two groups. Although recurrence and chronic groin pain rates are higher with Kugel repair, this was not statistically significant.

Key Words: Inguinal hernia, Lichtenstein, Kugel.

INTRODUCTION

Inguinal hernia repair is one of the most commonly performed general surgical procedures. Edoardo Bassini described the first true anatomical repair of inguinal hernia that reduced both the mortality and recurrence rates of hernia repair to less than 2%[1]. More recently, the operation has been simplified and the recurrence rate is further reduced by the adoption of tension free repair using synthetic prosthetic materials.

Lichtenstein tension free repair has gained wide acceptance because of its simplicity and consistent results. Kugel described a pro-peritoneal tension-free technique that aimed to combine the utility of the open operation with advantages of minimal access procedures (smaller incision, pro-peritoneal mesh placement, avoidance of neuropathic pain)[2].

The aim of this retrospective study is to compare the immediate and long-term outcomes of Lichtenstein and Kugel methods of inguinal hernia repairs in a single surgeon's practice.

MATERIALS AND METHODS

From 1996 to 2006, 219 patients underwent elective hernia repairs. Twenty-three of these were for recurrent and 196 for primary hernias. Operations were performed at the Royal Victoria Hospital Belfast, and at the Ulster Independent Clinic, a private hospital. All cases operated on by the consultant during this period were included, except where a Stoppa procedure was deemed appropriate (eight patients with giant, bilateral or multiple recurrent hernias).

A Lichtenstein repair was performed in 92 patients and a Kugel patch was used in 127 patients by a single consultant surgeon; although junior surgeons operated under supervision in those cases performed at the Royal Victoria Hospital (Consultant 83, Registrar 29, Senior House Officer 9 repairs). Patients ranged from 18 to 87 years of age (mean: 54 years).

The Lichtenstein tension free repair is performed using a polypropylene mesh placed over the posterior wall of the inguinal canal secured with 2/0 polypropylene sutures after reduction of the hernia sac. The choice of mesh evolved during the study period, to lighter weight meshes with absorbable components. The hernial sac was not transfixed or excised.

The Kugel patch repair involves making a 2.5 cm incision immediately above the deep ring. A self-expanding two-layered mesh with an extruded monofilament polymer ring is

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then placed in pro-peritoneal space, deep to the transversalis fascia covering the inguinal and femoral hernial orifices from "the inside" (Fig 1). The transversalis fascia is usually closed with a single interrupted stitch that also includes the anterior layer of the mesh to prevent its migration. In latter years, the mesh was also secured to the back of the pubis with an endoscopic tacker ("tacked").

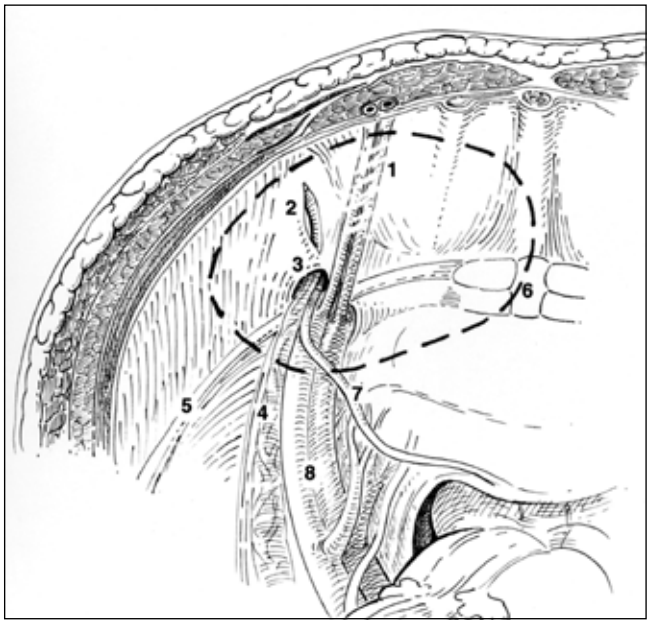

Fig 1. Preperitoneal view of groin: 1. inferior epigastric vessels 2. position of transversalis incision made to enter the preperitoneal space 3. internal ring 4. testicular vessels 5. inguinal ligament 6. symphysis pubis 7. vas deferens 8. external iliac vessels. Dotted line represents the preperitoneal position of Kugel patch from inside.

All procedures were performed under general anaesthesia. The ilio-inguinal nerve and wound were infiltrated with a long acting local anaesthetic during the procedure in all the patients. Although our current practice is to perform all hernia repairs under local anaesthesia (with a concomitant increase in day surgery rates), this study predates that change in practice. Prophylactic intravenous antibiotics (1.5 gm Cefuroxime at induction) were used routinely. Immediate complications were assessed by retrospective review of hospital records. To assess the long-term complications, questionnaires were mailed to patients with pre-paid return envelopes. Those who did not respond to the postal questionnaire were contacted by telephone. Patients who described a recurrent swelling or pain were reviewed. Patients who missed an appointment were given a second appointment. Any swelling associated with cough impulse was considered a recurrence. Outcomes were compared between the two types of procedures in the SPSS statistical analysis software using the chi-squared test for contingency tables or Fisher's exact probability test, as appropriate.

RESULTS

There was no significant difference in the immediate postoperative complication rates between the two groups (Table I). Duration of hospital stay was similar in the two groups (Table II). Only 46% of the patients were managed as day cases, even though most were admitted with this intention. Hospital stay was significantly longer in patients operated at the Royal Victoria Hospital compared to the Ulster Independent Clinic. Seventy five percent of Ulster Independent Clinic patients but only 22 percent of the Royal Victoria Hospital group were discharged within 24 hours of operation (odds ratio: 10.7; 95% CI: 5.5-21.2)(Table III).

Long-term complications were assessed by postal questionnaire that was mailed along with a pre-paid return envelope. Seventy-two percent of patients returned the questionnaire. This was followed by telephone interview for the non-responders giving an overall response rate of 80%. The median follow up was 60 months (9 – 132 months). Among the respondents 71 had Lichtenstein and 101 had Kugel patch repairs. In those with persistent pain, the severity was graded as mild, moderate or severe (Table IV). No patients in the Lichtenstein group and 1.6% in Kugel patch group graded their pain as severe.

TABLE I:

Immediate postoperative complications - Lichtenstein group vs. Kugel group

Immediate Complications	Lichtenstein group n=92	Kugel group n=127
No complications	87 (94.6%)	118 (92.9%)
Haematoma*	0	1 (0.8%)
Seroma*	1 (1.1%)	2 (1.6%)
Cord thickening	1 (1.1%)	1 (0.8%)
Haematoma and cord thickening	0	1 (0.8%)
Wound infection	0	1 (0.8%)
Testicular pain	0	1 (0.8%)
Hydrocele	0	1 (0.8%)
Chest infection, cardiac events, urinary retention	3 (3.3%)	1 (0.8%)
*requiring intervention		

TABLE II:

Postoperative hospital stay - Lichtenstein group vs. Kugel group

	Lichtenstein group n=92	Kugel group n=127
Day case	37 (40.2 %)	64 (50.4 %)
Overnight	15 (16.3 %)	30 (23.6 %)
2 days or more	40 (43.5 %)	33 (26 ,0%)

TABLE III:

Postoperative hospital stay - RVH group vs. UIC group

	RVH group n=121 patients	UIC group n=98 patients
Day case	27 (22.3%)	74 (75.5%)
Overnight	31 (25.6%)	14 (14.3%)
2 days or more	63 (52.1%)	10 (10.2%)

TABLE IV:

Persistent postoperative pain - Lichtenstein group vs. Kugel group

Chronic Pain	Lichtenstein group n=92	Kugel group n=127
None	40 (43.5%)	68 (53.5%)
Mild	22 (23.9%)	19 (15%)
Moderate	9 (9.8%)	12 (9.4%)
Severe	0	2 (1.6%)
Non responders	21 (22.8%)	26 (20.5%)

Eight of the Lichtenstein group and eighteen from the Kugel group indicated that they noticed a swelling in the inguinal region. All were requested to attend a surgical clinic for assessment of recurrence. Three of the Lichtenstein group and two of the Kugel group did not attend despite a reminder. Of the remaining patients who did attend, one of the Lichtenstein patients (1.1%) and eight of the Kugel patients (6.3%) were confirmed to have clinical recurrence. The difference in the recurrence rates is not statistically significant (p = 0.09). The remaining patients had soft tissue prominence at the wound site but no recurrence. Lichtenstein repair was performed in 14 of the 23 patients with recurrent hernias and Kugel repair was performed in the remaining nine. None of them had a recurrence. In the Kugel group, 22 hernias were tacked and 105 were not tacked. There were two recurrences in the tacked group and six recurrences in the untacked group (p=0.5 Fisher's Exact test; OR=1.2, 95% CI: 0.2 - 7.5).

DISCUSSION

The Lichtenstein anterior tension free mesh repair is widely regarded as the gold-standard hernia operation. It is easy to learn, reproducible and carries a low complication rate. The Kugel patch operation employs a 2.5 cm incision immediately above the deep ring, through which a mesh is placed deep to the fascia transversalis and can be secured to transversalis and Cooper's ligament. Placement of the mesh deep to the muscle layers should theoretically reduce inguinal pain, by avoiding scar tissue around the ilio-inguinal and genito-femoral nerves. There is also a theoretical mechanical advantage by applying the prosthesis to the back of the abdominal wall as the higher intra-abdominal pressure actually contributes to the integrity of repair.

Immediate complication rates of both the procedures are similar in our series and are comparable to those reported by a specialist hernia centre in the UK. The British Hernia Clinic reported wound haematoma in 2%, infection requiring antimicrobial treatment in 1.3% and testicular swelling in 1%[3]. The senior author previously reported wound haematoma and infection rates of 3.3% and 1.1% with two-layered hernia repair using absorbable sutures[4]. Infection rates of less than 1% are reported with mesh repairs of inguinal hernias[5]. Although routine use of antibiotics is not considered necessary, we considered the severity of occasional sepsis in the mesh sufficient to justify a single shot of a broad-spectrum cephalosporin. In the current era with concerns about *C.difficile* infection, this policy has been revised. The response rate of 80% to the questionnaires is comparable to the similar studies in literature[4,6].

Outcome analysis in hernia surgery is usually performed by assessing postoperative recurrence rates and long-term pain. Recurrence rate remains the most traditional outcome measure of the efficacy of hernia repair. However, there is no universal agreement on whether a bulge or cough impulse at the site of original operation or only those that require reoperation should be considered a recurrence[6]. Other confounding factors are the duration of follow up and the loss of patients to follow up. We included all positive cough impulses as recurrences, even though most of these patients have elected not to have the (often small) recurrent hernia repaired. We were unaware of most of the recurrences until we contacted the patients.

In our series, the Kugel repair is associated with higher recurrence rates (6.3%) than the Lichtenstein repair (1.1%). The difference is, however, not statistically significant (p = 0.09 Fisher's Exact test). Similarly, rates of chronic pain are similar between the two groups. Complication rates are reported to be similar between the two procedures in the only published prospective, randomised comparative study[7]. Recurrence rates of Lichtenstein repair are reported to vary from 0% -1.3%[5]. A 2-3 cm overlap over the pubic tubercle with medial fixation is recommended to prevent the recurrence[8] and this technical detail alone may reduce the risk of recurrence by 50%[9]. Kugel reported a recurrence rate of 0.62%[2] that further reduced to 0.4%[10] with experience. There are conflicting reports of high recurrence rates of 7.7%[11] and 3.7%[12] and low recurrence rates of 0.8%[13] and 1.9%[14].

The Kugel patch undoubtedly has a learning curve with recurrence rates as high as 18% reported during a surgeon's first 36 cases, reducing to 2.9% thereafter[11]. In our series, 5/8 (62%) of recurrences occurred in the first 50% of cases.

Chronic neuralgia can be associated with any groin hernia repair and is attributed to nerve entrapment, perineural fibrosis and development of neuromas at the cut ends of the nerve. The frequency of chronic groin pain is reported to vary from 0% to 37% of patients undergoing conventional hernia repair[9]. It was for this reason that we wished to explore the role of the Kugel patch technique. Kugel repair might be expected to have a lower incidence of chronic pain as the incision is much higher than conventional groin hernia incisions and the mesh is not placed on the major inguinal cutaneous nerves (ilioinguinal and genitofemoral). Kugel advises care to avoid damage to the cutaneous nerves that course on the internal oblique, meticulous haemostasis and minimal manipulation of the cord structures[10] to avoid chronic pain.

The reported incidence of chronic pain with Kugel technique varies from 0% - 3.5%[12-14]. Bay-Nielsen *et al* observed moderate to severe pain in 3.9 percent of patients with no significant difference between open mesh, Shouldice and Marcy repair[15]. Aroori reported a 9% incidence of severe chronic pain after inguinal hernia repair (Bassini, darn and Lichtenstein) in the Northern Ireland population[16]. In our series, 1.6% of Kugel group complained of severe chronic groin pain but none in the Lichtenstein group. Recurrent hernias and large scrotal hernias are independent risk factors for recurrence and younger patients are at greater risk of chronic pain irrespective of the open technique used[17].

The low day case rates in this study are disappointing. It is

known that day case surgery is not fully developed in the UK[18]. In this series, patients at the Royal Victoria Hospital were admitted to a general ward (combined medicine and inpatient surgery) and not a specialist day surgery facility. Most were admitted with the intention of discharge the same day. Since the patients operated on at the Ulster Independent Clinic had higher day surgery rates with an identical surgical and anaesthetic approach, it can only be concluded that the lack of a dedicated day surgery unit was the main reason for delayed discharge.

This study was not intended to be a randomised trial, so comparisons between the groups must be made with caution. False negative long-term results were possibly reduced with a good response rate (80%) to the postal and telephone survey but were not completely eliminated. Furthermore the Kugel patch experience represents a learning curve for the procedure, whereas the Lichtenstein repair is well established.

We are not aware of any other study that has addressed the recurrence rate following prosthetic inguinal hernia repair in the Northern Ireland population. The results in this study show a significant improvement over our previous outcomes in the pre-mesh era, when the recurrence rate was 2.2%[4]. The overall chronic groin pain rate is comparable to published literature though the incidence of severe pain in our study is much lower (1.6%), with no severe chronic pain in the Lichtenstein group.

CONCLUSION

There is no significant difference in the immediate complication rates between the two operations. Although recurrence and groin pain rates are higher with Kugel repair, this is not statistically significant. Day case rates may be improved by the provision of appropriate dedicated facilities.

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The authors have no conflict of interest

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Medical History

Lobar pneumonia treated by Musgrave Park physicians

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SUMMARY

In the decade 1935-45 the treatment of lobar pneumonia in the developed and warring world underwent a series of evolutions—anti-sera, specific anti-sera, refinement of sulpha drugs, sulpha and anti-sera, the introduction of penicillin for bacteriology, then ophthalmology, and then for penicillin-sensitive bacterial infections such as lobar pneumonia with its many Cooper types of *Streptococcus pneumoniae*. Penicillin for civilian use was essentially banned in World War II, a ban that early in 1941 two Musgrave Park physicians tried to circumvent. Strict secrecy on the details of penicillin production was enforced. The treatment option chosen by the Musgrave Park physicians in 1941, and the non-availability of penicillin led to sequelae affecting the post-Belfast careers of both patient and physicians.

KEY WORDS: Sera, Sulpha, Penicillin

INTRODUCTION

At the start of his 1944 Campbell Oration[1], the newly knighted Alexander Fleming (Figure 1) mentioned his 40-year collaboration and mentorship with Ulsterman Sir Almroth Wright. He thanked his friend, housemate and long-time collaborator Victor Douglas Allison, Queen's MB, later DSc. Allison had been the JC White Lecturer in Bacteriology, Queen's University[6]. After working with Wright and Fleming, as a Beit Memorial Research Fellow, he became a Senior Consulting Pathologist to Belfast City Hospital and the Northern Ireland Hospitals[7]. Fleming also recalled his World War I service with the Professor of Medicine 1921-50 at Queen's, WWD Thomson, knighted in 1950[3,6,8].

When they returned to take the Belfast-Larne train, the Flemings discovered they were missing his lantern slides and lecture notes[3]. The Ulster authorities and British security knew that since 1941 all details of antibiotic production by the World War II Allies had been strictly classified secret. The train was delayed; the Larne to Stranraer ferry's escort rescheduled. The notes were found, vetted, and restored to Sir Alexander. The Flemings were then allowed on their way back to London and Allison's Highgate house where Allison kept a pied à terre for visits from Cardiff where he was stationed. The Flemings had been bombed out of their Chelsea home[2].

WORLD WAR I: FLEMING, THOMSON AND WRIGHT

Captain Alexander Fleming had worked under Colonel Sir Almroth Wright's command from 1915 to 1918 at Boulogne[2,7]. Captain WWD Thomson and Captain N Keith of Canada, later of the Mayo Clinic, were junior officers in this Unit devoted to the study of Allied War Wounds and their infection. Harvard's US 5th General Hospital was also stationed in Boulogne with Professor Harvey Cushing as Commanding Officer, and Professor Roger Lee as Chief of Medicine. Both were friends of Wright's group, and Cushing collaborated in Wright's work on war wounds[9,10]. In 1919 Harvey Cushing was awarded an honorary MD by Queen's, Belfast[10]. Cushing was in 1926-27 to train Hugh Cairns[11], later Nuffield Professor of Surgery at Oxford, at the Peter Bent Brigham Hospital, Boston. Cairns, in 1942, both abridged and amplified Cushing's experience[12]. Lee was to train Professor Maxwell Finland at Harvard[13-15]. Fleming, Keith and Thomson were frequent golfing companions at Wimereux where their golfing feats incurred Wright's displeasure, but did not strain their friendship. Sir Almroth Wright maintained his high regard for the trio. Fleming, when out of sight behind a dune, had dropped a "somewhat self-important Colonel's ball" so as to fake a hole in one, and demand the customary sequelae of drinks on the Colonel[16].

In his Campbell Oration, Fleming mentioned neither the secret work on penicillin in the United States since his visit to New York in 1939, nor the efforts of two Musgrave Park 31st General Hospital doctors to obtain penicillin in March 1941[17]. One of the pair, Max Rosenheim, later President of the Royal College of Physicians and enobled with an FRS, had also in March 1941 asked the Wright-Fleming group for advice on Type XIV anti-pneumococcal serum[7].

WORLD WAR II BELFAST

In March 1941, under optimal circumstances, the preferred treatment regimen for lobar pneumonia was to determine as expeditiously as possible the Cooper type of infecting pneumococcus: to take a blood sample for culture was advised[18]. Before these results were obtained, polyvalent pneumococcal antiserum could be given intravenously with caution[18]. This done, a loading dose of sulphapyridine, then called M and B 693, was given, generally by mouth[18,19]. Sulphathiazine was thought to have less toxicity, but was new and expensive (Table I). The patient's hydration, nutrition and mental attitude needed to be bolstered during the course of the

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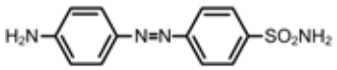
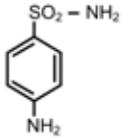
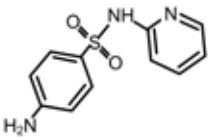
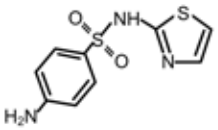
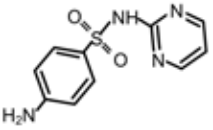
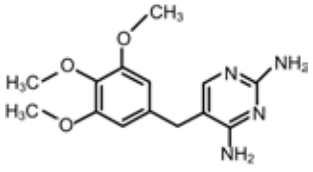
Fig 1. Professor Sir Alexander (1881-1955) and Lady (Sareen) Fleming on the steps of 25 University Square, Belfast just after D-Day[2,3].

The Allies had by June 1944 achieved their objective of ensuring that their Forces had enough penicillin to treat expected casualties in the Normandy landing and breakout. Fleming's Penicillin notatum (NRRL 1249), isolated 1929, was a producer only in surface culture. NRRL 1249 did not produce when submerged. After searching all over the world for Penicillin notatum-chrysogenum which could produce when submerged, the best strain proved to be from a cantaloupe in a Peoria, Illinois fruit market (NRRL 1951)[4]. Mutation sequence began on the best substrain, 1951-B25. Demerec of the Carnegie Institution of Washington's Cold Spring Harbor Laboratory, developed a superior X-ray mutant 1951-B25 X1612 which was commercially produced, but was superseded by strain Q-176, which was an ultraviolet-produced mutant derived from X-1612 by the University of Wisconsin[4,5]. Fleming's mold NRRL 1249 produced 2-4 Oxford Units per ml, 1951-B25. Q-176 produced 750 times Fleming's mold[4]. The United States efforts to ramp up the production of penicillin during World War II was given funding priority equal to the Manhattan project to develop uranium and plutonium bombs. Secrecy was strictly observed[4]. Sareen Sally McElroy was a trained nurse, the twin daughter of a County Mayo farmer. The Flemings were very happily married from 23rd December 1915, when Alexander was on leave from his duties in Boulogne with Ulstermen Sir Almroth Wright and Thomson until Sareen's terminal illness and death on 29th October 1949[2].

disease[28]. Both Musgrave Park physicians Benjamin Rycroft and Max Rosenheim knew penicillin was extremely effective against pneumococcal (now called streptococci pneumoniae) infections, and that penicillin did not appear to cause nausea, vomiting, heart arrhythmias and diarrhoea, as did M and B 693[29]. Both Rosenheim and Rycroft knew that penicillin was being produced at Oxford[30] and in New York at Columbia University,[17] "in a manner that took over many rooms".

TABLE I:

Sulphonamides In Order Of Therapeutic Introduction

1. PRONTOSIL  2. SULPHANILAMIDE  3. SULPHAPYRIDINE (M and B 693) 	1. Prontosil, $C_{12}H_{14}ClN_5O_2S$ [20,21] was developed by the Bayer team of H. Hörlein and G. Domagk who filed German patent application No. 607537 in 1932[22]. 2. Sulphanilamide, $C_6H_8N_2O_2S$ [23] was first synthesized by P Gelmo in 1908. The Tréfouëls advanced work on the therapeutically active component of Prontosil and published their results in 1935[24]. 3. Sulphapyridine, $C_{11}H_{11}N_3O_2S$ [23] was also known as M and B 693. N Grillet of Rhône-Poulenc ordered AJ Ewins of their subsidiary, May and Baker, to work with their chemists G Newberry and M Phillips[25]. LEH Whitby was recruited to test sulphapyridine by Ewins in 1936[26].
4. SULPHATHIAZOLE  5. SULPHADIAZINE  6. TRIMETHOPRIM 	4,5. In March 1941 sulphathiazole, $C_9H_9N_3O_2S_2$ [23] and sulphadiazine, $C_{10}H_{10}N_4O_2S$ [23] were obtainable in Belfast and could have been used instead of sulphapyridine (M and B 693). 6. The production of sulpha drugs, such as trimethoprim, $C_{14}H_{18}N_4O_3$ [23] has remained close to World War II levels with increased veterinary and animal husbandry use[27].

What Rosenheim did not know was whether specific type XIV anti-pneumococcal serum was available. My father* kept his copies of *The Medical Annual* in the library of our Dunmurry Lane home. The 1940 edition, which I inherited from him and still possess, has a section on "New Pharmaceutical

* Throughout this Medical History, "I" or "my" refers to the first author.

Fig 2. Sir Benjamin William Rycroft, OBE, FRCS, 1902-67. Photograph by Walter Bird. Reproduced with the permission of Moorfields Eye Hospital and UCL Institute of Ophthalmology solely for this Medical History.

Educated 1919-24 at St. Andrews University. After qualifying, he practiced as a general practitioner in Bradford, Yorkshire, from where, starting about five years later, he studied ophthalmology in London during the week, returning to work in Bradford at the weekends. On this regime he was admitted FRCS in 1931 and moved as Clinical Assistant to Sir Stewart Duke-Elder, knighted 1933, at St. George's Hospital[35,36]. Benjamin Rycroft published his first paper on human corneal transplantation in 1935[37]. From 1940 to 1942 he served in the 31st General Hospital at Musgrave Park. Torpedoed and rescued on the way to Algeria, he later advised Allied Mediterranean Command for which he received the OBE[36,38]. Rycroft published the first book in the English Language describing corneal grafts[39]. Sir Benjamin's obituary says "he rode to show-standard and hunted"[35]. He was an accomplished organist, and "all his life he maintained an interest in the piano"[35]. As Honorary Consultant to the Zoological Society of London, he operated on tigers and horses among other animals. Rycroft, Examiner in Surgery to Queen's University, Belfast, encouraged by Dickie Hunter, asked candidates in surgery at Queen's viva questions on wild animal surgery[40,41]. The average adult female tiger requires a number 15 Magill-type tracheal tube[41,42].

Preparations". The section on "Antipneumococcic Sera (Rabbit), Lederle, covers the 'higher types' of pneumococcal pneumonias for which horse sera have not previously been available"[31]. "Supplies of antisera are now available in 20,000 unit vials for all the 32 Cooper types except Types XV, XXV, XXVI, and XXX. These vials are manufactured by Lederle Laboratories Inc., New York, NY. Literature on application to the distributors CF Thackray Ltd, Park Street, Leeds"[31]. In March 1941, Type XIV was not available on demand in a timely manner from Lederle, New York, nor from the Leeds

TABLE II:

Ophthalmologists And Pre-March 1941 Penicillin Human Therapy

1. Drs Frederick Ridley and SR Craddock reported experimental extraction on April 10, 1929, of a concentrated penicillin[43]. Ridley was later a colleague of Rycroft at Moorfield's Hospital, London.
2. Professor Alexander Fleming, late in 1929, treated Dr KB Rogers, an assistant to Sir Almroth Wright. Pneumococcal conjunctivitis was promptly and completely cured[2].
3. Dr Cecil G Paine, a St. Mary's graduate, grew his own penicillin from Fleming's strain and in 1933 with ophthalmologist Albert Nutt successfully treated ophthalmia neonatorum at Sheffield Royal Infirmary[44,45]. From 1932-35 Howard Florey was Professor of Pathology at Sheffield[45].
4. CG Paine, for his eighth case, successfully treated with penicillin a colliery manager who had an intraocular foreign body and pneumococcal infection. Successful extraction was enabled[44,45].
5. On October 15, 1940 Dr Martin H Dawson of Columbia University, New York, NY, began to treat three patients with retinal Roth spots due to subacute bacterial endocarditis, with Columbia-manufactured penicillin[2,17,46]. By May 6, 1941, Dawson's group had treated a total of four patients[46].
6. On February 12, 1941, Dr Charles Fletcher of the Nuffield Department of Medicine at Oxford University started penicillin treatment on policeman Albert Alexander, aged 43. Following a rose scratch, post left-eye exenteration, Alexander developed endophthalmitis and orbital cellulitis. Treatment was initially successful but Alexander died on the 15th March 1941 after Oxford's supply of penicillin had been exhausted[2].

distributor. The reason that rabbits had supplanted horses was that production of the "higher types" of antipneumococcic serum killed about a third of the horses. This high equine mortality was not experienced in producing lower types I, II and III; in these "original" types equine production probably had higher profit margins. There were more patients for types I, II and III and greater production from the sensitised horses.

As a result of his telephoned investigations, Rosenheim discovered Squibb was about to release "Antipneumococcic Rabbit Serum Type XIV"[32]. Type XIV lobar pneumonia was then relatively uncommon in the United Kingdom. One New York-based study reported type XIV pneumococcus as comprising 16.1 percent of lobar pneumonias in children, but only 2.6 percent in adults. Type XIV produced mortality rates as high as 14 percent in children and 23 percent in adults without bacteremia, and 28 percent in children and 69 percent in adults with bacteremia[33].

DISEASE COURSE

On a stormy dawn early in March 1941, I awoke in my bedroom at Windy Ridge, Dunmurry Lane with pain in my right side. I called my father who came in his dressing gown and then returned with a stethoscope[34]. After listening to my chest, he brought a glass of water, and told me to drink it, and that he would get Rycroft whom I already knew. I asked why I needed an eye doctor. "He kept the city of Bradford in order as a GP"[35], my father replied. Rycroft arrived about an

Fig 3. Professor Lord Rosenheim of Camden, KBE, DSc, PRCP, FACP, FRS, 1908-72. Oil on Canvas by Judy Cassab, CBE, AO, 1972. 2008 Artists Rights Society (ARS), New York/VI$COPY, Australia. Reproduced with permission of the Artists Rights Society, solely for this Medical History, from the Heritage Centre, Royal College of Physicians, London.

Max Leonard Rosenheim was President of the Royal College of Physicians of London from April l966 to April 1972. In May 1968 he presided over the 450th Anniversary of the College in a meeting held jointly with the American College of Physicians in Boston, Massachusetts[47]. Educated at Shrewsbury School and St. John's College, Cambridge. At University College Hospital by pioneering the treatment of urinary infections with mandelic acid[48] and hypertension with pentamethonium[49,50] he pioneered major advances in therapeutics. Max led a Professorial Unit at UCH judged second to none. His Military Service started at Musgrave Park in 1941.

hour later and took a venous blood sample and several throat swabs (Figure 2, Table II).

Later, a tubby, cheerful man appeared in civilian clothes and said to me and my nurse, "I am Max" (Figure 3). He told me that the next three to five days would be like climbing a mountain. I would probably get more breathless and the pain in my right chest was best put up with. He then listened to my chest and said "Angus and the eye doctor are right". Max gave me an intravenous injection which he said had been made by Sir Almroth Wright and Professor Fleming[2] and left, saying he would be back when he had checked up on the eye doctor. A few hours later Rycroft appeared with some pills he made me swallow (Figure 4). Rycroft said in future he would announce his arrival by playing on the piano in the room beneath my bedroom.

That evening I asked my father who Max was, to be told he was a Salopian Johnian[52]. The nurse, who was from Sligo, said that Max was very nice. "Where was he from?" My father

Fig 4. Sir Almroth Edward Wright, KBE, MD, FRCPI, FRS (1861-1947). Oil on canvas, 1934, by Sir Gerald Kelly, KCVO, PRA, LLD (Cantab and TCD). Reproduction courtesy of St. Mary's Hospital Archives (Imperial College Healthcare NHS Trust), London.

At the age of fifteen, his father being vicar of St. Mary's Church, Crumlin Road, Belfast, Wright entered Royal Belfast Academical Institution from where he proceeded to TCD reading English, French, German, Spanish and Italian. This Instonian won the Gold medal in his BA in 1882. He also read medicine concurrently. He qualified MB from TCD in 1883[2,7]. Aged 23, Almroth Wright went to Leipzig to study with Cohnheim, and later Ludwig and Weigert. He returned to the United Kingdom to become pathologist to the Brown Animal Sanatory Institute. John Scott Burdon Sanderson, later knighted and Regius Professor of Medicine at Oxford, was the Brown Institute's first superintendent. He was followed as superintendent by CS Roy, Victor Horsley and CS Sherrington. When Roy became head of Pathology at Cambridge University in 1886, he appointed Wright Demonstrator in Pathology[51]. Roy soon sent Wright to von Recklingshausen in Marburg. After proposing the citration of blood he was offered and accepted the Professorship of Pathology at the Army Medical School at Netley. He was thirty-one. This Army appointment led to the flowering of one of the most productive and influential careers of the last century. In 1902, Wright became Professor of Pathology at St. Mary's Hospital Medical School. Friendly with Arthur J Balfour, Lord Haldane and G Bernard Shaw, Wright was both knighted and elected FRS in 1906. At St. Mary's he mentored and nurtured Alexander Fleming for almost forty years. Wright and Fleming, together with SR Douglas, founded and ran the Vaccine Laboratory of the Department of Therapeutic Inoculation. Until after the end of World War II, the Inoculation Department had control of their own patient beds at St Mary's[2].

replied, "The Massachusetts General Hospital". So I asked if he was an anaesthetist. "No, he was Belton Pollard Fellow with Albright and Bauer," my father replied[52]. Late the next day Max reappeared and said he had made a lot of people work including Angus and the eye doctor, so he was going to give me back some of my own medicine—so started my intravenous course of Type XIV antipneumococcal serum[32]. I asked what Rycroft had been forced to do. "Argue with Oxford," was the reply.

The next day but one, Rycroft changed his piano tune from "Smoke Gets in Your Eyes" to "The Blue Danube". He came upstairs and said, "John, you are better or Max's army career is over before it begins". "Yes, I am," I replied. "Can I go and see my pony?" "Not yet." Max reappeared somewhat later. He said he had called Whitby[53-56]. I replied, "My ancestors there

are dead". Max said he had also been talking with Wright's people at Mary's. They had reminded him how to do a Quellen reaction and a precipitin test to type the pneumococci[53-57]. He said they had no spare penicillin. "Try Oxford and New York," advised Sir Almroth. So he had given that job to Rycroft, "Because eye-doctors couldn't get into trouble because of the Duke (Figure 5). Ophthalmologists know more about penicillin than anyone else". "Good-bye," said Max. "Go to a college on the Backs of the Cam".

1941 UNITED STATES IN ULSTER

I never saw Max in uniform during his posting to Musgrave Park. When I asked for an explanation, I was told, "Because he was dealing with the Yanks." The next month after my pneumonia, April 1941, was the time of the Belfast blitz. The still neutral US War Department issued RAINBOW-5, which detailed the deployment of 30,000 US troops in Ulster. On June 12, 1941, the construction contract for US bases and hospitals in Northern Ireland was signed[61]. Rosenheim, with his recent Harvard experience advised on what Harvard's Fifth General Hospital[34] and other US Medical Services would require. He liaised with Professor WWD Thomson[8] for WWD's own experience at Boulogne of Harvard's Fifth General Hospital in World War I.

THERAPEUTIC ALTERNATIVES

To determine the pneumococcal type from the samples obtained by Rycroft, Rosenheim used concurrent techniques described by Lionel Whitby, Pathologist to the Middlesex Hospital. "Type may be determined by an immediate direct method, by mouse inoculation or by agglutination of a culture"[54]. In the direct method, a small fleck of fresh sputum is well mixed on a slide with a drop of the type I, II or III serum. "After the serum has penetrated into the sputum, a cover-slip is placed over the preparation and it is examined with the 1/6th lens and x10 eyepiece. The capsule of an organism, when in contact with its own specific serum, becomes swollen and the organism itself loses its definition"[54].

"The white mouse is very susceptible to pneumococcal infection, and if inoculated intraperitoneally with a sample of pneumococcal sputum, not only are the mucus and the cellular elements liquefied, rendering the pneumococci free, but the cocci also multiply rapidly"[54]. The peritoneal cavity of the mouse is aspirated after four hours and the direct method repeated. Under microscopic examination, the capsule of the diplococcus is swollen by its own specific serum. If no swelling occurs, as it did not in my case, the search continued with expensive specific serum for the remaining known, as of 1932-1941, twenty-nine types.

Rosenheim then used mouse inoculation as described by Whitby and obtained evidence of agglutination of a mouse heart blood sample. A suspension of the culture is tested for agglutination in dilutions varying from 1:1 to 1:20 with each of the type-specific sera. The tubes should be incubated in a water bath for one hour at 37°C. The peritoneal washings of an incubated mouse can also provide a suitable suspension for this test. Further confirmation that the infecting pneumococcus was type XIV was provided by the precipitin reaction using the polysaccharide haptene known as Specific Soluble Substance, or SSS from urine[54].

Fig 5. Sir Stewart Duke-Elder, GCVO, MD, DSc, FACS, FRCS, FRCP, FRS (1898-1978). Oil on canvas by Ruskin Spear, reproduced with the permission of Moorfields Eye Hospital and UCL Institute of Ophthalmology, solely for this Medical History.

"The Duke" was Surgeon Oculist to Their Majesties Edward VIII, George VI, and Elizabeth II. Educated at St. Andrews and London Universities, Howe Lecturer, Harvard University, 1930, Craig Prizeman, Belfast, 1952. Brigadier General 1940-46, later Consulting Ophthalmic surgeon to the British Army, 1946-61. Married in 1928 Phyllis Mary Edgar, MB, BS (London), who helped her husband with his legendary texts[58,59] including his Craig Prize Oration[60]. Ruskin Spear also portrayed Lord Ashby, Vice Chancellor of Queen's Belfast and Master of Clare.

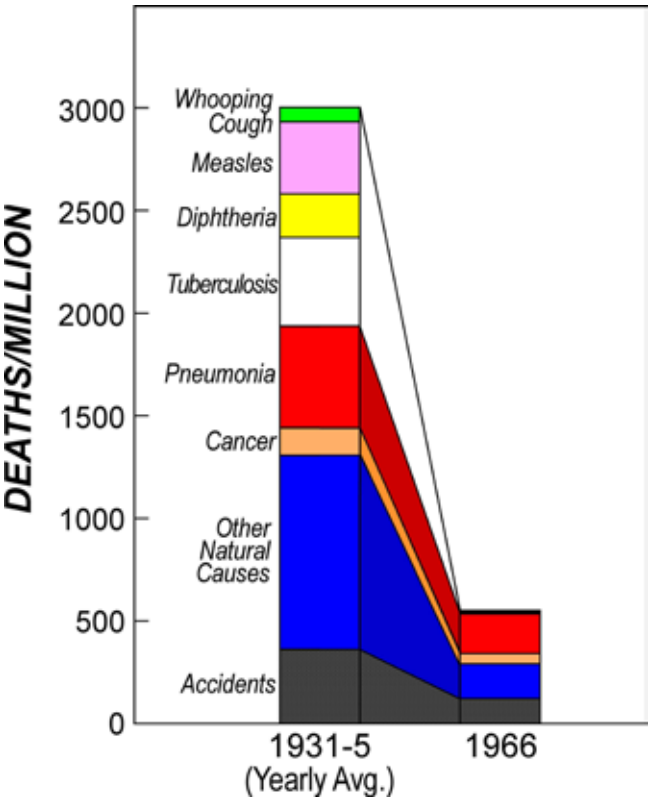


Fig 6. Comparison between childhood death rates before and after the introduction of sulphanilamide and antibiotic chemotherapy. Figures were provided by the Association of the British Pharmaceutical Industry to Professor Ronald Hare[43].

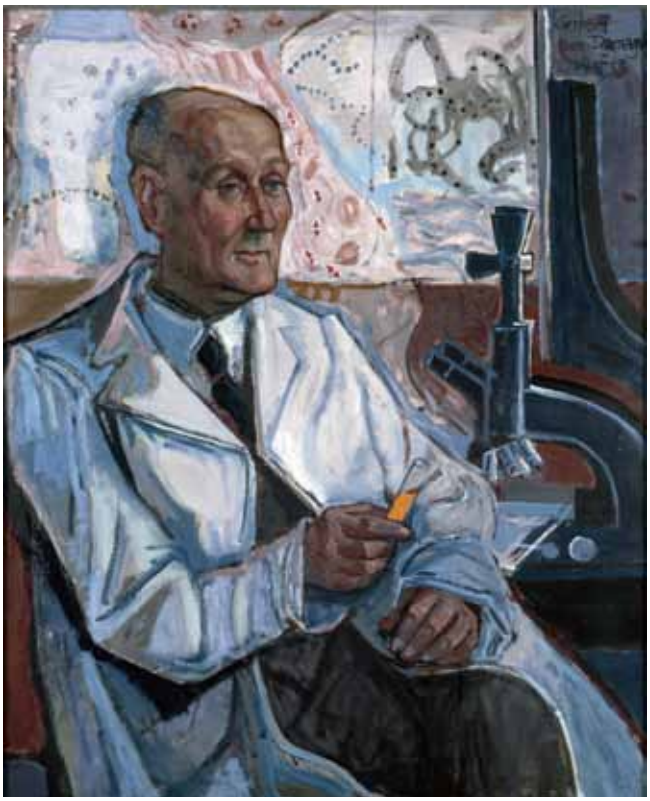


Fig 7. Otto Dix: Portrait of Professor Gerhard Domagk, MD, DSc, FRS (1895-1964), oil on canvas, 1953. Art Collection, Bayer AG, Leverkusen, Inv. No. 0474. © 2008 Artists Rights Society (ARS), New York/VG Bild-Kunst, Bonn. Reproduced with permission of the Artists Rights Society/VG Bild-Kunst solely for this Medical History.

Gerhard Domagk was born in Laagow, Brandenburg, Germany, and trained at the University of Kiel Medical School and at Münster for post-graduate studies. In 1927 Domagk was appointed Director of Research in Experimental Pathology and Bacteriology at Bayer. In 1928, he was concurrently appointed Professor of Pathology at Münster. After testing many azo-compounds, Domagk added a sulphonamide group to chrysoidine and produced in 1932 prontosil[67] which in 1936 saved the life of Franklin Delano Roosevelt Jr. at the Massachusetts General Hospital[68]. A few months before, in 1935, at the Pasteur Institute in Paris, the husband and wife team, Jacques and Thérese Tréfouël, showed that sulphanilamide, which they synthesized, was the active component of prontosil, and less toxic than the larger molecule[24]. In 1937 and 1938 Lionel Whitby published his classic papers on 4-(p-aminobenzine-sulphonamide) pyridine treatment of pneumococcal pneumonia in mice and humans[26,69]. Domagk was awarded the Nobel Prize for Medicine in 1939 but Hitler, having imprisoned him for a week, forbade its acceptance[22]. In 1947, Domagk gave his Nobel Oration in Stockholm[70]. The Caroline Institute never paid Professor Domagk the monetary prize[22].

As Whitby states, "Recognition of the characteristic change requires much practice"[54]. This was the justification for Rosenheim's telephone calls to Professor Thomson and to Whitby's and Wright's groups. Agreement was reached that the infecting pneumococcus was type XIV. Where was the antiserum? And did it need to be given as well as the sulphapyridine (M and B 693) they had already started me on, or should sulphathiazine, or even sulphadiazine[62,63] be given? (Table I). These sulphonamides are not bacteriocidal in therapeutic doses. Max Finland's group at Harvard in the previous year had shown that results were better if both the specific anti-serum and the sulphapyridine (M and B 693) were given as early as possible in the course of the lobar pneumonia[14,15].

In 1939, an annotation in this journal on the treatment of pneumococcal infections stated that for a child of seven, an initial dose of M and B 693 of 1.5 0.5g tablets should be followed by 1 tablet every four hours. The *Ulster Medical Journal* continues, "It is of importance even with this brand of drug that every case should be typed." "Physicians…may wish to supplement their treatment …with administration of specific serum"[19]. In 1940 a study from Birmingham showed that the mortality in 1,685 successive patients, with lobar pneumonia admitted to the Dudley Road Hospital dropped from 20.5 percent in 1936 and 1937 to 5.3 percent after the introduction of M and B 693. In Birmingham, type I pneumococcus predominated 43%, type III 16%, type II 11%, type XIII 5%. The other types were "encountered only sporadically and types XIII, XIV, XXII, XXVI and XXX not at all"[18]. In Los Angeles, California, in the five years from January 1934 through December 1938, type XIV lobar pneumonia represented only 1% of 1,469 consecutive cases of lobar pneumonia[64]. Things were different in Harlem, NY, where type XIV had been shown to be a virulent pneumococcus "selecting by preference infants and young children, in whom the pneumonias are usually of long duration—it is especially prone to invade the blood and prove fatal"[33] (Figure 6).

PERSONAL SEQUELAE

My parents complained of the paltry British Army pay. So I asked the cost of my treatment. The M & B 693 sulphapyridine cost £1 per day. My illness cost "a fiver". The anti-sera were free samples. "The Germans invented a dye called prontosil, for which Professor Domagk was awarded the Nobel Prize in '39[22,65,66] (Figure 7). The French[24] stole it and the English improved it so you got better and did not go pink or blue"[31]. I later asked what a Quellen test was and why Mary's had had to coach Max. "To discover you are Type XIV". So I asked why I was Type XIV. "Because you probably kissed someone". "I don't kiss girls". "John, you had better go to the Dragon School."

TABLE III:

Penicillin Production In The USA, UK and Australia

Monthly Production In Oxford Mega Units			
Date	USA	UK	AUSTR
Jan. 1942	2	<1	
June 1942	10	20	
Jan. 1943	100	100	
June 1943	5,000	700	
Jan. 1944	100,000	2,000	3,000
June 1944	750,000	5,000	6,000

Production figures derived from Lord Florey's *Antibiotics* published in 1949[44] and US figures declassified in stages post-World War II[4]. The 150-fold increase in US production from June 1943 to D-Day was largely due to irradiation procedures. War-time secrecy and patent protection inhibited and delayed US to British Empire information transfer[4]. The University of Toronto delivered approximately 1,000 Oxford Mega Units to Canadian Armed Forces in May 1944[43].

Fig 8. Professor Sir Lionel Whitby, CVO, MC, MD, DSc, LLD, FRCP. 1895-1956. Oil on Canvas by Waldron West, photographed by Chris Titmus, Hamilton Kerr Institute, Fitzwilliam Museum, Cambridge. Reproduced by permission of the Master and Fellows of Downing College, Cambridge, solely for use in this Medical History.

Sir Lionel Whitby was educated at Bromsgrove and Downing College, and is here portrayed in his Cambridge MD gown. He was a Royal Fusilier in 1914, later machine gun officer in Serbia, Gallipoli, Salonika and a hero at Passchendale, where he was awarded the Military Cross as a Major. In 1918 he was severely wounded and had to have a leg amputated. After the Natural Sciences Tripos he was Freeman Scholar at the Middlesex: in 1929 as Assistant Pathologist he attended King George V in his serious illness[55]. It was largely Whitby's work that led to the success of sulphapyridine (M and B 693) in the treatment of pneumococcal pneumonia[26,53,69]. In World War II Whitby was in charge of the Army Blood Transfusion Service and also treated Prime Minister Churchill's 1943-44 infections[74]. Lady Whitby was a physician and consummate hostess. Her husband was Visiting Professor of Medicine at Harvard and Cutter Lecturer in 1946. Sir Lionel died after an operation at the Middlesex[55].

My father wrote to the Dragon Preparatory School on Bardwell Road, just north of Oxford University. Father was told that they were full. So when my father next met his friend Hugh Cairns, Nuffield Professor of Surgery at Oxford, he claims he made him feel guilty for procrastinating on the release of penicillin for me. The excuse was they had "run out on a rose scratch case". If I had been given the penicillin I would have been the third patient in the first Oxford series[30] (Table III). Professor Cairns, as propitiation, said he would call on the Lynams (Hum and son Joc, co-Head-Masters), and there would be no trouble. I entered the Dragon as a boarder in September 1942 to learn that the most prominent of the Oxford Dons that founded the school in 1877 was a Mr George, who thereafter had his Dragons both male and female: all to be aged seven to thirteen. We Dragons aspired to "robust informality and relaxed vigour"[71].

Fig 9. Joe Waldbillig, MAXWELL FINLAND (1902-1987), Oil on canvas, Harvard Art Museum, Fogg Art Museum, Harvard University Portrait Collection, Harvard Medical School, H826. Photo: Imaging Department President and Fellows of Harvard College.

Born near Kiev, in the Ukraine, Max graduated from Boston English High School, and gained a scholarship to Harvard College, where he became a chemist under the tuition of Professors James Bryant Conant, later President of Harvard University, and Louis Fieser[75,76]. In 1922 Max entered Harvard Medical School and subsequently interned on the 2nd Medical Service of the Boston City Hospital. He was promoted to "pneumonia resident", but he also worked in Professor Milton Rosenau's Department of Preventive Medicine and Hygiene where anti-pneumococcal serum was being produced. He remained at the Boston City Hospital and became Head of its Thorndike Memorial Laboratory, and George Richards Minot Professor of Medicine at Harvard Medical School. Harvard and Boston City Hospital severed almost all relationships in 1973, and the Thorndike moved to the Harvard Medical School campus. Maxwell Finland was elected a member of the US National Academy of Sciences. In 1982 Harvard granted him an honorary DSc, an unusual honour for its own faculty. The citation read "A distinguished and loyal son for (over) sixty years"[75].

Max Rosenheim left Belfast to become officer in charge, Medical Division, in various countries in the Middle East and North Africa, ending his Army service as a Brigadier General and consulting physician to the Allied Land Forces South East Asia[52].

At one of our teas or Sunday lunches that the Cairns family gave me at their home around the corner from the Dragon School, I asked why Max had been sent so far away. Professor Cairns replied, "Because of your penicillin". "But I didn't get any, and anyhow Rycroft did the asking." "Yes, but we all knew Max was behind it". Professor Cairns then said "Did you know Rycroft had to swim for awhile on the way to North Africa? He was torpedoed and they had trouble picking him up[35]. He's good at using penicillin[72].

Dragon Elizabeth Cairns and Old Draconian David Cairns and I were joined on occasion by Charles Florey who became a Dragon in January 1945 after returning from being evacuated to Yale to live with John and Lucia Fulton in Connecticut. Fulton, Sterling Professor of Physiology[10], had been a Rhodes scholar at the same time as Florey. Cairns, like Florey from Adelaide, was friendly although not contemporaries. I remember Cairns' assistant Captain Calvert[73] handing the tea around on at least one occasion.

In preparation for Cambridge in 1951, I suggested I try to manipulate the sulphonamides. I was allowed to work in the chemistry Laboratories of King's College, Newcastle-upon-Tyne. I read Lionel Whitby's classic papers[26,53,69] about which Max had called Whitby a decade earlier (Figure 8). I was having trouble getting accepted by Clare. My father suggested I ask to see Whitby, Master of Downing and Regius Professor of Physic. In Master Whitby's sitting room we discussed my treatment by Max and Ben. He then asked whether I was applying to Downing. On the train to Cambridge I had thought of my reply. "When I was seven, Professor Rosenheim told me to go to a college on the Backs. I fancy Clare". "I shall talk to Henry and tell him to make up his mind." Sir Henry Thirkill during his long mastership of Clare was a one-man admissions process. On January 15th, 1952, he had written to Harrow, with a copy to my father, "Hedley-Whyte's performance in the Clare Entrance was very poor indeed…I am wondering whether he is likely to be able to tackle the Natural Sciences Tripos." Thirkhill relented; Whitby was reigning Vice-Chancellor.

In July 1960, when I arrived at Harvard, Walter Bauer, Head of Medicine at the Massachusetts General Hospital, knew of my treatment by Max and Ben. So did Max Finland who was to become head of Harvard's Thorndike Laboratory and George Richards Minot Professor of Medicine (Figure 9). Finland was contacted by Rosenheim in 1941, and again after my wife Tessa[77] and I started work in Boston.

When we were doing rounds and combating infection in our Harvard Intensive Care Units, Max Finland advised us[78-83]. On the enoblement of Max Rosenheim, Finland remarked to our team, "In medicine there is only one great Max, and now he is Lord Max".

WHO ON PNEUMOCOCCAL VACCINES

Recently there has been increased emphasis on prevention of pneumococcal pneumonia, especially in children, the elderly and the chronically ill. In 2007 the World Health Organization (WHO) attested to the success of antipneumococcal vaccination and strongly recommended 7-valent pneumococcal conjugate vaccine (PCV-7), which was effective against 65-80% of serotypes associated with invasive pneumococcal pneumonia disease in young children from western industrialized populations. This WHO Position Paper pointed out the variability of coverage among populations in developing countries and noted progress in the development of vaccines with wider serotype coverage[84]. Recently serotype 19A strep. pneumoniae was shown to account for over 28% of invasive pneumococcal disease in Alaskan children under two years of age. Serotype 19A was not countered by the PCV-7 these children had received[85]. A 23-valent pneumococcal polysaccharide is the subject of an October 2008 WHO Position Paper[86] and is now endorsed against a moving target of invasive pneumococcal disease[87].

POSTSCRIPT

Memory, while obviously fallible, is said to be most reliably implanted at seven years of age. My recall has been aided by my father Angus' notes on the course of my lobar pneumonia, which are on pages 5,6 and the inner cover of his copy of Osler's Medicine which had survived bombing in Rennes on June 17th, 1940.[34] Memory was reinforced in later years by meeting with my physicians in Belfast, Cambridge, London and Boston[47] and by parental and uxorial admonitions.

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Case Report

Inferior Vena Cava Thrombosis in Young Adults – a review of two cases.

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ABSTRACT

We present two cases of clinically extensive bilateral DVTs associated with inferior vena caval thrombosis. Young patients presenting with symptoms of DVT should be investigated not only to establish any thrombophilic pre-disposition, but to ascertain the proximal extent of thrombus which may itself influence treatment.

Keywords: Deep vein thrombosis, inferior vena cava thrombus, retroperitoneal haematoma, congenital malformation.

INTRODUCTION

Thrombosis of the inferior vena cava (IVC) has similar aetiological factors to lower limb deep venous thrombosis (DVT)[1]. Hypercoagulability related to haematological or neoplastic abnormalities, venous stasis secondary to extraluminal pressure from tumours or inflammatory processes and vessel injury due to trauma have all been implicated as primary mechanisms in the pathophysiology of IVC thrombosis[1].

We present two cases of spontaneous bilateral IVC thrombosis in previously active young men. Case-A was a 23-year old patient who presented with an IVC / bilateral iliac vein thrombosis thought to be secondary to a retroperitoneal haematoma of benign origin. Case-B was a 25-year old patient diagnosed with a significant IVC / bi-iliac / bi-femoral venous thrombus secondary to a previously undiagnosed congenital IVC malformation.

CASE SERIES

Patient A

A 23-year old male student presented with a 1-week history of severe lower back pain initially felt when climbing stairs. The pain radiated to both thighs, being worse on the right side. He had associated anorexia, nausea, night sweats and mild diarrhoea. He had been previously fit and healthy with a history of mild asthma. There was no significant family history and he was a non-smoker.

On examination, he was haemodynamically stable but had a temperature of 38.2ºC. Cardio-respiratory examination was unremarkable and his abdomen was soft with mild lower abdominal tenderness. There was tenderness in the medial aspect of each thigh and no evidence of erythema, oedema or trauma. Haematological analysis confirmed a mild normocytic anaemia with haemoglobin 11.3 g/dl and mean corpuscular volume of 95 fl. The lactacte dehydrogenase level was elevated at 661 U/L and the C-reactive protein was markedly elevated at 210 mg/L. All other haematological, coagulation, and biochemical analyses were normal. Plain X-rays of the chest, abdomen and lumbar spine were normal.

A CT (computerised tomography) scan of the abdomen and pelvis revealed a 5.5 x 4.7cm mass in the right retroperitoneum located anterior to and indenting the psoas muscle between the IVC and the right kidney. The adjacent IVC was compressed, and inferior to this, the IVC and bilateral iliac veins were significantly distended and probably thrombosed. Numerous collateral vessels were demonstrated within the pelvis and on the right side of the abdomen. A single 5mm aorto-caval node was also identified. The initial differential diagnosis included a lymphoma or connective tissue tumour. CT-guided biopsies of the mass confirmed the presence of skeletal muscle, haematoma and normal caval wall. Repeat biopsies demonstrated the same with no evidence of lymphoma or sarcoma. An ultrasound of the testes was normal. Tumour markers carcinoembryonic antigen (CEA) and alpha feto-protein (AFP) were normal at less than 4 ng/ml and 10 kU/L respectively.

Doppler ultrasound confirmed bilateral common femoral vein thrombus. An IVC venogram via the right jugular vein demonstrated occlusion of the IVC inferior to the right atrium. Magnetic resonance imaging (MRI) suggested that the retroperitoneal mass was a haematoma which had been compressing the adjacent IVC. MRI also demonstrated intraluminal thrombus extending proximally up to the confluence of the hepatic veins immediately inferior to the right atrium with distal extension to the femoral veins bilaterally (Figures 1a & b). Thrombophilia screen did not reveal any abnormality.

The patient was treated conservatively with subcutaneous low molecular weight heparin followed by oral warfarin and the application of compression hosiery. Subsequent MRI

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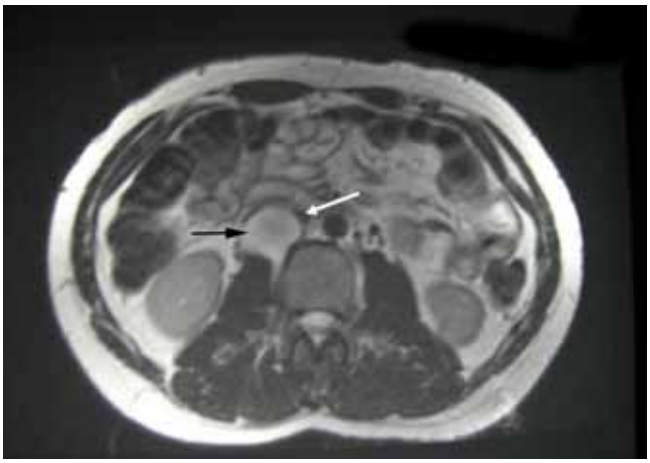

Fig 1a. T2-weighted axial MRI demonstrating the mass (predominantly high signal) in the right retroperitoneal space anterior to psoas muscle between the IVC and right kidney (Black Arrow) compressing the overlying IVC (White Arrow).

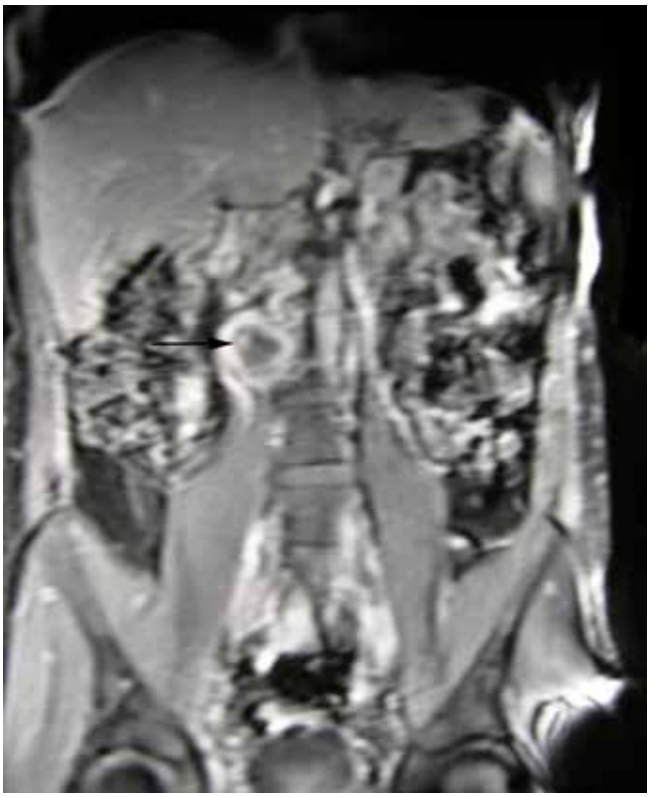

Fig 1b. Coronal MRI post-gadolinium enhancement showing the retroperitoneal lesion with a high signal rim (Black Arrow).

imaging demonstrated complete resolution of the mass and return of full patency of the IVC at 4-months (Figure 2). It remains unclear whether the IVC thrombus was preceded by the haematoma or vice versa. It was felt on balance that treatment should be directed towards the thrombus, especially in view of the early scans indicating speedy resolution of the haematoma. His bilateral lower limb pain resolved at an early stage and the patient remains well two years later with regular vascular and haematological clinical review. Warfarin was discontinued after one year. Subsequent haematological evaluation did not reveal any thrombophilic predisposition.

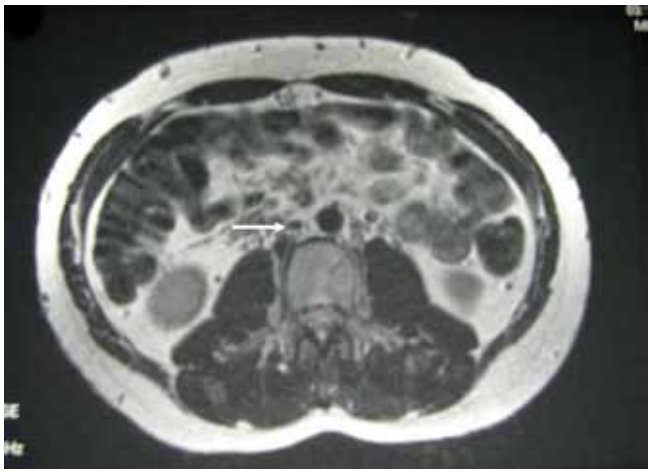

Fig 2. T2-weighted axial MRI comparable in position and image acquisition to Figure 1a demonstrating complete resolution of haematoma and IVC (White Arrow) without thrombus after 4-months of oral anticoagulation therapy.

Patient B

A 25-year old male office employee was admitted with a 3-day history of recent onset low back pain radiating to both thighs and bilateral lower limb swelling. The pain increased in severity over the preceding 48-hours and resulted in the patient having difficulty mobilising. There were no precipitating factors. He was a non-smoker with no other co-morbidities or significant family history.

On examination, he had a low-grade pyrexia of 37.8°C with a pulse rate of 110 beats/min and blood pressure of 128/73 mmHg. He had significant lower back discomfort and bilateral lower limb swelling with pitting oedema extending to above the inguinal ligaments. Venous distension was visible on the lower anterior abdominal wall. Both lower limbs appeared dusky in the supine position with further exacerbation of the dark discolourisation on standing. Bilateral lower limb arterial examination was normal. Both lower limbs were tender on palpation. Haematological analysis showed a platelet count of 93 $x10^9$/L, white cell count of 11.0 $x10^9$/l, C-reactive protein

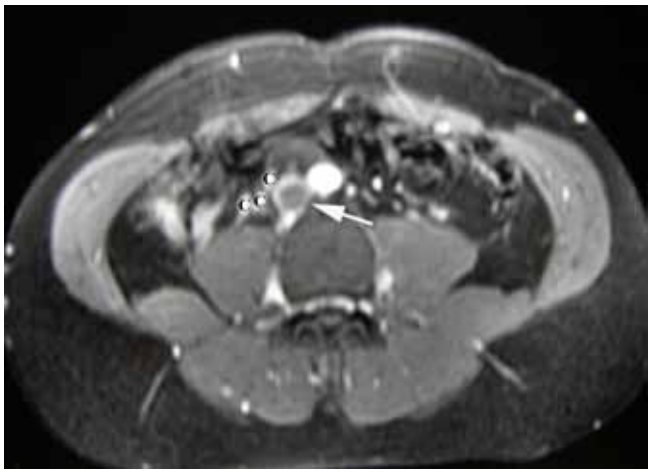

Fig 3. T2-weighted MRI demonstrating iliofemoral thrombosis extending proximally into the infrarenal vena cava (White Arrow) with extensive collateralisation (C) around the upper retroperitoneum.

of 92 mg/l and a d-dimer >20 g/ml (reference range 0.01-0.5). Bilirubin was 76 mol/l and lactacte dehydrogenase was elevated at 566 U/L. All other haematological and biochemical analyses were normal. Plain X-rays of the chest, abdomen and lumbar spine were normal.

Doppler ultrasound of the femoral veins demonstrated marked expansion of both vessels with intra-luminal thrombus. A CT scan of the chest/abdomen/pelvis revealed atypical venous anatomy where the IVC appeared slit-like between the hepatic and renal segment associated with marked dilatation of the infra-renal IVC, both common iliac veins and both external iliac veins. MRI imaging confirmed the CT findings and revealed a well developed collateral pathway through lumbar, azygous, hemi-azygous and subcutaneous anterior abdominal wall veins suggestive of long-standing caval obstruction (Figures 3 and 4). MRI also demonstrated IVC stenosis between the renal and hepatic segments, with a large thrombosed tortuous left renal vein, and no evidence of haematoma (Figure 5). The superficial renal portion of the IVC was narrowed thereby consistent with a congenital malformation of the IVC. A transthoracic echocardiogram did not reveal any intra-cardiac or aortic root anomaly. Thrombophilia screens, anti-cardiolipin antibodies, serum electrophoresis, direct Coomb's, auto-immune, complement, anti-neutrophil and immunoglobulin screens were normal.

The patient was commenced on low-molecular weight heparin and after 72-hours of treatment, his symptoms had significantly improved and his platelet count had normalised. The lower limb swelling resolved weeks later, aided by compression hosiery. The patient remains well 12-months later and is to continue with life-long warfarin.

DISCUSSION

Although the lifetime incidence of venous thrombosis is 0.1%, it still remains a rare condition especially in patients below 30 years of age[2-4]. Predisposing factors include alterations in blood flow (stasis), injury to the vascular endothelium and abnormalities in the constitution of blood hypercoagulability (Virchow's Triad)[5]. Endothelial damage is invariably an acquired phenomenon whereas hypercoagulability may result from both congenital and acquired risk factors (especially in the peri-operative period). The classical presentation of IVC thrombus varies according to the level of the thrombosis with up to 50% of patients presenting with bilateral lower extremity swelling and dilatation of superficial abdominal vessels. Whilst some patients remain asymptomatic, lower back pain, nephrotic syndrome, hepatic engorgement, cardiac failure and pulmonary embolus have also been described[6]. Tsuji *et al* reported a series of 10 patients where 40% were pyrexic at presentation with an associated elevation in d-dimer levels and inflammatory markers (white cell count, C-reactive protein)[7]. The majority of these classical features were present in both our patients, however only the second patient had lower limb swelling.

Idiopathic IVC thrombosis is extremely rare. Chikaraishi *et al* described a case of apparent idiopathic IVC thrombosis in a 57-year old woman who presented with chest pain secondary to pleurisy with a background history of pyelonephritis but no other pro-thrombotic risk factors[8]. Kaneko *et al* described a further idiopathic IVC thrombosis in a 73-year old man

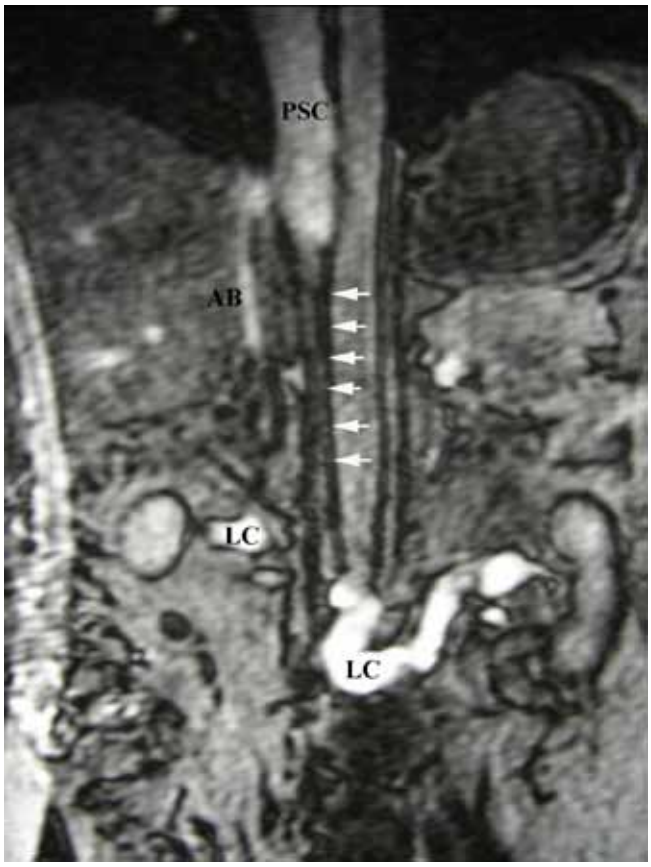

Fig 4. Coronal gradient echo MRI showing atresia of IVC between renal and hepatic segments (Sequential White Arrows) with a patent hepatic and suprahepatic IVC (PSC). Extensive, well developed collateralisation through ascending lumbar veins, azygous system and anterior abdominal wall subcutaneous veins (LC).

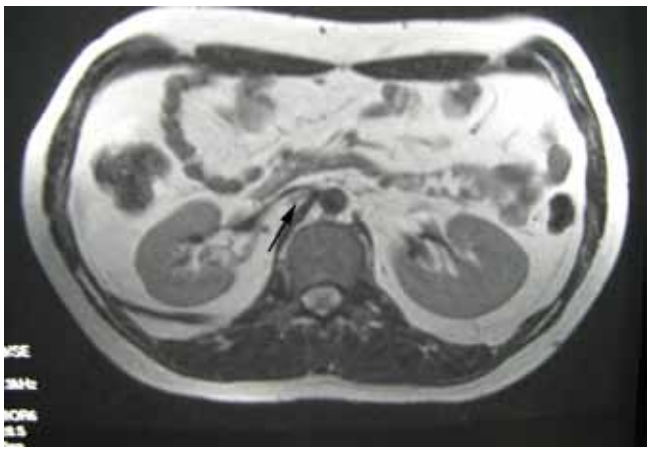

Fig 5. T2-weighted axial MRI showing apparent stenosis of IVC at renal level (Black Arrow).

who presented with a pulmonary embolism complicated by bronchopneumonia. There were no specific thrombotic risk factors except for age and dehydation[9]. Following exclusion of May Thurner syndrome and other pathologies, it is possible that in Patient A's circumstances the thrombus was an idiopathic primary event, and the surrounding retroperitoneal haematoma a secondary phenomenon.

Idiopathic spontaneous retroperitoneal haematoma has also been previously described[10-12]. The work of Chia *et al* and the initial investigative work-up of Patient-A in this series demonstrate the difficulties associated with a diagnosis of a retroperitoneal haematoma[10]. The condition presents a significant diagnostic challenge both due to its similarity to more sinister pathologies, and the requirement to achieve a tissue diagnosis. This distracts the clinician from allowing time for the "*Mass*" to resolve and the less sinister nature of the underlying pathology to reveal itself. We hypothesise that in the case of Patient-A, trauma to the iliopsosas muscle from the simple act of climbing stairs caused the retroperitoneal haematoma which led, via mass effect, to compression of the IVC, hence intraluminal thrombus.

Shrestha *et al* described an endemic variant of IVC thrombosis in Nepalese patients leading to hepatic venous outflow obstruction (HVOO) which caused obstruction or stenosis of the IVC hepatic segment near the cava-atrial junction[13]. Ostia of one or more of the hepatic veins were commonly occluded. This chronic disease is characterised by upper abdominal pain, hepatosplenomegaly, ascites with a high protein content and dilated superficial veins in the trunk having cephalad blood flow. Previously, this variation of IVC thrombosis was endemic in Japan, however it is now only seen in developing countries, most notably Nepal[13-15]. This condition was originally thought to be caused by a congenital vascular malformation due to the observation of a membrane within the obstructing lesion[14]. Considerable evidence now suggests an acquired infective aetiology which results in thrombophlebitis leading to thrombus formation and a subsequent fibrotic stenosis[15]. Organisms thought to be involved are staphalococcus aureus and gram-negative enteric organisms with the resultant bacteraemia causing a transient protein-S deficiency[15].

The IVC is created by the fusion of three sets of paired veins, specifically the posterior cardinal, subcardinal and supracardinal veins during weeks six to eight of embryonic development[16]. It is failure of these paired veins to fuse into a unilateral right–sided venous system which leads to an anomalous IVC[16]. Congenital malformations or interruptions of the IVC are unusual with a 0.3% to 0.6% prevalence in the general population[17]. These interruptions or absence of the IVC are usually limited to the intrahepatic segment and include an interruption in the IVC with azygos and hemi-azygous continuation, the transposition or duplication of the IVC, circum-aortic venous rings, and a retroaortic left renal vein[16]. The prevalence of these defects increases to 2% in patients with other congenital cardiovascular defects such as dextrocardia, transposition of the great vessels, pulmonary artery stenosis and a single atrium[17]. Co-existent visceral anomalies include situs inversus, polysplenia, asplenia and hypoplasia of the kidney[7].

Caval aberrancy has been reported to occur in 5% - 16.2% of young patients presenting with DVT.[5,18-20]. A lower limb DVT is three to eight times more frequent on the left side, whereas bilateral iliofemoral thromboses are uncommon, occurring in less than 10% of cases[21]. However in the presence of caval aberrancy, bilateral iliofemoral thrombosis, has been reported in 66-75% of patients[5,22]. An aberrant IVC may also remain asymptomatic as alternative pathways of collateralisation develop through the azygous / hemiazygous and portal circulations to counteract venous stasis, as identified in the second patient[7,23]. Raju *et al* state that common iliac vein patency is the crucial link to the rich potential collateralisation via the retroperitoneal venous network which is usually only of importance in embryological development. Concurrent occlusion of the common iliac(s) as well as the IVC, with distal extension of thrombus leads to clinical symptomatology in patients with both normal and abnormal IVC anatomy[23].

Anomalies of the IVC are also linked to thrombophilia disorders such as Factor V Leiden, prothrombin gene mutation, low protein S levels, high homocysteine concentration, methylenetetrahydrofolate reductase gene mutation and antiphospholipid antibodies[18,24-28]. It is unclear whether IVC thrombosis is purely related to an anomalous IVC or whether an interaction between an anatomical abnormality and thrombophilia tendency is required[22]. Gayer *et al* state that further research is required to assess this interaction due to considerations regarding anticoagulant therapies and treatment durations.

Recent advances in the utilisation of ultrasound, CT and MRI imaging as well as endovascular procedures have resulted in an increase in detection rates of IVC anomalies, as well as the incidental discovery of such abnormalities during unrelated investigations, therapeutic endovascular or surgical procedures[7]. Contrast venography remains the standard for diagnosis of IVC thrombosis with a low false-positive rate and the advantage of access for immediate treatment if required. However, it is an invasive procedure associated with a 2% -10% incidence of post-procedural DVT[1]. Duplex ultrasound scanning has become an accurate non-invasive method of diagnosing IVC thrombosis and is often the first-line investigative modality[1]. However, duplex USS is operator dependant and can be limited by body habitus or the presence of bowel gas and may occasionally fail to identify any IVC anomaly[1,29]. CT imaging is a rapid non-invasive method which can accurately diagnose and assess the extent of thrombus as well as delineate any associated abdominal or pelvic abnormality[1]. MRI imaging is now replacing CT as the optimal investigative tool avoiding radiation and giving more accurate delineation of thrombus as well as any IVC anomaly. MRI is also used to follow-up patients to determine morphological changes in the thrombus following therapy[30].

Treatment options in the case of IVC thrombus without anatomical variance include anticoagulation, mechanical thrombectomy, systemic thrombolytic therapy, transcatheter regional thrombolysis, pulse-spray pharmacomechanical thrombolysis and angioplasty[1,31]. There is no specific literature describing the ideal duration of anticoagulation in these instances, however, case evidence identifies a trend toward treatment for a minimum of one year with the interplay of hypercoagulability disorders needing to be factored into any decision. Surgical reconstruction of the IVC and bypass of an aberrant section are both recognised modalities reserved for the most severe cases and are associated with morbidity and mortality risk[32]. Endovascular stent placement in combination with angioplasty is recommended in the cases of residual stenosis and chronic IVC occlusion[32].

In the case of IVC thrombus associated with an aberrant IVC, with no other predisposing factors, treatment involves

anti-coagulation. The duration of this treatment is widely debated with no extensive literature to provide an evidence-based approach. Dean *et al* take a similar view to us, that a caval anomaly is a permanent risk factor for venous stasis and thrombosis and that anticoagulant treatment should be lifelong[21].

CONCLUSION

IVC thrombosis is associated with a significant acute and chronic morbidity. A high index of suspicion is warranted for IVC thrombus in the young patient with lower back and limb pain, swelling of the lower limbs, dilatation of superficial abdominal veins, with a concurrent rise in inflammatory markers and pyrexia. In these cases, further investigational modalities are mandatory following ultrasonic identification of an ileo-femoral thrombosis especially when bilateral. CT or preferably MRI imaging, are required to delineate IVC anatomy and ascertain proximal extent of the thrombus. Although invasive therapeutic modalities exist, long-term and commonly life-long anticoagulation is often required.

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Case Report

Kikuchi-Fugimoto Disease (Cervical Subacute Necrotising Lymphadenitis): An important benign disease often masquerading as lymphoma

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ABSTRACT

Objectives: We describe a rare cause of posterior triangle cervical lymphadenopathy in a third decade female, outline the clinical and histopathological features and discuss excision biopsy as the investigation of choice in this age group, with lymphoma as the diagnosis of exclusion.

Case report: A thirty-four year old female was referred to our Head and Neck clinic with a one-month history of left posterior triangle lymphadenopathy. She reported no other symptoms and haematological investigations were normal. She was "Red Flagged" as a possible lymphoma. Excision biopsy revealed extensive histiocytic necrotising lymphadenitis providing a diagnosis of Kikuchi-Fujimoto disease.

Conclusions: Persistent posterior triangle lymphadenopathy in the 16-40 year old age group warrants "Red Flag" referral to rule out serious pathology such as HIV, metastatic cancer or lymphoma. When the ENT examination and haematological work up is negative, we advocate proceeding straight to excision biopsy as the quickest way to obtain a diagnosis, which sometimes comes up with the unexpected as in this rare case of Kikuchi-Fujimoto disease.

Key Words: Kikuchi-Fujimoto disease, cervical lymphadenopathy, Red Flag referral, Excision biopsy.

INTRODUCTION

Persistent cervical lymphadenopathy is an important "Red Flag" referral criterion to Head and Neck Clinics. In adults over the age of 40, when lesions of thyroid and salivary glands are excluded, the majority (75%) of neck lumps are malignant. Metastatic lymphadenopathy from a carcinoma of the aerodigestive tract is of particular significance in this age group, especially if there is a history of heavy smoking and drinking, and localisation of the primary tumour must be made without delay. In contrast, cervical lymphadenopathy in patients aged between 16-40 years is most commonly the result of infection; other causes in this age group include rare inflammatory processes and neoplastic lesions such as lymphoma.

We describe a 34-year-old woman who presented with cervical lymphadenopathy due to Kikuchi-Fugimoto disease (KFD, or subacute necrotising histiocytic lymphadenitis), a rare and important cause of benign lymph node enlargement.

CASE REPORT

A 34-year-old female became aware of lump in her left lower neck in mid May 2008. She attended her General Practitioner approximately 4 weeks later who noted the presence of two enlarged lymph nodes low on the left side of her neck, which were painless, firm but mobile; he also felt a lump in her right axilla. She was apyrexic, haematological investigations at that time revealed a haemoglobin of 12.9g/dl, white cell count of 4.1 x10^9/l with normal differential and an ESR of 12 mm/hr. The patient was a non-smoker who denied any weight loss, itching or night sweats and was in otherwise good health. She was referred as a "Red Flag" case of possible lymphoma to the local Head & Neck clinic, where she was seen 5 days later. Clinical examination at that time confirmed a 2 cm diameter prominent painless rubbery lymph node in the left posterior triangle and several similar but smaller lymph nodes just above and below this largest lymph node. There was a mild operculitis of her partially erupted lower wisdom teeth but nil else of note within her mouth or throat. In particular, there was no lesion on her scalp or neck skin and no axillary or groin lymphadenopathy was detected. She had no other complaints and still felt well. The clinical suspicion of lymphoma persisted in spite of the absence of other symptoms or signs and an excision biopsy was performed three days later.

At surgery, an enlarged friable 2cm lymph node was found in Level V, removed and submitted for histopathological assessment. The most striking feature of the lymph node on microscopy was the presence of extensive areas of geographic necrosis bounded by relatively broad zones of histiocytes

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and activated lymphoid cells. Many apoptotic cell fragments were present being ingested by histiocytes (Figure 1) but there was no neutrophil infiltrate, multinucleate giant cell formation or granulomatous inflammation. In other areas of the node, there was expansion of the paracortical regions with many dispersed histiocytic cells; only a few small reactive lymphoid follicles were present. The histopathology suggested a necrotising lymphadenitis without neutrophil infiltration, virtually diagnostic of KFD - occasionally such changes can be associated with systemic conditions, in particular systemic lupus erythematosus (SLE). The patient was tested for autoantibodies including ANA, the most commonly detected autoantibody in SLE; the results were negative. The patient was followed-up for six months and made a spontaneous uneventful recovery.

DISCUSSION

The differential diagnosis of enlarged cervical lymph nodes is wide and a full discussion is beyond the scope of this article but the principal conditions to be distinguished in posterior triangle lymphadenopathy are lymphoma, metastatic tumour from the scalp or more distant site, drainage phenomena from infective lesions in the dependent skin, and systemic reactive conditions such as infectious mononucleosis, human immunodeficiency virus (HIV) infection and rubella.

In this case there was no history of previous surgery or clinical findings suggesting metastasis from tumour elsewhere; there were no oral or head and neck manifestations to suggest systemic viral infection, including HIV. There was no skin lesion in the drainage area to indicate a local inflammatory cause for the lymph node enlargement and the intraoral inflammation related to the partially erupted third molars was not thought to be contributory. Given the absence of systemic upset, no serological investigation of specific viral infection markers was preformed.

KFD was first described independently in 1972 by Kikuchi[1] and Fugimoto[2]. In 1982 the first cases of KFD were reported in North America and Europe[3] and the disease is now recognised worldwide. KFD commonly affects young women with a peak age of incidence occurring in the third decade[4], but rarely affects patients under 16 years of age. A handful of cases have been reported in children under the age of ten. The ratio of disease occurrence between females and males is 4:1, although less apparent gender differences occur in Asian populations when compared to Western populations.

The aetiology of KFD remains unclear. Several infective agents including EBV, parvovirus B19 and HHV-6[5], have been postulated as causative although no relationship has yet been established. Due to the similar histology seen in KFD and the lymphadenitis of SLE and that both diseases most often occur in young females, Dorfman and Berry[6] suggested KFD could be an attenuated form of SLE. Another explanation[7] proposed that KFD might be a self-limiting SLE-like autoimmune reaction to viral infected transformed lymphocytes. Whatever the pathogenesis, it is likely that the development of KFD is a multifactorial process involving environmental, biological and genetic influences.

The majority of patients with KFD present with cervical lymphadenopathy usually of 1 - 4 cm in diameter, the posterior cervical triangle being the most commonly affected site[8]. Other less common signs and symptoms include splenomegaly, fever and weight loss – one third of patients have a rash at presentation, findings that can heighten the clinical overlap with infectious mononucleosis, SLE and lymphoma. A number of non-specific haematological abnormalities may occur in KFD. Approximately 50% of cases show a mild neutropenia[9] with leucopaenia also present in 25-40% of cases[4]. Other non-specific findings include a raised CRP and ESR but their absence does not exclude KFD.

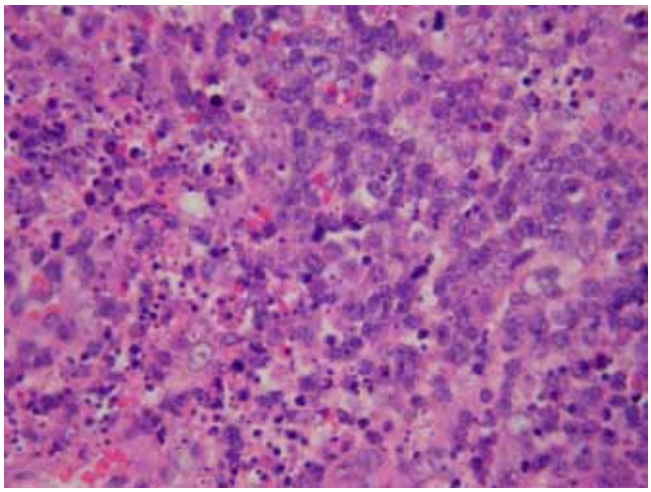

Fig 1. High power view of area of necrosis showing many histiocytes packed with cell fragments but without neutrophil infiltration. (H&E, x 400 original magnification)

Fine needle aspiration cytology (FNA) has been able to provide a diagnosis in cases of KFD but correct interpretation depends on sampling affected areas of the node and in many cases the exclusion of non-Hodgkin's lymphoma may not be possible on FNA alone. In our opinion there should be a low threshold for open excision biopsy in patients less than forty years of age presenting with persistent lymphadenopathy. In this age group FNA can often be an additional non-diagnostic step, delaying the excision biopsy, which is required for the accurate diagnosis. In our case, we proceeded directly to open biopsy for this reason.

The histopathological features of KFD are quite distinctive and the only mimic is SLE lymphadenitis. The lymph node changes in Kawasaki disease (mucocutaneous lymph node disease), cat scratch disease and atypical mycobacterial infection are quite different, being characterised by intravascular fibrin thrombi and neutrophils, stellate microabscesses with neutrophils and necrotising stellate granulomatous inflammation respectively[10].

CONCLUSION

We describe a case of KFD presenting as an unusual cause of posterior triangle cervical lymphadenopathy that mimicked lymphoma. Whilst the histopathological findings were classical and allow the diagnosis of KFD to be achieved without difficulty, the case highlighted the usefulness of prompt referral for biopsy of persistent unexplained lymphadenopathy.

The authors have no conflict of interest.

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Case Report

Epstein - Barr virus Pneumonitis

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ABSTRACT

Epstein-Barr virus is an unusual pathogen in the aetiology of alveolitis. We describe a case of Epstein-Barr virus induced pneumonitis and its successful treatment with Aciclovir.

Keywords: Epstein-Barr virus, Pneumonitis, Computed Tomography, Lung, Aciclovir

CASE REPORT

A 62-year-old female with a history of polymyositis was admitted with a four-week history of increasing dyspnoea. She had been treated with maintenance oral steroid therapy over the previous 4 years, augmented with oral cyclophosphamide over the preceding 4 weeks. On examination there were fine crepitations to the mid-zones. The patient was hypoxic with a $Pa0_2$ of 10.2 KPa on inspired FiO_2 of 0.6. C reactive protein was elevated at 212 mg/L. Echocardiogram was normal. Initial chest X-ray was normal (figure 1). A CT Pulmonary Angiogram (CTPA) was then performed and thrombus excluded, however inspiratory and expiratory high-resolution (HRCT) scans were obtained subsequent to the CTPA due to the grossly abnormal appearance of the lung parenchyma on lung windows. High resolution scan images demonstrated

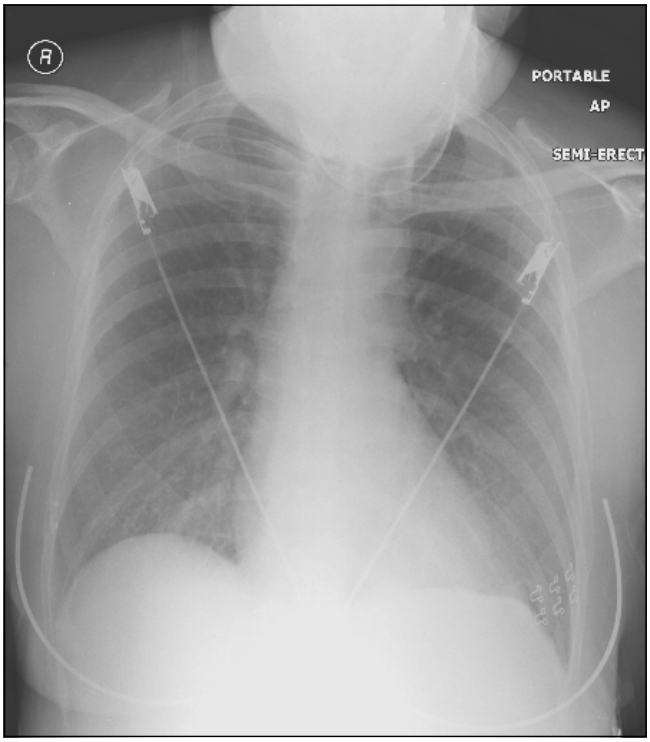

Fig 1: Normal chest radiograph on admission.

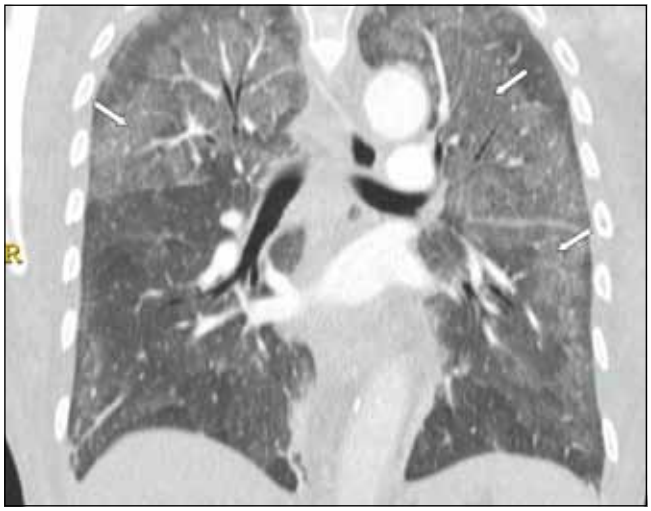

Fig 2a: Coronal reformat reproduced from CTPA study demonstrating wide spread ground glass opacity (white arrows).

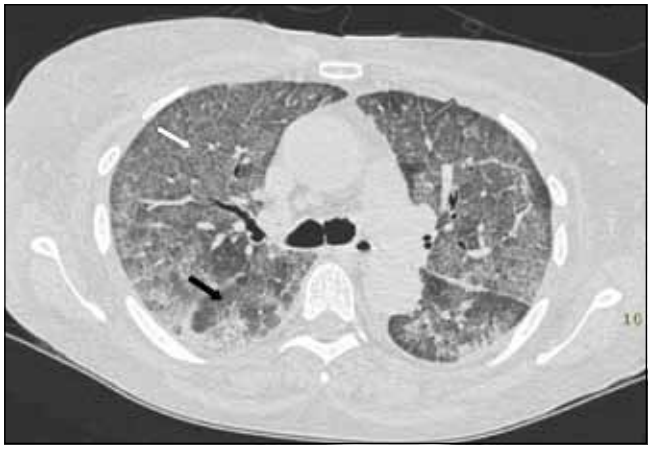

Fig 2b: Transaxial HRCT image at level of the carina showing intralobular interstitial thickening (black arrow), interlobular septal thickening (grey arrow) and ground glass opacity (white arrow).

widespread marked ground glass opacity with intra and interlobular septal thickening in keeping with a diffuse alveolitis (figure 2a and 2b). Ground glass opacification describes the findings on HRCT of the lungs in which there

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is a hazy increased attenuation of lung with preservation of bronchial and vascular margins. This appearance can be caused by partial filling of air spaces, interstitial thickening, partial collapse of alveoli, normal expiration, or increased capillary blood volume[1]. The presence of numerous intra and interlobular septa almost always indicate the presence of an interstitial abnormality, only a few septa should be visible in normal patients. Septal thickening can be seen in the presence of interstitial fluid, cellular infiltration or fibrosis[2]. Diffuse alveolitis refers to the combination of these appearances throughout both lung fields suggestive of an acute inflammatory process of the pulmonary alveoli.

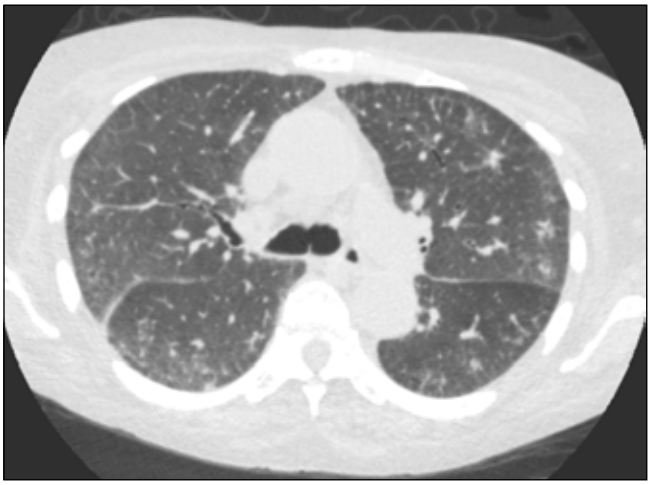

Fig 3: Follow-up transaxial CT chest image demonstrating marked improvement in interstitial changes.

The patient subsequently required intubation and ventilation; EBV was identified on endotracheal aspirate with a copy number of 28,420/ml on quantitative PCR. No other bacterial, viral or fungal infection was identified. The patient was then treated with IV Aciclovir with subsequent dramatic clinical and radiological improvement (figure 3). EBV was not detectable on repeat airway aspirate following treatment.

This patient was predisposed to infection in the setting of chronic disease and ongoing immunosuppression. The normal echocardiogram findings combined with the absence of features of cardiac failure make pulmonary oedema less likely as a contributing factor. This is also supported by the presence of an inflammatory response, which responded to antiviral treatment and associated radiological resolution.

EBV has been proposed in the pathogenesis of cryptogenic fibrosing alveolitis and more recently has been implicated in interstitial lung disease resembling sarcoidosis[3]. The role of EBV as an infective agent in the development of lung disease is controversial and there are few reports of symptomatic pulmonary involvement directly attributable to EBV infection. There is no single anti-viral agent specifically indicated in the treatment of pulmonary EBV infection. There have been case reports describing favourable outcomes with the use of Aciclovir[4]. This case supports the use of IV Aciclovir in EBV associated pneumonitis.

The authors have no conflict of interest

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Letters

ANTIMICROBIAL RESISTANCE IN *CAMPYLOBACTER* ISOLATES FROM SPORADIC CASES OF ACUTE HUMAN GASTROENTERITIS IN NORTHERN IRELAND

Editor,

Thermophilic campylobacters, particularly *Campylobacter jejuni*, continue to remain the most common cause of acute bacterial enteritis in Northern Ireland. Most recent confirmed data for 2006 recorded 937 laboratory reports for Northern Ireland (http://www.cdscni.org.uk/surveillance/Gastro/Campylobacter_sp.htm), approximating to 53.8 cases per 100,000 individuals, compared to an attack rate of 86.7 and 42.8 cases per 100,000 individuals for England & Wales and the Republic of Ireland, respectively. However, in a previous epidemiological study[1], it was estimated that the true prevalence of this infection was approximately 10.3-fold higher, due to patient under-reporting.

In relation to antibiotic resistance of local campylobacters, we have continued to map resistance trends[2,3] during the perod 2004-2007 (n=1102) (Table I). The worrying finding of this study has been the marked increase in resistance to ciprofloxacin, rising to 31.7% in 2007, which is the highest level of resistance of these organisms to this agent that has ever been reported in Northern Ireland. Susceptibility data relating to ciprofloxacin resistance in local human clinical isolates were first reported in 1996 (9%) and this resistance rate has since risen steadily. Presently, the reason(s) for this increase in resistance is unclear. The most likely explanation for this is the ingestion of campylobacters which are more resistant to this agent, rather than the acquisition of resistance *de novo* in the human gastrointestinal tract, epecially as these organisms do not form part of the ecological microflora of the human gut. This therefore encourages examination of reservoirs and sources where such resistant organisms may enter the food chain. One possibility may be consumption of imported poultry meat from origins outside the EU, where veterinary controls of the use antibiotics in animal husbandry may not be stringent, thus leading to the development of fluoroquinolone resistant isolates in chickens prior to slaughter. A previous report in 2003[4] described the importation to Northern Ireland of 500 tonnes of chicken meat per week, which had a resistance to ciprofloxacin of 14% of isolates tested. Similar studies from Belgium[5] and Spain have suggested ciprofloxacin resistance in poultry to be 42% and 99%, respectively.

TABLE I:

Percentage of wildtype Campylobacter isolates resistant to three antibiotic agents over the period 2004-2007.

	Year			
Antibiotic	2004 (n=237)	2005 (n=297)	2006 (n=309)	2007 (n=259)
Ciprofloxacin	20.3%	18.9%	23.6%	31.7%
Erythromycin	2.5%	3.4%	1.9%	1.2%
Tetracycline	20.2%	19.5%	19.7%	22.8%

Another explanation for this rise in ciprofloxacin resistance in local human infections may be the acquisition of more resistant strains outside of Northern Ireland, particularly relating to travel abroad. The arrival of several budget and low cost airlines to Northern Ireland has lead to a marked increase in Northern Ireland residents travelling to countries which have a higher endemic rate of fluoroquinolone-resistance in campylobacters originating from animals, as well as humans. In 2007, airport passenger traffic to EU destinations increased by 21% at Belfast International Airport, resulting in 1,490,775 passenger journeys (http://www.caa.co.uk/docs/80/airport_data/2007Annual/Table_10_1_EU_and_Other_Intl_Pax_Traffic_2007.pdf). Urgent attention now needs to be directed at this resistance issue in order to ascertain the origins of this marked rise in ciprofloxacin-reisitance in local campylobacters.

In conclusion, primary care practitioners, specialists in infectious diseases, microbiologists and epidemiologists need to be aware of the local increase in antibiotic resistance of thermophilic campylobacters to ciprofloxacin (31.2%) and the relative susceptibility of local wildtype isolates to erythromycin (1.2%).

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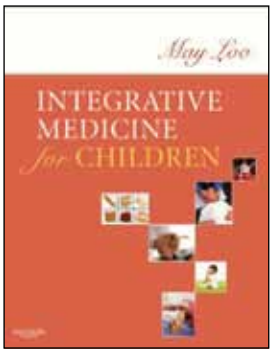
Book Reviews

INTEGRATIVE MEDICINE FOR CHILDREN. May Loo. Saunders Elsevier. September 2008, Hardback, 536pp. £36.99. ISBN 978-1-4160-2299-2



Increasingly patients and their parents are turning to complementary and alternative medicines (CAM). As paediatricians, CAM practitioners and indeed parents ourselves we need to understand these therapies to take a full medical history, considering merits and potential adverse effects of CAM, in order to offer an educated opinion to our patients. Many books exist dealing with individual therapies but this reference book aims to symbiotically blend conventional medical diagnosis and treatment with all of the major CAM. The author is Clinical Professor of Paediatrics and Anaesthesiology in Stanford, California while the 32 contributors and consultants have backgrounds as diverse as Professor of Pharmacy, Attending Physician in Neurology, Clinical Nurse Specialist from a Paediatric Integrative Medicine Program to Chinese Herbal Consultants.

The first section of the book presents the history, theory, current evidence-based information, applications and contra-indications of CAM. The chapters are nicely written, informative and well researched, although my own personal, scientific and religious bias made some modalities such as past life regression and Qigong, magnet or energy medicines difficult to comprehend. Conventional medicine would clearly benefit from the increased time, thoroughness and breadth of the clinical history taking in all the modalities. Of interest the principles of naturopathic medicine "primum non nocere": first do no harm, "tolle totum": treat the whole person, "docere": doctor as teacher and "prevenir": prevention with adoption of a healthy lifestyle show clear parallels to the Hippocratic oath. Unbiased comprehensive reference lists including recent papers from high impact medical journals (New England Journal of Medicine, Archives of Disease in Childhood and Lancet to name a few), an occasional Cochrane collaborative review, as well as larger texts for further study were impressive, with links to a few reputable regularly updated websites. Illustrations and tables range from body maps of acupuncture points, massage endangerment sites, tables of vitamin and mineral toxicity or deficiencies and botanical agents to be used in caution with children or lactating mothers.

The second section is a focused reference for 55 acute and chronic paediatric conditions with such random complaints as asthma, cancer, cerebral palsy, epilepsy, fifth disease, inflammatory bowel disease, umbilical hernia and urinary tract infections. The introductory conventional medical diagnosis and treatment section is often scanty and occasionally predictably controversial, such as the proposal that the MMR vaccine is involved in the immunological aetiology of autism. The CAM section is often repetitive - tea tree oil discussed under 3 modality headings within 3 pages on acne, with the same paper discussed and re-referenced 3 times, including a typing error! Much effort has been made to back the CAM recommendations with a solid but scientifically small evidence base but certain statements do alarm for example p136 "for acute abdominal pain caused by more serious conditions, such as that due to early appendicitis, administering a homeopathic remedy early in the course, as the patient is on the way to seek emergency care, may avert the need for surgery". The naturopathic and nutritional advice is generally useful, particularly regarding constipation, headaches and obesity, but would need co-operative, highly motivated, educated and well financed patients and parents. Many of the psychology and spirituality techniques described, such as visualisations for depression, are practical.

In summary this book is a useful reference for a medical library, certainly offers an encyclopaedic base to broaden knowledge of CAM, and would be a useful starting point for further research into CAM options available for a specific patient.

Nuala M Flanagan

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Cover legend: Diagram showing the peritoneal view of the groin. From Dasari B et al Page 115