Editorial

The decline in lung cancer and the genetics of nicotine addiction

Smoking causes over 85% of lung cancers (figure) in men and 70% in women. The incidence has declined over recent years and a paper from the Harvard School of Public Health has now shown that recent lung cancer risk in younger age cohorts in Ireland has declined faster than previously, particularly in males.[1] This is good news for patients and given the smoking ban in Northern Ireland introduced on 30th April 2007, this decline should be expected to accelerate further.

We know that lung cancer is generally not a hereditary disorder as most cases are smoking related, but nicotine addiction is strongly inherited and several genes have now been isolated, including CHRNB3 – the β3 nicotine receptor subunit gene[2,3]. It is now recognised that gene carriers (and in particular, females) are more sensitive to nicotine and have a lower addictive threshold. This may be a possible reason for the slower decline in lung cancer deaths in females when compared to males, as females find it harder to give up.

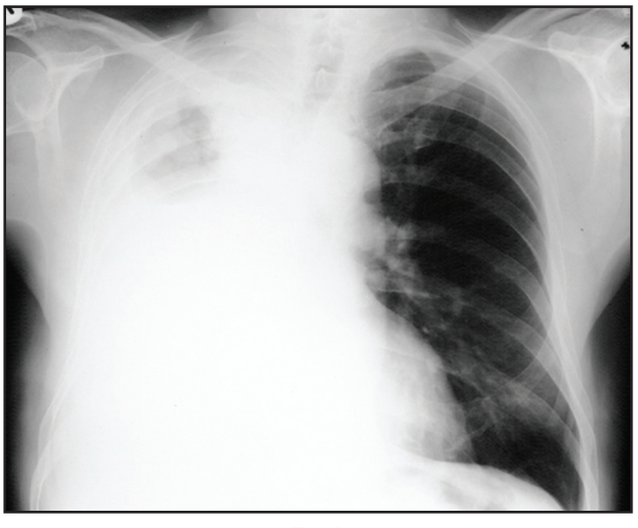

Fig 1.

What can be done about this? The smoking ban will help[4] – standing outside in a drafty and wet environment will encourage giving up. Tax increases on cigarettes will reduce consumption further. Health advice will contribute - General Practitioners (GP's) are practising what they preach in that only 4% of GP's smoke compared to 29% of the population[5], and they are taking plenty of exercise and are deemed physically 'active'. The health of bar workers in the Republic of Ireland has greatly improved since the smoking ban was introduced there in March 2004. Blood carbon monoxide (CO) levels when compared to a year before and after the ban, fell by 79% and salivary cotinine by 81%[6]. Clearly, the ban has been a success.

Life expectancy will rise further if this trend continues and pension provision will get worse as treasury funds shrink from lack of cigarette advertising and tax revenue. Governments do not like this sort of trend and are perhaps cynically hoping that the rise in obesity - and a soon to follow reduction in life expectancy - will be the salvation of the pension crisis. Even if all smokers quit tomorrow, the downward trend of lung cancer will take time to reach a low level. Respiratory physicians and oncologists should not worry about empty clinics just yet – they will still have to wait until around 2040 before retraining as obesity specialists.

Those of us in most of the British Isles (but not England where the smoking ban is still to come into force) can now enjoy smoke free dining, but do not celebrate by eating too much!

Patrick J Morrison, Honorary Editor

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Ulster Med J 2007; **76 (2)** 66-67

Commentary

Perioperative Management of Patients with Implantable Cardioverter Defibrillators

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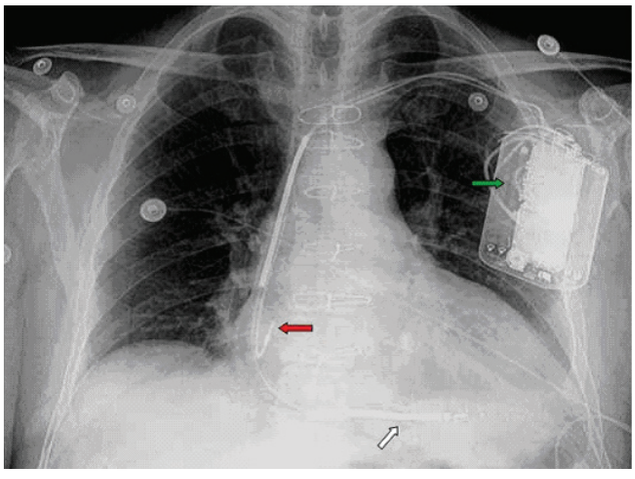
Accepted 2 March 2007

The first successful implant of an automated internal defibrillation system was described in 1980[1]. Since then the number of indications for implantable cardioverter defibrillator (ICD) therapy has grown and the number of implants has risen rapidly[2]. As a result, growing numbers of patients with ICD's are presenting for surgery, potentially giving rise to uncertainty about device management, especially in emergency settings. We have collated manufacturers' recommendations, professional guidance and the relevant literature to provide support for surgical decision-making when faced with a patient with an ICD (figure).

Electromagnetic interference (EMI) is the main safety concern that arises when patients with ICD's undergo surgery. Theoretically EMI from diathermy devices can interfere with ICD sensing which may result in spurious detection of a ventricular arrhythmia (oversensing) and delivery of a defibrillator shock. Other potential risks to the ICD include reprogramming, temporary inhibition of pacing functions or irreversible damage to the internal circuitry[3].

Two types of surgical diathermy are in common use: monopolar and bipolar of which the former is more widely used in practice. Monopolar electrical current enters the patient via an active electrode. The current travels through the patient and returns to the generator via a dispersing ground electrode. The active electrode usually discharges current through a surgical instrument. If the diathermy unit is activated prior to contact between the active electrode and the surgical instrument, the electric current may arc through the air toward the instrument and demodulate the electronic signal. Such a signal may be over sensed by the ICD resulting in an inappropriate discharge. Bipolar diathermy involves the flow of current between two tips of a bipolar forceps. Current passes from the active electrode at one tip through the patient (but only at the diathermy site) to the dispersive electrode at the other forceps tip. Therefore the theoretical risk of EMI associated with bipolar is substantially less than with monopolar diathermy.

Diathermy is not the only potential medical source of EMI; others include magnetic resonance scanners, radiofrequency ablation, lithotripsy, radiation therapy and transcutaneous electronic nerve stimulation (TENS) units[3]. Non-medical sources include anti-theft surveillance devices, slot machines, electric razors, showering and even household items such as washing machines. Interference with ICD functions has been described with all of these aforementioned technologies but studies that have addressed specifically the interaction



Chest X-Ray appearances of a dual chamber ICD. Green arrow: battery and pulse generator. Red arrow: right atrial appendage lead (bradycardia sensing and pacing). White arrow: right ventricular lead (bradycardia sensing and pacing, anti-tachycardia pacing and defibrillation).

between surgical diathermy and ICD's found no evidence of oversensing, reprogramming or device damage. This is a limited evidence base, the largest series involving 45 patients undergoing a variety of elective surgical and interventional procedures[4] and no studies have been performed in the emergency setting. Nonetheless it may be concluded that as a result of progressive refinements in ICD design (titanium shielding, signal filtering, interference rejection circuits and noise rejection functions) the risk of a harmful interaction between surgical diathermy and an ICD is very small.

When a patient with an ICD comes for elective surgery, pre-procedural planning can be undertaken to minimise the risk to the patient, operators and device[3, 5-7] (Table). Reprogramming to monitor mode involves deactivation of the ICD's ability to sense and treat ventricular tachycardia and ventricular fibrillation. It allows electrical signals to be recorded throughout the procedure but no action will be taken should they be interpreted as a ventricular arrhythmia. Clearly under such circumstances arrhythmias should be treated as they would in a patient who does not have an ICD. Arrhythmic

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Table:
Perioperative ICD management recommendations[7]

Elective Surgery

- Establish the device manufacturer and program from the patient-held card
- Arrange interrogation of the ICD, if not performed within the last six months
- If diathermy will be required, reprogram the ICD pre-operatively to monitor mode. Bipolar diathermy is preferred and low energy short bursts are desirable
- If monopolar diathermy is essential, low energy, short bursts are preferred. Diathermy cables and the grounding electrode should be remote from the ICD
- Arrange for ICD interrogation post-operatively

Emergency Surgery

- Where possible follow elective surgery guidance
- If the device can not be switched to monitor mode pre-operatively
  - Restrict diathermy usage and where possible use bipolar diathermy
  - Ensure that cardiopulmonary resuscitation facilities are available
- If an appropriate ICD shock occurs, correct any reversible causes
- If recurrent ICD shocks occur, follow standard CPR guidelines
- Arrange for ICD interrogation post-operatively

precipitants (hypoxia, hypotension, metabolic derangements) should be corrected and standard cardiopulmonary resuscitation measures should be implemented in the event of cardiac arrest. If external defibrillation is required the risk of damage to the ICD and myocardial injury will be minimized if an antero-posterior (A-P) pad position is adopted. If this is not possible, the pads should be placed at least 10–15 cm from the ICD.

If a patient presents with a life-threatening surgical emergency[7], preoperative ICD interrogation and reprogramming may not be available. This should not be interpreted as a contraindication to emergency surgery. Rather, the diathermy precautions outlined in the Table should be followed. As previously mentioned the risk of a harmful interaction between surgical diathermy and ICD's appears to be largely theoretical and a much greater risk is likely to be caused by delay or deferral of potentially life-saving surgery in patients with surgical emergencies.

Despite the exponential increase in ICD implants, there is limited expert guidance about the best perioperative management of patients with ICD's, especially in emergency settings. However the available published information suggests that surgical diathermy poses a substantially smaller hazard than many other medical and indeed non-medical electromagnetic sources.

The authors have no conflict of interest.

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Ulster Med J 2007; **76 (2)** 68-71

Commentary

Emergence of community-associated MRSA (CA-MRSA) in Northern Ireland

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Accepted 22nd February 2007

In the summer of 2006, a previously healthy 16 year old individual presented to the local Accident and Emergency Department, of a Northern Ireland hospital, with a 1.5cm diameter abscess over the left great toe, surrounded by cellulitis. The lesion had failed to respond to oral flucloxacillin prescribed by the family doctor. Apart from trauma to the toe three weeks previously, the patient had no significant past medical history and no risk factors for the acquisition of meticillin-resistant *Staphylococcus aureus* (MRSA). The lesion required incision and drainage on two occasions. Culture of pus revealed MRSA and treatment was changed to oral doxycyline. Phenotypically, the organism behaved unusually, in that it was sensitive to ciprofloxacin, unlike the majority of other MRSA isolates seen. Detailed molecular work-up of the isolate demonstrated that it carried the Panton Valentine Leukocidin (PVL) gene locus and belonged to subclass IV of the Staphylococcal Chromosomal Cassette (SCCmec), a typical microbiological characteristic of community-associated MRSA (CA-MRSA).

To date, there has been an extensive awareness of MRSA within healthcare facilities, particularly hospitals. More recently, there has been increased reporting of MRSA occurring in the community amongst healthy individuals who have no hospital association.[1] Most recently, the first nosocomial outbreak of community-associated MRSA, has been described in the West Midlands.[2] Eight cases of Panton-Valentine Leukocidin (PVL) positive community-associated MRSA (CA-MRSA) were identified among individuals in a hospital and their close household contacts, of whom four individuals developed an infection, which was fatal in two cases. Transmission of the CA-MRSA strain appeared to have occurred on two separate wards and went undetected until a fatal case was examined in detail.

These organisms are termed CA-MRSA (community-associated MRSA) and differ significantly from healthcare-associated MRSA (HA-MRSA). Although all are *Staphylococcus aureus,* they have distinct epidemiological and microbiological characteristics which are summarised in Tables I and II. Notably CA-MRSA are more likely to produce PVL, a cytotoxin that causes leucocyte destruction and tissue necrosis, than HA-MRSA.

Community-associated MRSA has recently emerged in the US as a clinically significant and virulent pathogen. It is associated with serious skin and soft tissue infections, particularly in young healthy individuals in the community and those who have no risk factors for acquisition of HA-MRSA.[1] Several reports have described this organism in individuals in prisons, military personnel, athletes (especially those involved in combat and ball sports, including rugby, American football, wrestling, fencing), male homosexuals and ethnic populations (native American Indians, Hawaiian islanders, Alaskan native people). Risk factors for its acquisition include close physical contact, abrasion injuries and activities associated with poor communal hygiene (e.g. sharing towels). This organism is now emerging in several European countries, including the UK.

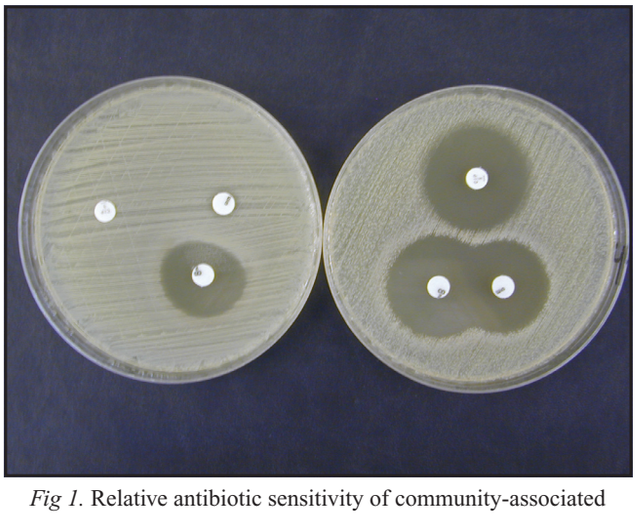

Fig 1. Relative antibiotic sensitivity of community-associated MRSA (CA-MRSA) (right plate) and resistance of healthcare-associated MRSA (HA-MRSA) (left plate) to ciprofloxacin, erythromycin and clindamycin by standard disk diffusion assay (Photo: Courtesy of Mr. Lester Crothers and Mr. Mark McCalmont, Northern Ireland Public Health Laboratory, Department of Bacteriology, Belfast City Hospital)

While HA-MRSA cause heterogeneous invasive infections, CA-MRSA is usually limited to skin and soft tissue infections, particularly folliculitis, pustular lesions and abscesses. Less commonly, CA-MRSA can cause severe and rapidly fatal infections such as necrotizing pneumonia and necrotizing fasciitis.

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TABLE I:

Comparison of clinical, epidemiological and microbiological characteristics of community-associated MRSA

Characteristic	***Staphylococcus aureus***	**Healthcare-associated-MRSA (HA-MRSA)**	**Community-associated-MRSA (CA-MRSA)**
Population affected	immunocompetent and immunocompromised individuals in the community.	Hospital/healthcare/nursing home patients/residents elderly, preterm neonate immunocompromised neonates.	Usually young healthy individuals in the community. Those who have no risk factors for acquisition of HA-MRSA. Individuals in prisons, military personnel, athletic population (especially those involved in combat and ball sports), male homosexuals, ethnic populations (native American Indians, Hawaiian islanders, Alaskan native people).
Site of infection	Predominantly wound, bacteraemia, (including infective endocarditis), enterotoxin-mediated food-poisoning.	Bacteraemia & wound infections Also symptomatic infections of respiratory and urinary tracts.	Mainly skin (abscesses and cellulitis, furunculosis, severe skin and soft tissue infections (sSSTIs). In severe cases, septic shock & bacteraemia.
Risk factors	Colonisation with *S. aureus*, trauma, body piercing, drug abuse.	Indwelling devices, catheters, lines, haemodialysis, prolonged hospitalisation, long term antibiotic use.	Close physical contact, abrasion injuries, activities associated with poor communal hygiene (e.g. sharing towels)
Transmission	Patients' own skin flora	**(i). Person-to-person spread** Healthcare staff (e.g., nurses, doctors, surgeons, physiotherapists), visitors, patients. **(ii). Environment-to-patient spread** e.g., hospital equipment (iii). **Animal-to-patient** spread	person-to-person shared facilities (e.g. Sports equipment. towels, pools, etc) environment
Microbiological characteristics			
Susceptibility to methicillin	Yes	No	No
Susceptibility to other antibiotic agents (fluoroquinolones, aminoglycosides, erythromycin, clindamycin) (see Figure 1)	Yes	No	Yes
Presence pvl gene locus	Variable (usually limited)	low (<5%)	high (>95%)
SCCmecA type	not present	predominantly subclasses I, II or III	Mainly IV (& subtypes a-h), V
Treatment	Oral or IV flucloxacillin	Oral: doxycyline IV: vancomycin/teichoplanin/ daptomycin	clindamycin or co-trimethoxazole

Therapy for CA-MRSA infections presents a challenge for the clinician. They are resistant to the agents most likely to be prescribed for *S. aureus* infections in the community i.e. β-lactams. Small abscesses may respond to incision and drainage alone but antibiotic treatment is indicated if the patient does not respond rapidly. Current UK guidance suggests consideration of doxycycline and rifampicin for such infections. Patients should also be screened for CA-MRSA carriage and a decolonization schedule, as employed for HA-MRSA used where carriage is demonstrated. For severe

TABLE II:

Key points associated with community-associated MRSA (CA-MRSA). (Adopted from Elston[1])

Characteristic	Description
Epidemiological	CA-MRSA was first described over a decade ago and only recently emerged as a significant clinical and virulent Gram +ve pathogen in the US.
	It has not been described in Northern Ireland until now
	Approximately 85% of CA-MRSA infections present in skin, usually with abscesses, cellulitis and/or folliculitis.
	Elsewhere, they can mimic a spider-bite and consider this if patient has recently returned from an endemic area, where spider bites are common, e.g. USA.
	Different epidemiology to HA-MRSA. Mainly present in young health individuals with no risk factors for the acquisition of MRSA. High-risk populations include individuals in prisons, military personnel, athletic population (especially those involved in combat and ball sports), male homosexuals, ethnic populations (native American Indians, Hawaiian islanders, Alaskan native people) and children in playgroups/nurseries.
Presentation	Young otherwise healthy individual in high-risk population, As detailed above, with spontaneous abscess, cellulitis and a collection of pus
Treatment	Surgical drainage of skin abscess. Many patients respond to drainage alone.
	Seriously ill patients should be hospitalized
	Most infections in clinically well patients are treated appropriately on an out-patient basis with oral antibiotics
Microbiological	Taxonomically, all organisms are *Staphylococcus aureus*.
	Virtually all CA-MRSA are positive for the Panton-Valentine Leukocidin (PVL) gene locus
	Most CA-MRSA isolates belong to SCCmec IV (+ subclasses) and V
	No simple laboratory test for microbiological confirmation of CA-MRSA status. Requires testing with PVL and SCCmec PCR techniques, usually at specialist or reference laboratory
	Microbiological suspicion of the presence of CA-MRSA should be given to MRSA isolates which are sensitive to ciprofloxacin
	All suspect ciprofloxacin-sensitive MRSA isolates should be sent to Dr Angela Kearns, *Staphylococcus aureus* Reference Laboratory, Health Protection Agency, 61 Colindale Avenue, LONDON, for molecular confirmation and characterization.

and overwhelming infections caused by these organisms, antimicrobial agents may be ineffective because the patient receives the treatment too late. Such patients require full intensive care support. Optimal antimicrobial agent therapy is unknown but combination therapy may be helpful. Agents which have been used in this setting include vancomycin, rifampicin, cotrimoxazole, linezolid and clindamycin. The latter two agents have the advantage of suppression of bacterial toxin production. Finally, the addition of intravenous immune globulin (which contains anti PVL antibodies) should be considered in fulminant cases.

Microbiologically, CA-MRSA are difficult to differentiate from HA-MRSA and at present, there is no phenotypic testing method available in most primary diagnostic clinical microbiology laboratories in the UK, that can reliably distinguish between these two organisms, for definitive identification purposes.

In a recent study adopting molecular (PCR) techniques to aid in their differentiation, our group have identified 4/224 (1.8%) consecutive MRSA isolates, as CA-MRSA, which had been classified generically as MRSA.[3] Therefore, given the important clinical and epidemiological differences between these types of MRSA, it is important that local physicians have a comprehension of CA-MRSA and that any presumptive CA-MRSA isolates that begin to emerge in Northern Ireland are confirmed and further characterized, so that we can quickly gain an understanding of the diversity/relatedness of such isolates to help guide local guidelines/practice and interventions to minimize its occurrence.

In conclusion, this initial report of CA-MRSA in Northern Ireland, from a 16 year old patient, is typical of CA-MRSA presentation. Firstly, it occurred in a young otherwise healthy individual, with a history of recent trauma. Secondly, the signs and symptoms, namely cellulitis with a large abscess,

requiring drainage, was consistent with CA-MRSA skin/soft tissue infection. Thirdly, the resulting cultured MRSA was unusual, in that it was sensitive to ciprofloxacin on *in vitro* antibiotic susceptibility testing, suggesting the presence of a CA-MRSA organism. Thus, GPs, dermatologists and A&E physicians should beware of the emergence of CA-MRSA locally and should consider and manage such an organism in patients presenting with such symptoms.

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Ulster Med J 2007; **76 (2)** 72-82

Review

Disorders of keratinisation: from rare to common genetic diseases of skin and other epithelial tissues.

WH Irwin McLean,[1] Alan D Irvine[2,3]

Accepted 2 January 2007

THE STRUCTURAL AND FUNCTIONAL DIVERSITY OF EPITHELIA

Epithelia are the first line of defence between the human body and its environment. For example, the skin, the largest organ in the body, is covered by the epidermis – a multilayered, stratified, cornified epithelium that is highly specialised to protect the body from a diverse range of external insults that include mechanical trauma, microbial invasion, chemical damage and entry of allergens. Similarly, the anterior corneal epithelium protects the outermost surface of the eye; mucosal cells line the entries and exits of the body; the gastrointestinal tract is covered by layer of fast-turnover epithelial cells and the lung is lined by a mixed epithelium which also secretes defensive mucous. In other words, epithelia very often function as protective barrier tissues. In addition, many epithelial cells are adapted to perform glandular functions. The liver and pancreas, for example, are composed of functionally modified epithelial cells. These and other organs are also covered by a protective mesothelium – the "epidermis" of internal organs. On a smaller scale, the sweat and sebaceous glands of the skin also contain glandular epithelial cells. The sweat and sebum produced by these tiny glands of the skin are exported to the epidermal surface via ducts formed by epithelial cells, so here again, cells directly in contact with the exterior environment of the organism are epithelial in origin.

In each of these barrier tissues, epithelial cells are required to be mechanically resilient. This, however, poses a question which until recent years remained a mystery: how do human cells, which can be considered crudely as a tiny "bag" of water and proteins bounded by a protein-lipid membrane only a few nanometres thick, possibly resist the mechanical forces experienced in everyday life? Simply walking down the street subjects the weight-bearing surfaces of the plantar epidermis to incredible stresses. Other organisms address this mechanical problem in a fairly obvious manner. Bacteria and plants possess a rigid cell wall composed of carbohydrates and other tough polymers, which in the case of trees, is so mechanically strong one can use this material to build houses. In stark contrast, mammalian cells appear to have only their thin and fragile plasma membrane for strength. Somewhat surprisingly, the study of human keratinizing disorders provides an answer to this basic biological conundrum. Mammalian cells in general and epithelial cells in particular, gain their strength from a network of protein fibres extending throughout the cytoplasm known as the intermediate filament cytoskeleton (Fig 1).

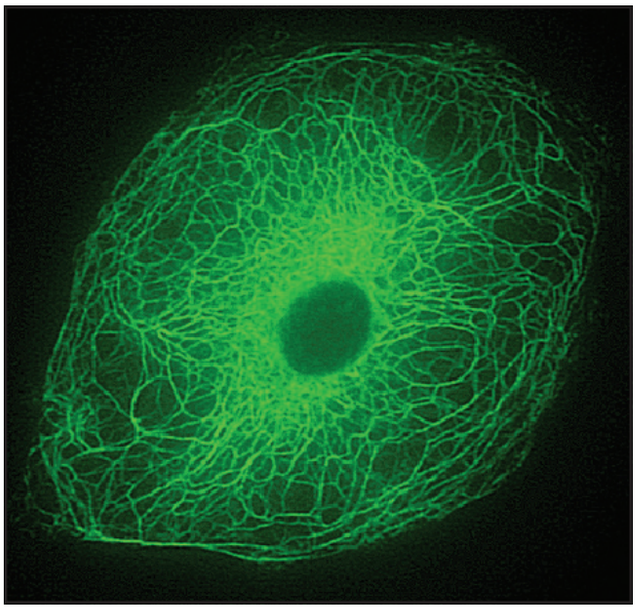

Fig 1. An epithelial cell in culture stained with a keratin antibody (green) reveals a dense meshwork of keratin intermediate filament bundles. This protein scaffold and associated molecules represent the main stress-bearing structure within epithelial cells.

THE STRUCTURAL MOLECULES WITHIN EPITHELIAL CELLS

Intermediate filaments are a large group of structurally resilient polymeric proteins that impart mechanical strength to cells[1], as shown in Figure 1. The keratins are specialised intermediate filament proteins that form dense fibrous networks throughout the cytoplasm of epithelial cells[2]. The human genome possesses 54 functional keratin genes located in two compact gene clusters, as well as many non-functional pseudogenes, scattered around the genome[3]. Keratin genes are exquisitely specific in their expression patterns. Each one

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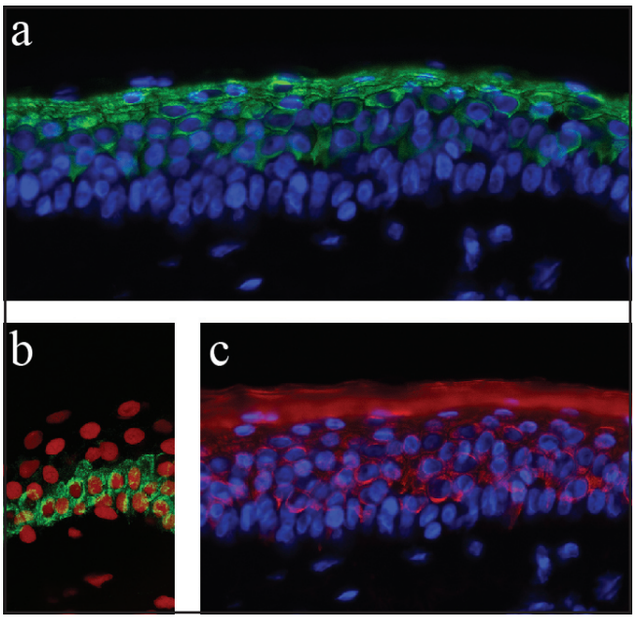

Fig 2. Keratin genes/proteins are differentially expressed according to the many epithelial cell compartments of the human body, exemplified here by the epidermis, stained for just three keratins. (a) Shows K2e expression in the outermost layers of the epidermis (green staining; nuclei counterstained blue). (b) Shows K5 expression (green) in the basal cells, the lowermost cell compartment where cell division takes place (nuclei counterstained red). (c) Shows K10 expression in all suprabasal layers (red staining) but not the basal layer (nuclei counterstained blue).

of the many highly specialised epithelial tissues has its own profile of keratin gene expression, as exemplified in Figure 2. When genetic mutations occur in one of the genes encoding a keratin protein, or in one of many types of keratin-associated protein, the result is very often a keratinizing disorder – an inherited disease where a specific epithelial tissue or a specific subset of epithelial tissues is abnormally fragile[4]. The affected tissue tends to blister or flake apart and often, in response to this inherent fragility, the tissue "fights back" by overgrowing – a phenomenon known as hyperkeratosis. The majority of keratinizing disorders affect the epidermis and/or its adnexal structures such as hair and nail, or sweat and sebaceous glands, although a number of these diseases affect other epithelia such as mucosal or corneal epithelia. In addition, the keratin cytoskeleton is attached to cell membranes and in some cases, the extracellular matrix, via transmembrane structures which act as rivets bolting cytoskeletons of neighbouring cells together and anchoring them to the underlying stroma[5]. Thus, the epithelial cytoskeleton is not an isolated structure confined to each individual cell but actually extends through the entire tissue, which is well anchored to adjacent tissues. In an analogy, this is like building a wall from bricks which are properly cemented together rather than just piling the bricks on top of one another – the former structure is obviously much stronger. When genetic mutations occur that affect one of the many proteins that make up these "rivets" between the cells, again the result is structural failure and another set of related keratinizing disorders. In some situations where even further strength is required, the keratin cytoskeleton is chemically cross-linked or modified in other ways, analogous to changing the composition of concrete or adding reinforcing rods[6,7]. Again, mutations in the genes encoding these modifying enzymes or additional keratin-associated proteins lead to a further group of keratinizing disorders. The hardest epithelial tissues of all are hair and nail. These tissues express modified keratins containing inordinate amounts of the amino acid cysteine which forms numerous chemical cross-links to further strengthen the cytoskeleton[8]. Defects in these genes lead to hair and nail disorders.

Overall, human epithelial cells are the building blocks of many important tissues in the body and are constructed from these cells. Within these cells is a dense meshwork of strengthening fibres made from keratin and keratin-associated proteins which can be altered according to the structural requirements of a given epithelium. Failure of any part of this system due to spontaneous or inherited mutations leads a disorder of keratinisation.

Our early research careers in human genetics began in Queens University, Belfast with Doctoral experience under the tutelage of Dr. Anne Hughes, encouraged by the tremendous support of Professor Norman Nevin. Since the early 1990s, our research has focused on identifying the genetic basis of this group of conditions and many of the original discoveries in the field have arisen from our clinician-scientist partnership, often with the help of the excellent clinical networks throughout Ireland but also including many colleagues worldwide. The purpose of this article is to review the human keratinizing disorders using clinical examples of the diseases as they present to clinicians as well as giving some insights into what is known about the defective gene/protein systems that cause them.

HUMAN KERATINIZING DISORDERS

At the end of the 1980s the causes of human keratinizing disorders remained unknown. In 1987, the first human skin disorder gene was identified, the steroid sulfatase (*STS*) gene on the X-chromosome[9]. The entire *STS* gene is completely deleted in many males with X-linked ichthyosis, allowing its identification by early molecular genetics techniques. However, the vast majority of hereditary defects involve minute changes in a gene, usually the alteration of a single base pair of the DNA code. It was the invention in 1988 of the polymerase chain reaction (PCR), a enzymatic process which allows rapid isolation, sizing and sequencing of DNA fragments from any individual[10], that opened up the study of all genetic diseases, including keratinizing disorders.

In the late 1980s and early 1990s, a series of elegant research projects led to the discovery of the first mutations in human keratin genes. Cell biology studies where dominant-negative mutant keratins were expressed in cultured keratinocyte cell lines showed that these defective proteins led to major structural defects of the cytoskeleton[11,12]. In a landmark experiment, the expression of a dominant mutant keratin 14 (K14) in the basal cell layer of mouse epidermis[13], led to a phenotype that clinically and histologically resembled the inherited skin blistering disorder *epidermolysis bullosa simplex*, EBS (Fig 3), in which keratin aggregates could be seen by electron microscopy[14]. In parallel, genetic linkage studies in families with EBS revealed that the causative gene lay in one of the two keratin gene clusters[15]. The discovery of disease-causing mutations in the two basal-cell specific keratin genes, K5 and K14 soon followed[16-18].

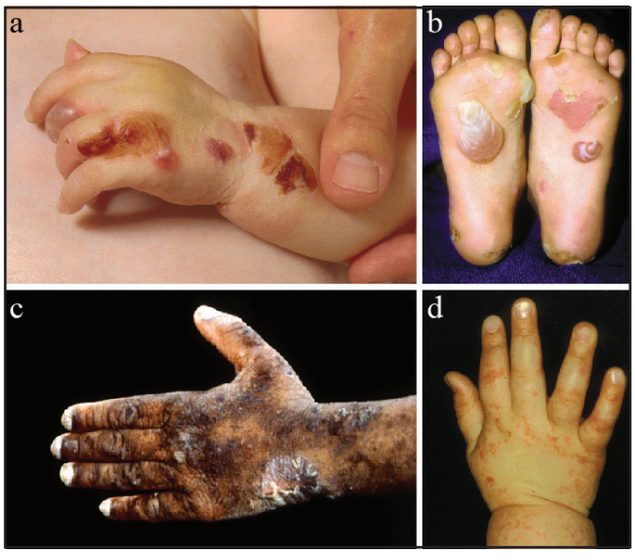

Fig 3. The clinical features of epidermolysis bullosa simplex (EBS). (a) A baby with the severe Dowling-Meara form of EBS, characterised by widespread clustered blisters. (b) The more common Weber-Cockayne type of EBS affects mainly hands and feet. (c) Recessive EBS is more common in certain cultures where consanguineous unions are prevalent. (d) EBS with mottled pigmentation, caused by certain mutations that appear to affect pigment transportation as well as causing mild skin blistering.

The various clinical subtypes of EBS were shown to be due to mutations in particular functional domains of the keratin molecule. A schematic diagram of the keratin protein structure is shown in Figure 4. The more severe phenotype, the Dowling-Meara form of EBS (Fig 3), was caused by mutations affecting the ends of the keratin rod domain[17,18]. These mutations interfere with end-to-end association of the keratin subunits in the assembly of keratin intermediate filaments[19]. Mutations outside of these functionally critical areas lead to the milder, site-limited variants of EBS (Fig 3), such as Weber-Cockayne EBS[20,21], where skin blistering is limited to hands and feet, or EBS with mottled pigmentation[22,23]. The vast majority of EBS-causing mutations in K5 and K14 are dominant-negative mutations – one mutated copy of the gene produces a faulty protein which binds to and disrupts the function of the wild-type protein produced from the other, normal allele. Thus, most cases of EBS are dominantly inherited and so 50% of the offspring of an affected person inherit the condition and both sexes are equally likely to be affected. A few recessive cases of EBS are also known where the K14 gene is completely inactivated by a nonsense or other null mutation[24]. Carriers of such a mutation have only one active copy of the gene but have perfectly normal skin. However, inheritance of two such mutations leads to complete loss of K14 expression in the skin and a fairly severe form of EBS (Fig 3). This type of EBS is very rare in Western countries but accounts for about a third of cases in cultures where cousin marriages are more common[25].

The discovery of keratin mutations in EBS conclusively demonstrated that the primary function of the intermediate filament cytoskeleton is to impart mechanical strength to epithelial cells. When this intracellular network of fibres

TABLE I

Keratin(s)	Main expression site	Genetic diseases
K5, K14	Basal cells of stratified epithelia	Epidermolysis simplex (EBS; variants EBS-DM, EBS-WC, EBS-K, R-EBS) Dowling-Degos Disease (DDD) Nageli-Franceschetti-Jadassohn syndrome (NFJS)
K1, K10	Suprabasal cells of stratified, cornified epithelia	Bullous congenital ichthyosiform erythroderma (BCIE) Nevoid BCIE Variant form of epidermolytic palmoplantar keratoderma (EPPK) Ichthyosis hystrix of Curth-Macklin Striate keratoderma Cyclic ichthyosis
K9	Palmoplantar epidermis	Epidermolytic palmoplantar keratoderma (EPPK)
K2e	Upper suprabasal cells	Ichthyosis bullosa of Siemens (IBS)
K6a, K16	Nail bed, palmoplantar epidermis, mucosal tissues, other sites	Pachyonychia congenita type 1 (PC-1)
K6b, K17	Nail bed, palmoplantar epidermis, mucosal tissues sebaceous glands, other sites	Pachyonychia congenita type 2 (PC-2)
K4, K13	Mucosal tissues	White sponge nevus (WSN)
K3, K12	Anterior corneal epithelium	Meesman epithelial corneal dystrophy (MECD)
K8, K18	Simple epithelia	Cryptogenic cirrhosis* Inflammatory bowel disease*
Hb1, Hb6, Hb3	Hair shaft	Monilethrix
Hb5	Hair shaft/nail matrix	Hair-nail ectodermal dysplasia (HNED)
K6hf	Hair follicle epithelia	Pseudofolliculitis barbae (PFB)*

* = data supportive of a genetic risk factor rather than a monogenic Mendelian disorder.

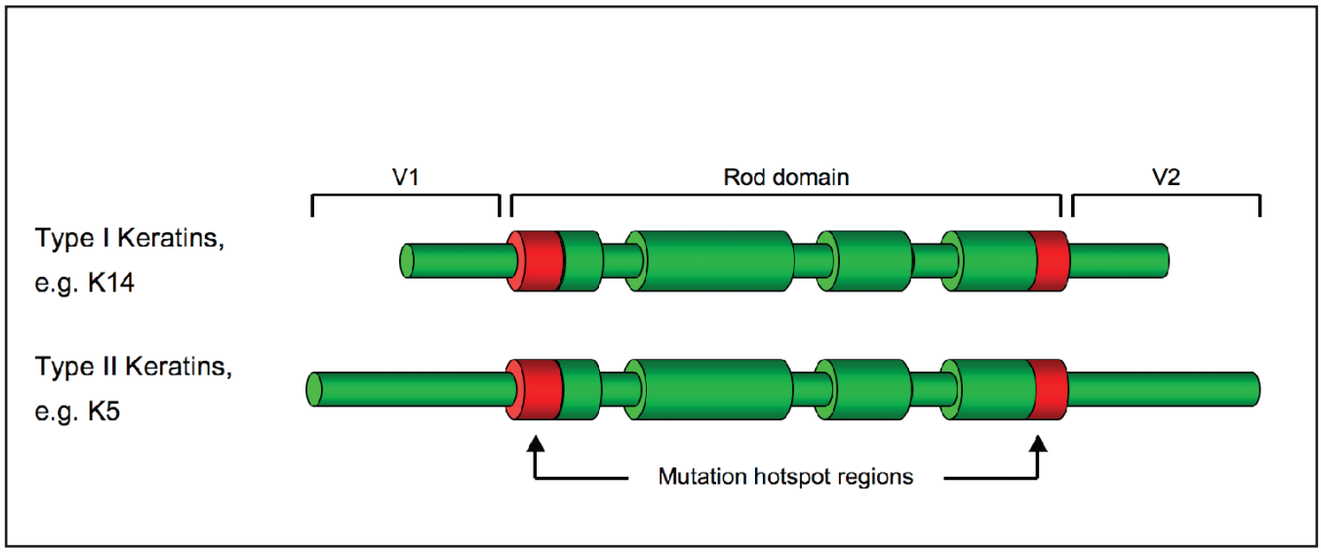

Fig 4. Keratin protein domain organisation. Keratins are rod-like proteins of two varieties, type I and type II, encoded by 54 different human genes. Specific pairs of type I and II proteins assemble into rope-like 10 nm intermediate filaments within epithelial cells (see Fig 1). During the assembly process, the areas shaded red, at either end of the rod domain, are in close contact and interact to allow elongation of the filament. It is these functionally important areas where the majority of the most severe keratin mutations are located since the latter disrupt the end-to-end interactions. Mutations elsewhere in the molecule allow filament assembly but the resultant filaments are weaker than normal. This type of mutation generally results in milder disease phenotypes.

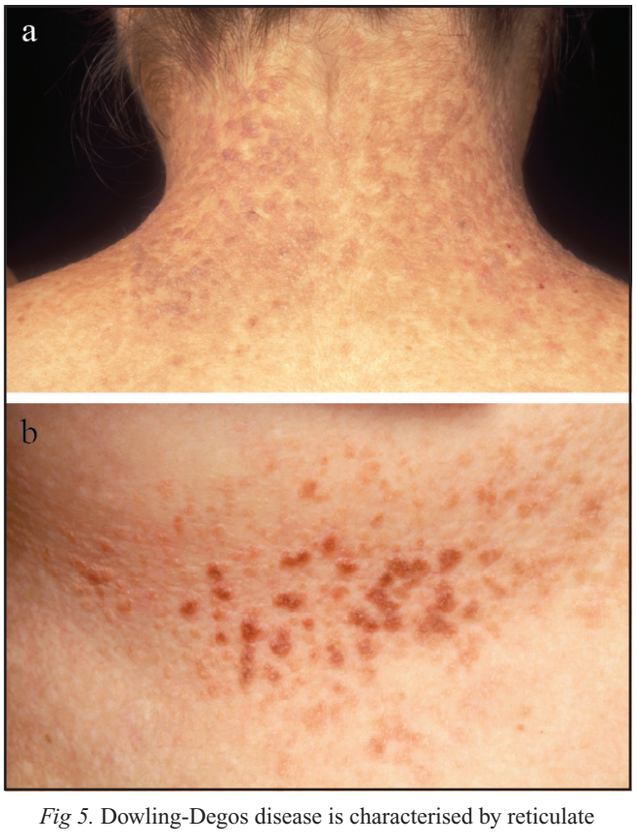

Fig 5. Dowling-Degos disease is characterised by reticulate pigmentary changes in the skin, without skin blistering, typically on the sub-exposed areas (a), and in the skin folds, such as the inframammary region (b).

is either disrupted or completely absent, cell fragility is the primary defect. More recently, insights have been gained into secondary functions of the cytoskeleton through human genetics. Mutations affecting the head domain of K5, a part of the protein not primarily involved in filament formation, have been shown to cause Dowling-Degos disease[26,27], a defect of skin pigmentation without any skin blistering phenotype (Fig 5). Similarly, certain other mutations in this domain of K5 cause a mild form of EBS with mottled pigmentation[23]. These findings have revealed that specific parts of the keratin molecule are involved in pigment uptake and/or transport within the keratinocyte – a hitherto unknown function of the intermediate filament cytoskeleton. In addition, a specific sub-set of mutations in the K14 gene have recently been linked to Nageli-Franscetti-Jadassohn syndrome, an ectodermal dysplasia where interestingly, patients lack dermatoglyphs (fingerprints) but do not have skin blistering[28]. This unexpected result sheds light on the developmental role of keratins in establishing and maintaining particular ectodermal structures.

Following the initial discoveries of basal keratinocyte keratins K5 and K14 mutations in EBS, there followed a steady series of genetic studies showing that very similar genetic defects in the keratin genes that are specifically expressed in differentiated epithelial tissues lead to a whole range of keratinizing disorders. In each of these genetic diseases, there is cell lysis within a specific subset of epithelial cells where the mutated keratin gene is expressed, as listed in Table I. Currently, 21 of the 54 known keratin genes have been linked to monogenic genetic disorders[1,29,30], and in a couple of cases, have been implicated in more complex traits, such as idiopathic liver disease[31] or inflammatory bowel disease[32]. In most of these disorders, fragility of the affected tissue is very often accompanied by overgrowth of the tissue, a phenomenon known as hyperkeratosis. This is particularly

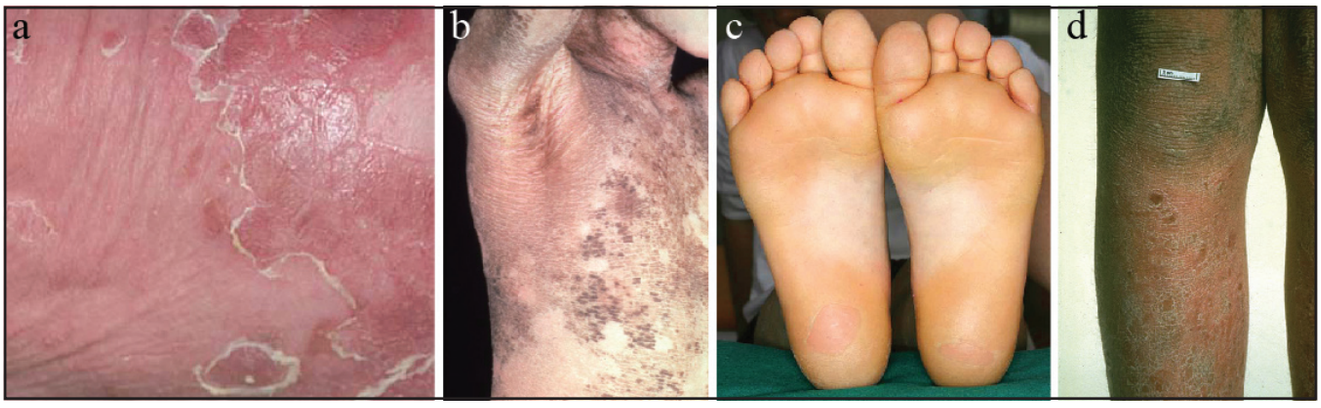

Fig 6. Hyperkeratotic disorders due to mutations in suprabasal keratins. (a) Newborn infants with mutations in K1 or K10, the major suprabasal keratins of the epidermis, are erythrodermic and may also blister, whereas later in life (b), they tend to have widespread epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma, BCIE). (c) Mutations in the palm/sole specific keratin, K9, give rise to epidermolytic palmoplantar keratoderma, EPPK, where epidermolytic hyperkeratosis is confined to palmoplantar epidermis. (d) Mutations in K2e, a keratin whose expression is limited to the uppermost layers of the epidermis (see Fig 2), result in ichthyosis bullosa of Siemens, IBS, a milder disorder closely related to and easily confused with BCIE.

the case where keratins expressed in the suprabasal layers of stratified epithelia are concerned, such as the outer layers of the epidermis. In these situations, the basal cell layer beneath the fragile epithelium, which is the proliferative compartment containing the stem cell population, is itself unaffected by cell fragility but is bathed in cytokines from the fragile cell populations above, leading to overgrowth. In the epidermis, this is exemplified by *bullous congenital ichthyosiform erythroderma* (BCIE; Fig 6), where the major suprabasal keratins K1 or K10 are mutated[33-36]. This disorder is characterized by blistering and erythroderma in infancy and widespread epidermolytic hyperkeratosis later in life, which is manifest as thickened, ichthyotic skin (Fig 6). Mutations in a minor keratin expressed in the outermost layers of the living epidermis, K2e, lead to a related but milder skin scaling condition, *ichthyosis bullosa of Siemens* (IBS; Fig 6),[37-39]. One keratin, K9, is specifically expressed in the suprabasal cells of palm and sole epidermis[40]. This epithelium is subjected to some of the most severe mechanical stress in the body and interestingly, this tissue expresses many accessory keratins in addition to those found throughout the rest of the epidermis, in order to give these cells the necessary mechanical resilience to survive in this demanding environment[41]. Mutation of K9, which is not expressed elsewhere, leads to thickening and scaling of palms and soles, *epidermolytic palmoplantar keratoderma*, EPPK, (Fig 6)[42,43]. Since many keratins are expressed in palm and sole, keratoderma is also a feature of a number of other keratin diseases, notably *pachyonychia congenita* (PC), where keratoderma is accompanied by hyperkeratosis of a number of other epithelia[44,45], in particular, the nails, which are abnormally thickened (hypertrophic nail dystrophy). PC comes in two main clinical subtypes, defined by the keratins involved and their differentiation-specific expression patterns (Fig 7). K6a and K16 are primarily

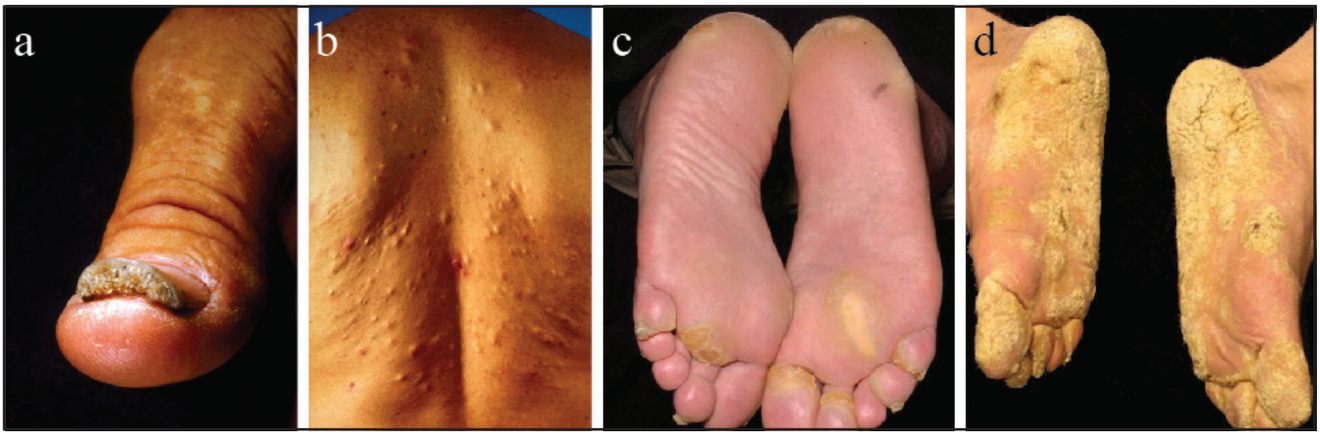

Fig 7. Some keratins have complex expression patterns and are found in several specific subsets of epithelial cells, such as K6a, K6b, K16 and K17. Mutations in these keratins cause the two major forms of pachyonychia congenita (PC-1 caused by K6a/K16 mutations, and PC-2, due to K6b/K17 mutations). (a) These keratins are found in the epithelial cells under the nail (the nail bed) where cell fragility results in hypertrophic nail dystrophy, the hallmark of PC. (b) Patients with either form of PC can have a number of skin cysts but these tend to be more prominent in PC-2. (c) All four PC-related keratins are expressed in palm and sole but K6b/K17 are less prominent in this tissue and patient with PC-2, seen here. (d) K6a and K16 are more highly expressed in palm and sole and so PC-1 patients tend to have more severe keratoderma, which is often very painful and debilitating.

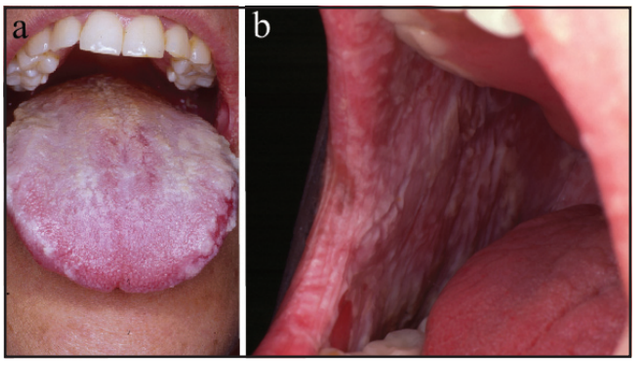

Fig 8. In pachyonychia congenita (PC, see also Fig 7), the keratins involved are expressed to varying degrees in the oral epithelia. (a) Shows a PC-1 patient carrying a K6a mutation, who has quite prominent lingual leukokeratosis. (b) The clinical appearance of these white oral lesions in PC, led to the discovery that mutations in the oral mucosal keratin, K4 and K13, cause white sponge nevus – a benign disorder often encountered by dentists.

expressed in palm, sole, nail bed and the buccal and lingual epithelia. Mutations in these genes cause PC type 1 where nail dystrophy and focal keratoderma is often accompanied by oral leukokeratosis[46,47]. In PC type 2, caused by mutations in K6b and K17, these symptoms can be accompanied by multiple pilosebaceous cysts since these keratins are strongly expressed in the epithelial cells lining the hair follicle and attached sebaceous gland[47,48]. Some PC-2 patients are born with a few abnormal, prematurely erupted teeth due to expression of these proteins in the developing tooth germ. These natal teeth are usually shed and replaced by normal primary and secondary dentition. History tells that Louis XIV of France had natal teeth, "to the considerable vexation of his wet nurses"[49]. There is, however, no record of him having other features consistent with keratinizing disorders.

The oral hyperkeratosis seen in PC (Fig 8), led to the discovery of mutations in keratins K4 and K13, which are expressed specifically in mucosal keratinocytes[50,51]. In this case the disease is *white sponge nevus* (WSN), which is characterized by spongy white plaques in the oral and sometimes, the anogenital mucosae (Fig 8). Similarly, the anterior corneal epithelium was known to express keratins K3 and K12 and by studying the genetics literature we hypothesized that these might be the causative genes for *Meesmann epithelial corneal dystrophy* (MECD). By studying two Northern Irish kindreds, we were the first to show that mutations in these keratin genes do in fact cause MECD[52]. We were also able to track down the descendants of the original MECD family described by the ophthalmologist Alois Meesmann in Northern Germany in the 1930s and identified their specific K12 mutation, which is widespread within the population inhabiting North Central Europe[52]. In MECD, there are myriad microcysts or tiny blisters in the corneal epithelium due to cell fragility, which can be seen by slit lamp illumination or histology (Fig 9). In the patients, this manifests as photophobia, foreign body sensation and in a small number of cases, scarring and loss of visual acuity.

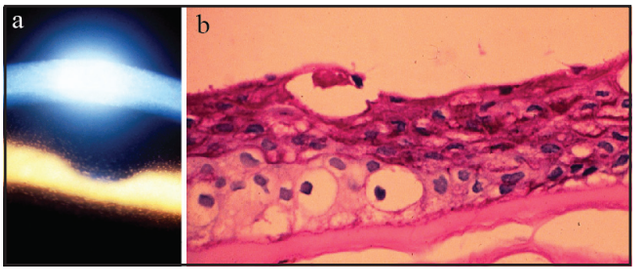

Fig 9. (a) Slit lamp examination of Meesman epithelial corneal dystrophy shows myriad fine cystic lesions throughout the cornea. (b) Light micrograph showing abnormal corneal epithelium of the proband. Bowman's membrane presents as a homogeneous eosinophilic subepithelial band. The epithelium appears acanthotic and disordered. Many keratinocytes contain periodic acid Schiff (PAS) positive fibrillar material (PAS stain, x200).

About half of the keratin genes are expressed in the hair follicle, which is the most complex epithelial structure in terms of its cellular complexity and patterns of gene expression. Three hair keratin genes *HB1*, *HB3* and *HB6* have been shown to be mutated in different families with the hereditary hair fragility and alopecia syndrome *monilethrix*[29,53,54]. This disorder represents a particularly good example of the phenotypic variability encountered to some extent in all keratin diseases[55]. Some individuals with *monilethrix* have very subtle fragility of the hair shaft that passes for normal. Others have almost complete alopecia and some have an intermediate phenotype (Fig 10). These very different presentations can be seen amongst individuals with the same keratin mutation and even in members of the same family. This may be partly environmental but is also presumed to be due to modifying genes. Recently, some insight has been gained into the identity of at least some genetic modifiers from detailed analysis of a family where members had severe or mild skin blistering[56]. The severely affected individuals were shown to have inherited a mutation causing mild EBS and a different, non-pathogenic polymorphism in the same keratin gene. The polymorphism is not sufficient to cause disease on its own but in combination with a mild mutation; it makes the clinical presentation more severe. Other examples of genetic modifiers are sure to emerge in the future.

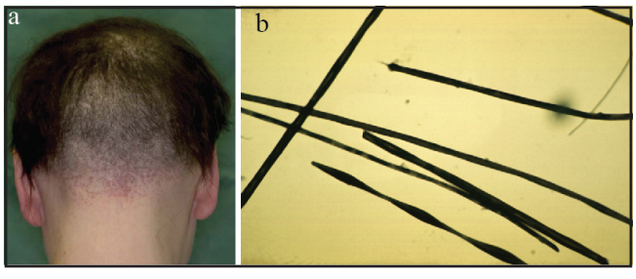

Fig 10. Monilethrix is characterised by brittle hair with varying degrees of alopecia. (a) Often there is perifollicular keratosis and erythema. (b) Light microscopy clearly demonstrates the beaded nature of hair in monilethrix. Nodes are separated by abnormally weathered and thinned 'internodes'.

In 2006, two papers presented direct and indirect evidence for recessive mutations in hair and nail keratins in the so-called 'pure' hair and nail type of ectodermal dysplasia. Studying large consanguineous Pakistani families with hair and nail ectodermal dysplasia, Ahmad and co-workers identified recessive mutations in the hair matrix and nail keratin

KRTHB5[30]. Subsequently this same group reported linkage to the type I keratin cluster on chromosome 17p12-q21.2, suggesting that the partner keratin of *KRTHB5* is a likely candidate[57].

KERATIN-ASSOCIATED PROTEINS IN HUMAN DISEASE

In 1996, the first mutations were described in the gene encoding plectin, a giant protein that links the keratin cytoskeleton to the hemidesmosome – a protein complex that anchors the basal cells of the epidermis and other multilayered epithelia to the underlying basement membrane[58,59]. Plectin is a multifunctional protein found in many tissues and in particular, it interacts with the intermediate filament protein desmin which is found in muscle. Loss of plectin expression in skin and muscle due to recessive mutations leads not only to skin blistering but also to muscle wasting in a rare disease known as *EBS with muscular dystrophy*, EBS-MD. The plectin gene is not only large but has an unusual, highly repetitive sequence, which made its isolation and routine analysis difficult. Lessons learned in the study of this type of gene proved to be valuable in our very recent work on the filaggrin gene, which is even larger and much more repetitive in nature.

Following the discovery of plectin mutations in EBS-MD, a number of other keratinizing disorders were linked to other proteins that associate with keratins. One example with a strong Ulster connection was the discovery of the first desmoplakin mutations in striate keratoderma by dermatologist Keith Armstrong and geneticist Anne Hughes and their colleagues in Belfast[60]. Desmoplakin helps link the keratin cytoskeleton of adjacent cells through a transmembrane structure known as the desmosome. This ground-breaking work led to the discovery of defects in other desmosome components causing other diseases of skin, hair and cardiac muscle, where desmosomes are structurally important[61-63].

DEFECTS OF THE STRATUM CORNEUM – FROM VERY RARE TO VERY COMMON DISEASE

The hemidesmosome proteins like plectin and the desmosomal proteins like desmoplakin can be regarded as the "rivets" that connect the keratin networks of adjacent cells or to the basement membrane. Another group of proteins chemically modifies the keratin cytoskeleton in tissues where even more strength or near-complete impermeability is required, such as the outermost layer of the epidermis, the stratum corneum[6]. This is the dead layer of terminally differentiated cells which accounts for the main skin barrier function and is the first line of defence between the body and the outside world. Epidermal keratinocytes arise in the basal cell compartment of the epidermis from an ill-defined stem cell population and migrate upwards to finally die and be shed at the skin surface (Fig 11). On their journey upwards, they express increasing numbers of keratins and keratin-associated proteins. In the granular layer, the last living layers, keratohyalin granules appear, which are predominantly composed of profilaggrin[64]. In the stratum corneum, the cells are dead and the keratins and associated proteins are heavily cross-linked by a number of transglutaminases, enzymes that catalyze the formation of covalent bonds between adjacent protein molecules, forming

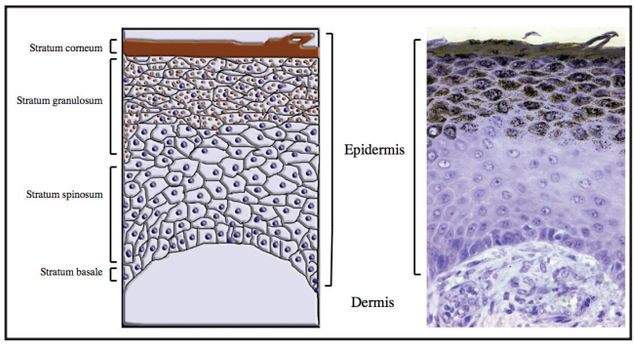

Fig 11. Filaggrin expression in the stratified cornified epidermis. Expression is first noted in the granular layer, where the pro-protein profilaggrin constitutes the major protein of the characteristic intracytoplasmic granules. Cross-linked filaggrin and keratin filaments are major constituents of the stratum corneum.

a plastic-like proteinaceous polymer. The stratum corneum also has complex lipid biochemistry which further contributes to skin barrier function[6]. This protein-lipid rich, highly resilient material forms the outermost skin barrier function which not only helps prevent water loss but also prevents the entry of pathogens, antigens, allergens and chemical irritants. Consequently, hereditary defects in genes involved in the biosynthesis and modification of lipid and/or protein components of these barrier layers cause a further group of keratinizing disorders.

The first of the stratum corneum disorders to be unravelled was *lamellar ichthyosis*, which is due to loss-of-function mutations in the transglutaminase 1 gene[65,66]. This is a rare, severe form of ichthyosis which can be quite devastating in its effects on quality of life. Like many recessive conditions, it is more common in cultures where consanguineous marriage is the norm. Transglutaminase-1 is clearly the major cross-linking enzyme of the stratum corneum, since we have recently shown that mutations in another related gene, transglutaminase-5, also found in this part of the skin, cause a very mild disorder known as *acral peeling skin syndrome*, APSS[67]. In APSS, the stratum corneum continually peels off, resembling sunburn peeling. The split in the skin here is at the junction of the granular layer and the stratum corneum and so there *TGM5* must crosslink a critical protein of unknown identity at this tissue junction. In contrast, *TGM1* presumably cross-links a wide range of proteins and so its loss leads to a much more severe disease. Defects in the lipids of the stratum corneum have also be linked to various forms of ichthyosis, which are usually very severe due to massive loss of skin barrier function. In particular, these patients dehydrate easily due to greatly increased transepidermal water loss and require heavy emollient use. Studies of this part of the epidermis recently led us to consider the filaggrin gene in relation to the most common skin conditions with a genetic component.

FILAGGRIN IN ICHTHYOSIS VULGARIS AND ATOPIC DISEASE

A survey of English schoolchildren in the 1960s reported that 1 in 250 were affected with *ichthyosis vulgaris* (IV), making this the most common of the single-gene keratinizing disorders[68]. The condition is characterized by excessively dry skin, often covered in a fine white scale (Fig 12). Other clues

to the diagnosis of IV are hyperlinearity of the palms and soles. Hyperkeratosis of the epithelium around hair follicles, *keratosis pilaris,* is another common feature of the disease. It has been reported that many individuals with IV also have *atopic dermatitis* (AD), commonly known as *eczema*[69,70.] AD is a chronic inflammatory skin condition affecting about 20% of children in the developed world (Fig 12). It is often accompanied by a range of allergic conditions including allergy, asthma and hay fever. Collectively, these conditions are known as atopy or atopic diseases and they have a strong tendency to occur in a temporal programme called the atopic march, which starts with eczema during early infancy, then a range of allergies, followed by asthma and finally, hay fever[71]. Collectively, these conditions are a major global healthcare burden, particularly in Westernized nations.

The cytoplasm of the outermost cell layers of the living epidermis, the granular cell layers, is filled with keratohyalin granules which are primarily composed of the giant precursor protein profilaggrin. In the last layer of living granular cells, profilaggrin is enzymatically cleaved into multiple copies of the filaggrin peptide. The liberated filaggrin binds to and condenses the keratin cytoskeleton and its many associated proteins which brings about a rapid process of cell compaction, leading to the formation of flattened squames – the dead cells which form the main impermeable barrier layer at the surface of the skin. This specialised form of programmed cell death is very tightly controlled by multiple

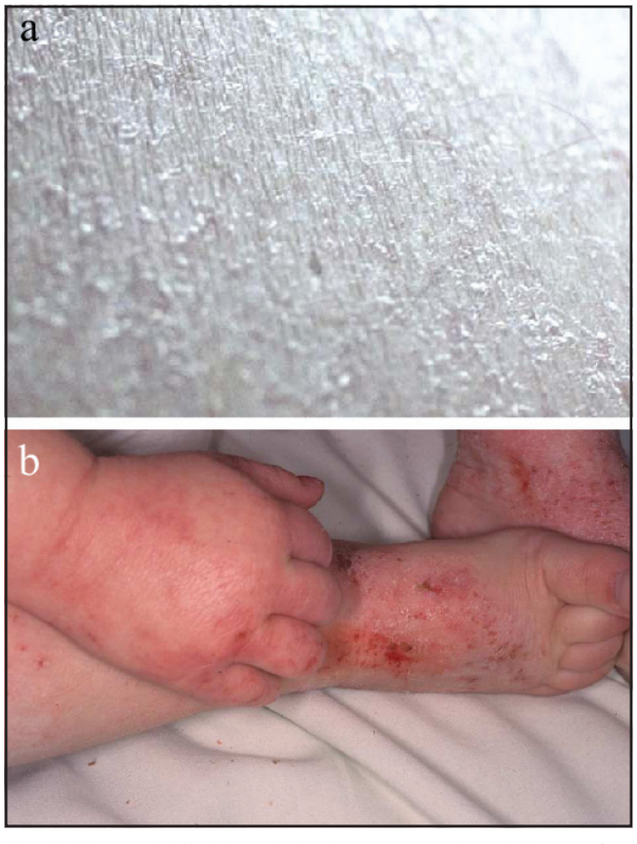

Fig 12. Tangential lighting nicely demonstrates the subtle very fine scaling seen in ichthyosis vulgaris (a). Atopic dermatitis (eczema) is a common disease of childhood that is characterised by itchy inflamed and often excoriated skin that is frequently secondarily infected (b).

systems that include calcium binding, proteases, protease inhibitors and phosphorylation/dephosphorylation. Following cell compaction, filaggrin undergoes further chemical modification and then is completely degraded to amino acids and hygroscopic derivatives thereof which may contribute to the moisturisation of the skin[72]. Thus, lack of filaggrin in the skin leads to two defects – impaired formation of the protective squamous cells and poor water retention.

A host of biochemical and genetic studies going back over 20 years pointed to a probable filaggrin defect in IV. However, some of these studies were contradictory and the situation only became clear when we reported the first IV-causing filaggrin mutations in 2006[73]. The filaggrin gene is incredibly large and has a highly repetitive sequence which makes analysis difficult and a number of genetics labs gave up on it. Using techniques Irwin McLean and colleague Frances Smith developed to clone and sequence the plectin gene, which is also large and repetitive, we took on filaggrin and with persistence, Frances solved the technical difficulties and identified the first filaggrin mutations. Interestingly, putting the genetic data together with careful and clinical observation, we discovered that ichthyosis vulgaris exists in two forms. The classical form is severe in its presentation, affects about 1 in 400 of the population and is due to inheritance of two filaggrin mutations. In addition, there is a more common, mild form of the disease which does not usually present clinically but where individuals have dry skin which may scale in the winter or in dry climates. This is due to inheritance of a single filaggrin mutation and affects about 10% of the white European-origin populations worldwide. This type of "semidominant" inheritance is unusual in humans and helped confound earlier genetic studies.

The first two mutations identified were null alleles of the filaggrin gene i.e. they inactivate the gene completely. These are highly prevalent and carried by about 10% of white European populations. Since many patients with IV also have AD, we went on to show that the same filaggrin null mutations are a major genetic factor in this disease in the Irish, Scottish and Danish populations. We employed a variety of complex trait genetics methods, initially proving the association in seven different ways. Filaggrin mutations are also a major predisposing factor for the related atopic diseases secondary to AD, for example, filaggrin mutations contributes to possibly 20-25% of all asthma but only asthma in the context of pre-existing AD[74]. Eczema and the related atopic conditions are driven through skin barrier deficiency which allows abnormally high transfer of antigens/allergens/irritants across the epidermis, which in turn, over-sensitises the immune system.

A major problem in the genetics of common, complex diseases such as atopy is that other laboratories are unable to reproduce the result and the initial association transpires to be was spurious. Happily, this is not the case with filaggrin and our results have been replicated now in more than 20 studies by various laboratories and using a range of methods[75-78]. No negative studies have been found in European populations, where these mutations are relevant, already making this one of the strongest gene associations in the field of complex trait genetics. Evidence is emerging that filaggrin mutations may predispose individuals to early onset AD that may be more

severe and persistent in nature and so genetic testing for these mutations, which we can now do quickly and cheaply, may have great prognostic value. Environmental factors influencing the penetrance of *FLG* null alleles require further explanation as does the influence of gene: gene interactions. As the phenotypic consequences of *FLG* null alleles become more completely understood, further avenues for exploration will emerge such as the possibility that *FLG* carriers identified early in life as being at risk for AD and related diseases can be targeted for environmental or pharmacological intervention programmes to prevent subsequent disease. Equally, carriers of *FLG* null alleles may have different responses to therapeutic interventions from non-*FLG* null allele carriers. These and other questions will occupy our and other's time and energy for some time to come.

CONCLUSIONS

Our studies of keratinizing disorders have taken us on a journey from very rare diseases that few clinicians or even dermatologists encounter, to the study of some of the most common diseases known to all, doctors and public alike. The route we took to these recent discoveries goes against the current trend in the genetics field, where DNA analysis is often carried out on a grand scale, at the cost of millions, to find genes for common diseases. Our more modest but highly effective approach shows what can be done when clinicians and scientists get together and make links between what is known about basic biological systems and the disease pathology as observed in the clinic. With many more skin diseases still unsolved, our work in this field is likely to continue for some time to come.

Conflict of interest – none declared.

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Ulster Med J 2007; **76 (2)** 83-87

Paper

Recent lung cancer patterns in younger age-cohorts in Ireland

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Accepted 6th February 2007

ABSTRACT

Background: Smoking causes 85% of all lung cancers in males and 70% in females. Therefore, birth cohort analysis and annual-percent-changes (APC) in age-specific lung cancer mortality rates, particularly in the youngest age cohorts, can explain the beneficial impacts of both past and recent anti-smoking interventions.

Methods: A long-term time-trend analysis (1958-2002) in lung cancer mortality rates focusing on the youngest age-cohorts (30-49 years of age) in particular was investigated in Ireland. The rates were standardised to the World Standard Population. Lung cancer mortality data were downloaded from the WHO Cancer Mortality Database to estimate APCs in death rates, using the Joinpoint regression (version 3.0) program. A simple age-cohort modelling (log-linear Poisson model) was also done, using SAS software.

Results: The youngest birth cohorts (born after 1965) have almost one-fourth lower lung cancer risk relative to those born around the First World War. A more than 50% relative decline in death rates among those between 35 and 39 years of age was observed in both sexes in recent years. The youngest age-cohorts (30-39 years of age) in males also showed a significant decrease in death rates in 1998-2002 by more than 3% every five years from 1958-1962 onwards. However, death rate declines in females are slower.

Conclusions: The youngest birth cohorts had the lowest lung cancer risk and also showed a significant decreasing lung cancer death rate in the most recent years. Such temporal patterns indicate the beneficial impacts of both recent and past tobacco control efforts in Ireland. However, the decline in younger female cohorts is slower. A comprehensive national tobacco control program enforced on evidence-based policies elsewhere can further accelerate a decline in death rates, especially among the younger generations.

Key words: Birth cohort; Lung cancer; Ireland; Smoking Ban

INTRODUCTION

Lung cancer is currently the most common cancer in the world[1], accounting for almost 1,500 deaths annually in the Republic of Ireland alone[2]. It has been argued that both cigarette consumption rates and smoking prevalence data are necessary to explain a tobacco epidemic, especially when using lung cancer death rate as an index of smoking-attributable mortality[3]. However, historical smoking history data, such as annual age and sex-specific cigarette consumption rates, are not available nationwide for many countries[4]. Also, it has been difficult to quantify the benefits of large scale, preventive interventions. Therefore, it is necessary to have alternative approaches to explaining the beneficial impacts of both recent and past tobacco control efforts.

Because 85% of male lung cancer deaths are attributed to tobacco smoking, any decline or deceleration in the observed lung cancer death rates could be attributed to anti-smoking interventions in the past[5]. Ireland does not have a comprehensive tobacco control program but pockets of tobacco control efforts were in place over the past 40 years or so. Lung cancer trends in young adults (30-39 years of age in particular) have been used as an early indicator of progress in tobacco control[6], and therefore any observed decline among the youngest age-cohorts would indicate the beneficial impacts of more recent anti-smoking activities. In addition, the relative change in lung cancer mortality rates between successive time-periods would also signal the need for additional aggressive anti-smoking strategies. However, in Ireland, it is premature to use age-specific lung cancer death rates to monitor the early consequences of the nationwide workplace smoking ban that was only introduced in March 2004[7].

This study estimates the annual-percent-changes in lung cancer mortality rates from 1958 to 2002 using the Joinpoint regression model (version 3.0) of the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program[8], with special emphasis on the youngest age-cohorts (between 30 and 49 years of age). A simple age-cohort modelling was also performed to explain the temporal patterns.

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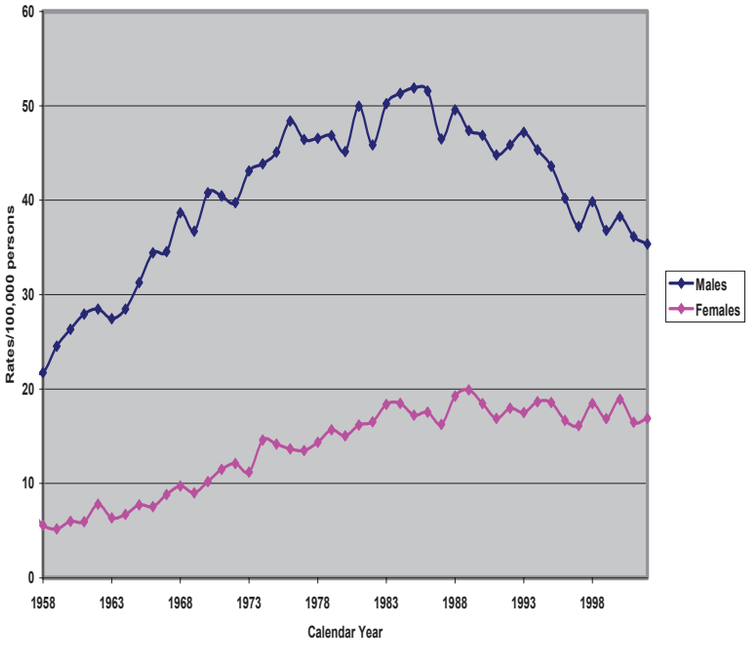

Fig 1. Age standardised (world population standard) lung cancer death rates in the Republic of Ireland (0-85 + age groups) for both sexes, 1958-2002

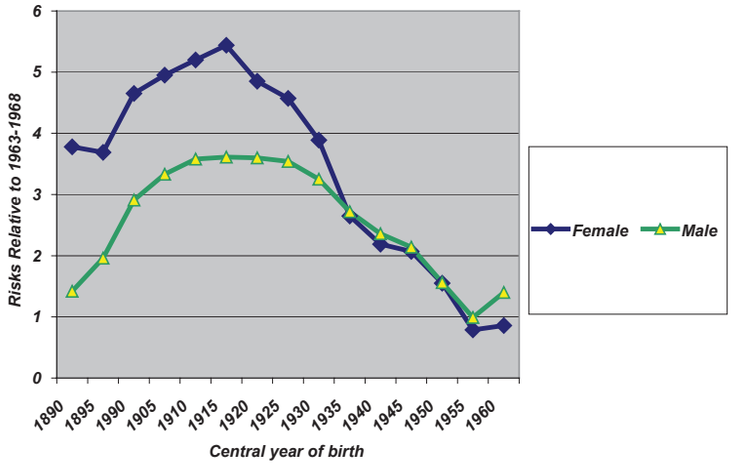

Fig 2. Relative Risk (RR) estimates of Lung Cancer deaths in the Republic of Ireland across different birth-cohorts.

METHODS

Lung cancer mortality data from 1958 to 2002 were downloaded from the WHO Cancer Mortality Database[9]. Age-sex specific adjusted lung cancer death rates standardised to the World Population are also available from the WHO Cancer Mortality Database[9]. Age-specific population estimates for the periods studied were obtained from the Irish Central Statistics Office website (www.cso.ie).

We looked at age-specific lung cancer death rates across the year of birth. In other words, a 'synthetic' birth cohort for each age group was created based on the year and age of death of each individual, using 5-year age and 5-year calendar-period intervals. Each birth cohort could be identified by the central year in the interval. To look at trends across birth cohorts, we employed a simple age-cohort modelling technique. Log-linear Poisson regression modelling (with an offset) was employed to estimate the effects across each birth cohorts adjusting for age relative to the youngest cohorts for both sexes, using the GENMOD procedure in SAS software (version 8.0). However, the use of classical age-period-cohort (APC) modelling techniques could have improved the "fit" of the model (albeit at the expense of extra degrees of freedom), but the random variation associated with parameter estimates might lead to erratic predictions[10]. The classical APC models are also limited with the "non-identifiability" problem. In addition, lung cancer temporal studies consistently show an age-cohort phenomenon rather than an age-period phenomenon in several APC model studies.

For continuous changes in lung cancer death rates across different time-periods, log-linear Poisson regression models were used to calculate APC and joinpoint analyses has been extensively used recently for estimating such temporal effects[11,12]. Because the focus of this study is on younger age-cohorts, we employed jointpoint regression analyses for estimating temporality only for age-groups between 30 and 49 years. Fewer lung cancer deaths per year for each of these younger age-groups necessitated to collapse every 5-calendar year periods into an average age-standardised lung cancer death rate for each of the 5-year age-groups studied (30-34, 35-39, 40-44, 45-49 years of age).

In brief, the Joinpoint[8] analysis fits a series of joined straight lines on a log scale to the age-specific and age-standardised lung cancer death rates. Line segments are joined at points called joinpoints. Each joinpoint denotes a statistically significant change in trend. In joinpoint analysis, the best-fitting points are the years of death that change significantly (increasing or decreasing trends). The analysis starts with the minimum number of joinpoints, and tests whether one or more joinpoints are statistically significant and should be added to the model. A maximum of three joinpoints can be added to the final model. Because of collapsed 5-year calendar periods from 1958 to 2002 and not using the single calendar year death rates for lung cancer trends, the joinpoint analysis could only test a maximum of two joinpoints for this particular study design.

RESULTS

Figure 1 shows the peaking of male lung cancer death rates in the late eighties and the beginning of stabilisation in female death rates when calendar periods were considered. When we looked at the effects across birth cohorts, males born ten years before the First World War had the highest lung cancer risk relative to the youngest cohorts, and females born around the First World War had the highest risk of dying from lung cancer (Figure 2, Table I). While females had a greater risk relative to the youngest cohorts when compared with males' lung cancer risk, those born around and after the Second World War showed a consistent decline in lung cancer risks, with little gender variations (Figure 2). So, those born after 1965

TABLE I.

Relative Risk (RR) estimates with 95% Confidence Intervals (CI) of Lung Cancer deaths in the Republic of Ireland across different birth-cohorts.

Birth-Cohorts	Males	Females
Central year of birth	RR (95% CI)	RR (95%CI)
1888-1892	1.42 (0.64, 3.13) *	3.78 (1.29, 11.08)
1893-1897	1.96 (0.94, 4.09) *	3.69 (1.37, 9.99)
1898-1902	2.91 (1.47, 5.81)	4.65 (1.84, 11.76)
1903-1907	3.33 (1.75, 6.37)	4.95 (2.09, 11.75)
1908-1912	3.58 (1.96, 6.58)	5.20 (2.33, 11.61)
1913-1917	3.61 (2.05, 6.38)	5.44 (2.59, 11.43)
1918-1922	3.60 (2.12, 6.13)	4.85 (2.45, 9.63)
1923-1927	3.54 (2.16, 5.81)	4.57 (2.43, 8.57)
1928-1932	3.25 (2.05, 5.16)	3.89 (2.18, 6.92)
1933-1937	2.72 (1.76, 4.19)	2.65 (1.57, 4.49)
1938-1942	2.36 (1.58, 3.53)	2.19 (1.36, 3.54)
1943-1947	2.14 (1.45, 3.15)	2.07 (1.33, 3.23)
1948-1952	1.56 (1.06, 2.28)	1.55 (1.02, 2.37)
1953-1957	0.99 (0.60, 1.60) *	0.79 (0.45, 1.38) *
1958-1962	1.40 (0.93, 2.10) *	0.86 (0.54, 1.37) *
1963-1967	Reference (RR=1)	Reference (RR=1)

* Not Statistically Significant

did have the lowest lung cancer risk in both sexes.

In figures 3 and 4, the age-specific lung cancer death rates were relatively high among males across all age-cohorts (same age groups across different calendar periods of birth), but were highest among the oldest age-cohorts (80-84 year olds) for both sexes. Not only lung cancer death rates are low among the youngest age-cohorts, but those between 30 and 39 years of age in males are also showing a dramatic decline in death rates across successive cohorts. There has been more than 80% relative decline in death rates in males between 35 and 39 years of age from 1958 to 2002 (Table II). The females also have shown a 50% relative decline in death rates among the same age cohorts (Table II).

When joinpoint modelling was performed for the relatively young age-cohorts (30-49 years of age), a significant five-year decline was observed among the males in particular (Table III). For example, those male cohorts between 30 and 34 years of age had a 3.7% decline every five years from 1958 to 2002, and those between 35 and 39 years of age also had a significant decline in lung cancer death rates by 3.2% every five years. The females of the same age cohorts (30-39 years of age) did show a downward trend in lung cancer death rates but the findings were not statistically significant (Table III). In contrast, the female cohorts above 40 years of age were

TABLE II.

Relative change in lung cancer death rates/100,000 among younger age-cohorts between two five-year time-periods in the Republic of Ireland

	Age-Groups			
	30-34	35-39	40-44	45-49
Males				
1958-1962 (Rates)	2.8	7.0	13.1	32.7
1998-2002 (Rates)	0.9	1.3	5.2	16.9
Relative change	-68%	-81%	-60%	-48%
Females				
1958-1962 (Rates)	0.7	2.1	3.7	9.2
1998-2002 (Rates)	0.7	1.0	6.7	11.0
Relative change	No change	-52%	+81%	+20%

experiencing a rise in the 5-year death rate, and again the findings are not statistically significant (Table III).

DISCUSSION

In Ireland, the overall lung cancer mortality rates from 1958 to 2002 shows a favourable trend for both sexes, especially among the youngest cohorts. This is consistent with the recent lung cancer incidence pattern[2], and also with the decreasing smoking prevalence in the relatively young adults[4]. The youngest birth cohorts not only had the lowest lung cancer risk but also showed significant decreasing rates in lung cancer death rates in most recent years. Such temporal patterns indicate the beneficial impacts of both the recent and the past anti-smoking interventions in Ireland. However, a slower relative decreasing rate among the youngest female age-cohorts identifies the need for additional and more aggressive tobacco control efforts targeting at specific population groups.

A recent study in Ireland reported a fall in teenage smoking prevalence from 20% in 1995 to 13% in 2003[13]. However it is too soon to estimate the effects on lung cancer rates of

TABLE III.

APC (Annual Percent Changes) with 95% CI (Confidence Intervals) of Lung Cancer Death Rates and Joinpoint Analysis among younger age-cohorts in the Republic of Ireland for both sexes, 1958-2002

Age-Groups	APC (95% CI) Males	APC (95% CI) Females
30-34	-3.7 (-6.7; -0.7)	-0.6 (-2.4; 1.3)
35-39	-3.2 (-4.5; -1.8)	-1.2 (-3.0; 0.7)
40-44	-2.4 (-3.6; -1.1)	0.5 (-1.4; 2.4)
45-49	-1.4 (-2.8; -0.2)	0.2 (-1.0; 1.3)

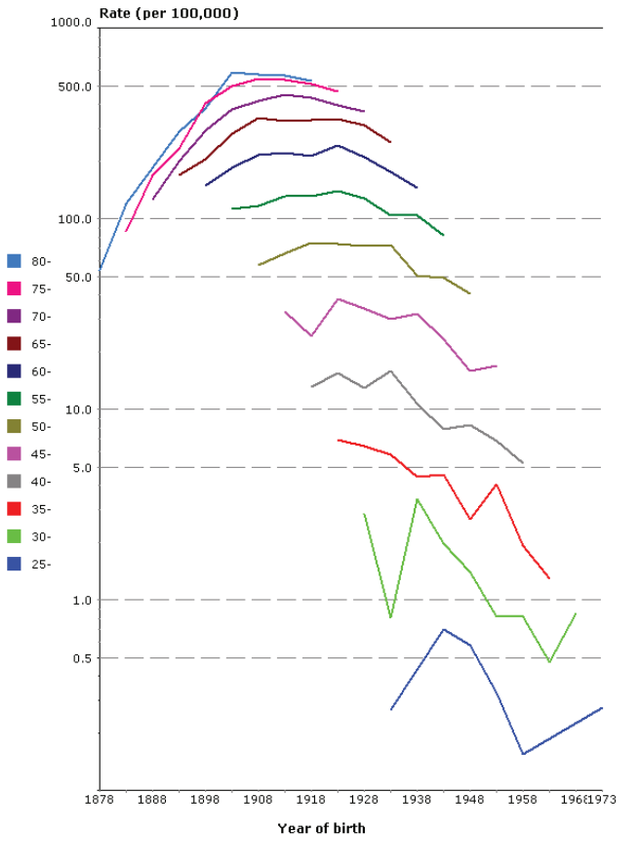

Fig3. Male age-specific standardised lung cancer death rates across different birth-cohorts in Ireland.

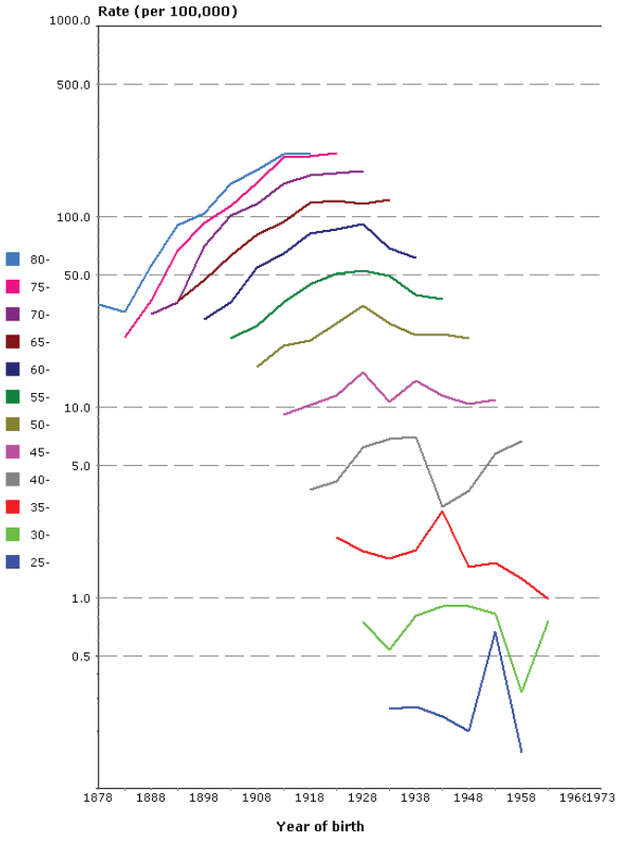

Fig 4. Female age-specific standardised lung cancer death rates across different birth-cohorts in Ireland.

high teen smoking initiation for the decade before 1995. Non cancer health gains are also evident following the nationwide workplace smoking ban[14,15]. Therefore, further health and social gains are realistically achievable if target populations, especially women, lower socio-economic groups and the youngest adults, are empowered and provided an enabling environment.

For further gains from the ill-health effects of smoking, especially on the younger generations, an accelerated decline in smoking prevalence and an increase in smoking quitting rates are essential. The Irish government is committed to a Tobacco Free Society[16]. However, for a faster decline in lung cancer rates, a comprehensive tobacco control program similar to the State of California that showed a 6% decline in lung cancer incidence within a decade has to be enforced[17]. With similar programs in Massachusetts in 1993[18], smoking prevalence in youths declined from 36% in 1995 to 30% in 1999 and from 17% in 1993 to 10% in 2000 in pregnant women[19]. Even smoking quit rates increased from 18% in 1993 to 26% in 2002[19]. In addition to smoke-free policies, both these states also exercised a regular increase in cigarette price. Evidence shows that a 10% increase in cigarette price can have a 4% decline in cigarette consumption rates and a 1-2% decrease in smoking prevalence in the developed world, particularly among youths[20]. Interestingly, a 10% increase in tax will also reduce lung cancer mortality rate by 1.2% in the first year[21].

In conclusion, current lung cancer death rates in Ireland are encouraging but an accelerated further annual decline is also realistically achievable in both sexes, especially among the younger generations, if evidence-based policies are introduced. Youths are price-sensitive and a 10% increase in cigarette price would allow 40,000 Irish smokers to quit smoking[16], and this would save thousands of productive life years lost due to tobacco-related premature deaths in Ireland. Future monitoring of the nationwide workplace smoking ban should assess trends in lung cancer death rates in young adults' once long-term lung cancer mortality data are available post ban.

ACKNOWLEDGEMENTS

The Royal City of Dublin Hospital (RCDH) Research Trust funded Dr Zubair Kabir (ZK) to undertake his PhD thesis in Trinity College Dublin. Currently, ZK is on a cancer research fellowship to the Harvard School of Public Health jointly funded by the US National Cancer Institute and the Health Research Board of Ireland. We thank Dr Kathleen Bennett for statistical advice on age-cohort modelling.

Conflict of interest – none declared

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Ulster Med J 2007; **76 (2)** 88-90

Paper

Who follows up patients after PEG tube insertion?

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Accepted 22 December 2006

ABSTRACT

Background: Community follow-up is often inadequate for patients discharged from hospital following commencement of PEG tube feeding.

Objective and methods: We performed a postal questionnaire to assess if patients/carers were trained in the care of the PEG tube pre-discharge and whether appropriate community follow-up was in place.

Results: Of 166 PEG tubes inserted during the study period, 66 patients were alive at least 6 months following PEG tube insertion. Response rate was 44% (29 of 66 patients). Of the 29 respondents, 21 (72%) had been taught how to manage the tube, feeds and feeding pumps prior to discharge; 17 (59%) had their swallow re-assessed following PEG tube insertion and 16 (55%) patients were able to take some food or liquids by mouth. Twenty-four (83%) patients had had dietetic assessment following discharge. Fifteen patients had encountered problems with the PEG tube, 14 of whom knew who to contact in the event of a problem, all of which were resolved. In six of the 14 cases the respondent felt that the experience was not satisfactory for the patient/carer and that the resolution of PEG-related problems could be improved. In 9 (31%) cases the PEG tube had been removed.

Conclusions: Over two-thirds of patients/carers had been trained regarding PEG tube care. As expected, dietetic follow-up was in place for the majority of patients. Approximately one third of patients had had their PEG tube removed. Ongoing PEG tube feeding may not be required in all of the remaining patients. Most PEG tube problems were resolved although there is still scope to improve the PEG follow-up service.

INTRODUCTION

Percutaneous endoscopic gastrostomies (PEGs) are an established supportive treatment for a variety of medical conditions including stroke, cystic fibrosis and neurological disorders affecting swallowing. Outpatient follow-up of patients who have had PEG tubes inserted is often inadequate and variable in different institutions. We carried out a postal questionnaire of patients/carers of patients who had a PEG tube inserted in our hospital at least six months previously to determine whether training had been given to the patient/carer pre-discharge and to determine what community follow-up was in place.

METHODS

All patients who had a PEG tube inserted in the Belfast City Hospital between 1st October 2000 and 31st December 2004 were identified from an endoscopic database. The Patient Administration System was reviewed to determine which patients had died since their PEG tube insertion, so that a questionnaire was not sent to them. A postal questionnaire was posted out at least six months following the latest PEG tube insertion. Non-responders were sent a second questionnaire six weeks after the first questionnaire had been sent. Medical charts of respondents were reviewed to identify if PEG tube training had been given pre-discharge and details regarding PEG feeding if this had subsequently been discontinued.

RESULTS

Of 166 patients (84 male; mean age 70.0 years) who had PEG tubes inserted, 66 (31 male; mean age 66.2 years) were still alive at least six months following PEG tube insertion with a median follow-up of 25.7 months (range 0.5 – 4.6 yrs). Of the 100 patients (53 male; mean age 72.4 years) who were identified as deceased, 31 had died within 30 days following PEG tube insertion, giving a 30-day mortality of 18.7%. Seventy-one patients had died within six months of PEG tube insertion, giving a 6-month mortality of 42.8%.

Twenty-nine of 66 completed questionnaires were returned (response rate 44%). The respondent was the patient in six cases (one male) and the main carer in 23 cases (five male). The mean length of time the PEG tube had been in-situ was 19.5 months (based on 24 responses). Of the 29 respondents, 19 (65%) indicated that they had been taught how to manage the tube, feeds and feeding pumps prior to discharge; 17 (59%) had their swallow re-assessed following PEG tube insertion and 16 (55%) patients were able to take some food or liquids by mouth. Twenty-four (83%) patients had had dietetic assessment following discharge.

Fifteen (52%) patients had encountered problems with the

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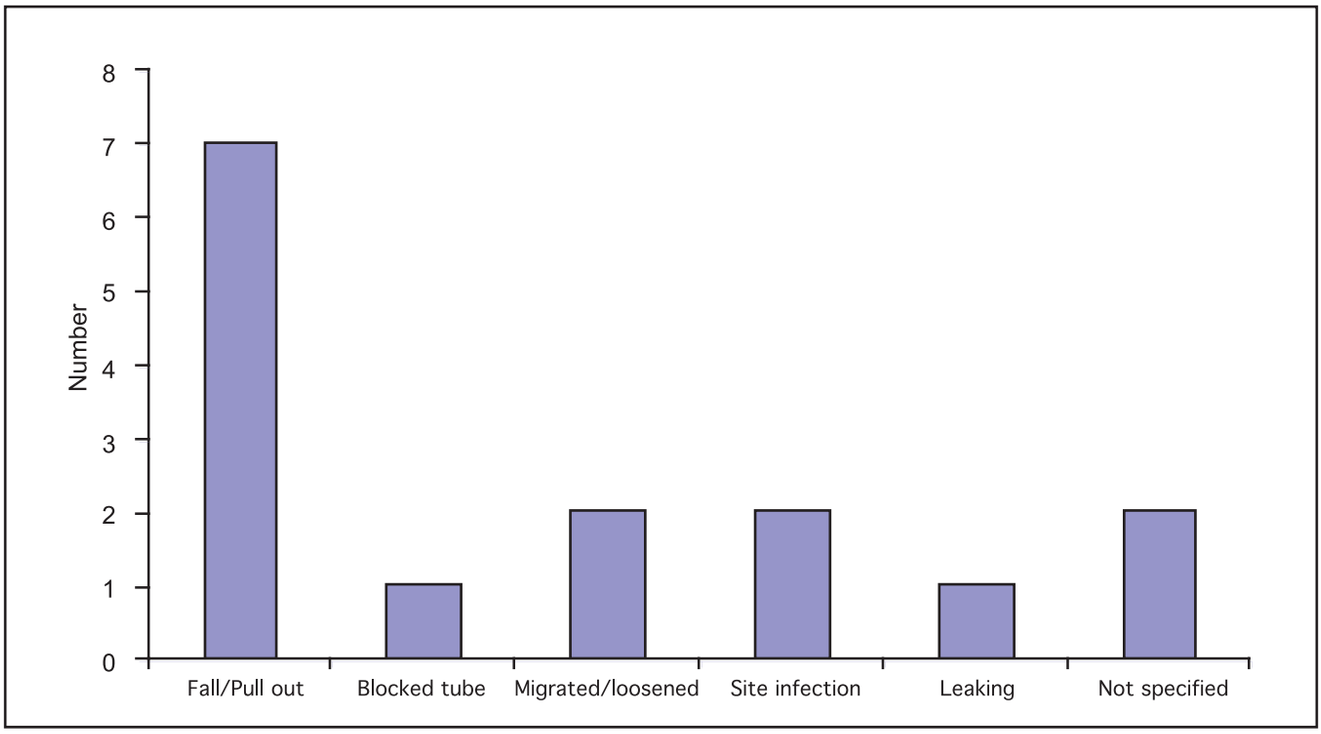

Fig 1. PEG tube problems encountered following discharge

PEG tube, 14 of whom knew who to contact in the event of a problem, all of which were resolved. In six of the 14 cases the respondent felt that the experience was not satisfactory for the patient/carer and that the resolution of PEG-related problems could be improved. The main problems encountered were PEG tube falling out (n=7); PEG site infection (n=2), migration / loosening of the PEG tube (n=2) and tube blockage (n=1) (Fig 1). Five respondents (17%) indicated that the PEG tube had subsequently been removed.

Following review of the medical records, the indications for PEG tube insertion in the 29 respondents are given in Table I. Six patients were identified as having their PEG tube removed from review of the medical notes, of whom four had not been clearly identified from the returned questionnaires, giving a total of nine patients (31%) in whom PEG tube feeding had been discontinued. The reasons identified in these nine patients were return of normal swallow reflex (n=8) [stroke in three; aspiration pneumonia in three; subdural haematoma in one; Parkinson's disease in one] and resolution of vomiting in gastroparesis (n=1). The PEG tube feeding was discontinued after a mean period of 5.4 months (range 1-12 months), by medical staff in five cases and the Nutrition Nurse Specialist in one case. Of the 19 cases in which PEG tube training was recalled by the patient/carer, documentation of training was confirmed on review of medical notes in six patients. In two further cases, training was documented in the medical notes, but the patient/carer did not recall this on the returned questionnaire, giving a total of 21 (72%) patients/carers who received training. No documentation of training was identified in 18 cases and three further patients were discharged to a Nursing Home familiar with PEG feeding. Training was given by Nursing staff (n=5), dietitian (n=1), Nutrition Nurse Specialist (n=1) and the Stoma Nurse (n=1).

DISCUSSION

In secondary care the main emphasis is on appropriate selection of patients for PEG tube insertion, the safe insertion of PEG tubes and the training of the patient/carer in the management of the PEG tube, including the correct use of the feeds and the feeding pumps[1]. Education of patients and caregivers by a multidisciplinary nutrition support team has been shown to promote independence and can limit subsequent demands on the service[2]. Due to limited resources there may be no formal care for PEG tube patients following discharge from hospital. Ideally all patients should have community follow-up by a dietician, speech and language therapist and an appropriately trained professional who can deal with problems and advise accordingly. Late recovery of swallow may occur following acute dysphagic stroke and these patients should have a follow-up swallowing assessment[3]. It has been proposed that a nurse specialist or dietician could establish a liaison service focusing on primary care and using hospital resources when appropriate[4].

We performed a postal survey of patients/carers to assess if training on PEG tube care was given and to assess the degree of community follow-up and the availability of appropriate care should problems arise. PEG tube training was carried out in 21 (72%) patients. Documentation in medical notes is frequently inadequate and the fact that the absence of a record of PEG tube training in the medical notes is not categorical evidence that it had not taken place. In two cases the patients/carers did not recall training having taken place when it had been documented and this may be as a result of the long period of follow-up in this study (median 19.5 months). As expected, dietetic follow-up was in place for the majority of patients. However, in view of the fact that 16 patients were able to take some food or liquids and 17 had

Table I

Indications for PEG tube insertion in 29 respondents

Indication	Number	%
Stroke	13	46
Cystic fibrosis	4	14
Aspiration pneumonia	4	14
Parkinson's disease	3	10
Sub-dural haematoma	2	7
Multiple sclerosis	1	3
Gastroparesis	1	3
Tongue carcinoma	1	3
Total	29	100

undergone follow-up assessment by a speech therapist, this raises the possibility that PEG tube feeding may not still be required in all of the remaining patients. Thirty-one percent of patients had had their PEG tube removed which is slightly higher than previous studies, and may reflect the indications present, some of which may be temporary (gastroparesis, aspiration pneumonia)[5].

To date it has been difficult to optimise the widespread availability of appropriately trained personnel in the community who can resolve PEG tube problems, as and when they arise. General Practitioners and district nurses may not have been trained in the insertion of balloon gastrostomy replacement tubes and this often results in patients attending busy Accident and Emergency departments when the PEG tube falls out, due the lack of adequately trained personnel in the community. Since PEG tube feeding is increasingly used following stroke, there is an urgent need for such training to be performed. Alternative appropriate personnel include community nurse specialists or nutrition nurse specialist, based in secondary care, but providing a service to the community.

Nutrition clinics have been proposed as a means of continually reviewing patients following PEG tube insertion. This requires a multi-disciplinary approach from dieticians, speech and language therapists, nutrition nurse specialist and medical endoscopists. It would have huge resource implications but it is one possible way to ensure that PEG tubes are maintained adequately and that patients have ongoing assessment to determine if ongoing PEG tube feeding is the best feeding option for the individual. One study has reported that it does not increase costs and does improve quality of care for these patients[6]. To date nutrition clinics have not been set up in many hospitals.

We performed a questionnaire to assess what follow-up was in place for patients in the community following discharge after PEG tube insertion. This study is somewhat limited by the poor response rate (44%) and the long follow-up period, which may limit recall by patients/carers. We decided to limit our postal questionnaire to those patients who were still alive at least six months following PEG tube insertion, and this limited the number in the study population under consideration. Whilst we have demonstrated that there is currently a reasonable quality of follow-up for these patients following discharge from hospital, further improvements in aftercare of these patients following PEG tube insertion could be made.

The authors have no conflict of interest.

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Ulster Med J 2007; **76 (2)** 91-97

Paper

Questionnaire Survey of PHysical activITy in General Practitioners (PHIT GP Study).

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Accepted 20 December 2006

ABSTRACT

Objectives**:** To assess the levels of physical activity and other health related behaviours of General Practitioners (GPs) and compare their reported levels of physical activity with those of the general population.

Study Design**:** Cross sectional postal questionnaire survey.

Methods: A questionnaire, which did not allow identification of individual respondents, was posted to all 1074 (GPs) in Northern Ireland. It included the validated International Physical Activity Questionnaire (IPAQ) and questions relating to smoking and alcohol consumption. A national survey of a representative sample of the general population of similar age (29-67 years; n = 3010) provided comparative data.

Results: 735 GPs responded (68.4%). IPAQ data indicated that fewer GPs (43.4%) were "physically inactive" compared to the general population (56.2%) (p <0.001) and to a subgroup of professionals (51.8%) (p < 0.016). Compared to the general population, relatively fewer GPs reported smoking (4.2% v 29%; p<0.001); more reported drinking alcohol (86.5% v 71.6%; p<0.001) but fewer reported drinking above recommended limits (12.6% v 16.9%; p < 0.001).

Conclusions: Our findings suggest that GPs are better than the general population at following health promotion advice. Since their personal habits influence the impact of their advice to their patients, their healthy lifestyles should be encouraged and further efforts should be made to promote activity among those who are physically inactive.

Keywords: Physical activity; Physician; Primary health care; smoking; alcohol consumption.

INTRODUCTION:

The physical and psychological benefits of physical activity are well documented and are highlighted in the Chief Medical Officer's report which recommends at least 30 minutes of moderate intensity physical activity a day.[1] It is recognised that the growing epidemic of obesity is linked to recent decline in physical activity levels.[2]

The more that doctors practise good personal health habits, the more likely they are to counsel their patients on a range of behaviours, such as physical activity, smoking, alcohol and diet[3, 4]. Doctors who are physically active themselves are three times more likely to regularly promote physical activity in their patients[5]. When doctors demonstrate their own personal health habits, patients find them to be more believable and better able to motivate changes in their diet and their physical activity levels[6]. One systematic review concluded that by counselling, GPs can increase physical activity in their patients[7]. A recent cluster randomised controlled trial showed counselling patients in general practice on exercise is effective in increasing their physical activity and improving their quality of life over 12 months[8].

Social class is thought to have a bearing on physical activity. The Whitehall II study showed that people in a lower social class do less physical activity than those in higher social classes or grades of employment[9]. In the Canada Health Survey 1981[10] only 39% of the general population were categorised as being active compared with 46% of professional / managerial people. By contrast however, in 1990, when the survey was repeated among a group of Canadian physicians, only 30% of them were found to be physically active[11]. A British study in 1992 comparing GPs and teachers showed that GPs reported taking significantly less exercise than teachers and very much less than they should advise their patients to take (at that time recommended levels were: at least twenty minutes, two to three times a week)[12]. During the past decade there has been an increasing emphasis on the role of primary care in providing health promotion. However there is lack of current evidence on physical activity levels and other health related behaviours of GPs.

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Ethical Approval: received 18th February 2004, Queens University Belfast, Research Ethics Committee. Application No: 48/04.

Table I.

Comparison of Physical Activity Category of GP cohort with NI population and Professional / managerial subgroup

	GP Cohort n= 650 (%)	NI Cohort n = 3010 (%)	Comparison of GP cohort with NI cohort.	Professional Cohort n = 514 (%)	Comparison of GP cohort with Professional cohort.
PHYSICAL ACTIVITY CATEGORY					
Category 1	282 (43.4)	1693 (56.2)	$\chi^2 = 41.3$	266 (51.8)	$\chi^2 = 8.2$
Category 2	210 (32.3)	835 (27.7)	$p < 0.001$	145 (28.2)	$p = 0.016$
Category 3	158 (24.3)	482 (16)		103 (20.0)	
PHYSICAL ACTIVITY CATEGORY (MALES ONLY)					
Category 1	182 (42.1)	773 (57.7)	$\chi^2 = 32.0$	170 (53.1)	$\chi^2 = 9.5$
Category 2	137 (31.7)	309 (23.1)	$p < 0.001$	86 (26.9)	$p = 0.009$
Category 3	113 (26.2)	257 (19.2)		64 (20)	
PHYSICAL ACTIVITY CATEGORY (FEMALES ONLY)					
Category 1	99 (45.6)	920 (55.1)	$\chi^2 = 10.5$	96 (49.5)	$\chi^2 = 0.7$
Category 2	73 (33.6)	526 (31.5)	$p = 0.005$	59 (30.4)	$p = 0.721$
Category 3	45 (20.7)	225 (13.5)		39 (20.1)	
INTENTION TO EXERCISE *					
1- No intention	31 (4.2)	718 (21.7)		70 (12.5)	
2- Considering it	93 (12.7)	380 (11.5)		68 (12.1)	
3- Not enough	261 (35.5)	1131 (34.1)	$\chi^2 = 151.8$	199 (35.5)	$\chi^2 = 34.7$
4- Regular <6/12	27 (3.7)	177 (5.3)	$p < 0.001$	29 (5.2)	$p < 0.001$
5- Regular>6/12	313 (42.6)	902 (27.2)		194 (34.6)	
Missing	10 (1.4)	7 (0.2)		0 (0)	

n= number; χ^2 = chi squared; t = independent t test; p = significance level; CI = confidence Interval; SD = Standard Deviation.
Category 1 = Inactive; Category 2 = Minimally Active; Category 3 = Health Enhancing Physical Activity.
Within group comparisons for difference between males and females for GP cohort $\chi^2 = 3.0$, $p = 0.224$; for NI cohort $\chi^2 = 35.1$, $p < 0.001$; for Professional cohort $\chi^2=0.8$, $p = 0.655$.
* Cohort prior to data removal for IPAQ analysis: for GP Cohort n = 735; for NI Cohort n = 3315; for Professional Cohort n = 560.

We aimed to assess the physical activity levels of a cohort of general practitioners using a validated questionnaire and to explore their other health related behaviours.

METHODS

Ethical approval was obtained from Queen's University Belfast Research Ethics Committee. All GP principals in Northern Ireland (NI) (n=1074), identified from the Central Service Agency's (CSA) mailing list, were sent an information sheet outlining the study and inviting them to participate, a freepost return envelope, a freepost reply card and a questionnaire. The reply card was used to ensure anonymity: it contained an identifier but the questionnaire did not. The respondent returned the reply card separately to certify completion of the questionnaire. Questionnaires were posted in early September 2004 and non-respondents were sent one reminder after 6 weeks. There was no coercion to take part in the study and consent was taken as implied with the return of the questionnaire.

The questionnaire included the validated International Physical Activity Questionnaire (IPAQ)(short form)[13]. This allowed an exercise category to be calculated for each respondent. Category 1 represented very low levels of activity, classified as 'inactive', Category 2 and Category 3 represented increasing levels of physical activity of at least current recommended levels i.e. 30 minutes of moderate intensity activity on most days of the week[14]. Other items in the questionnaire included sex, age, marital status, practice location, number of sessions worked, whether a shower facility was available at the surgery, intention to exercise, most common form of exercise undertaken.

Questions relating to other health related behaviours included smoking habits, alcohol consumption (we defined 'above recommended levels' of alcohol as greater than 14 units per week for women and greater than 21 units per week for men)[15] and when and if the GP had had blood pressure (BP) and cholesterol checks performed on themselves.

The age and sex distributions of the GP cohort of principals were obtained from the CSA. Data relating to the general population were obtained from the Northern Ireland Health & Social Wellbeing Survey (2001, NIHSWBS)[16] which included the IPAQ questions. Raw data were used for direct comparisons

Table II.

Comparison of characteristics of GP cohort with NI population and Professional / managerial subgroup

	GP Cohort n=735	NI Cohort n = 3315	Comparison of GP cohort with NI cohort.	Professional Cohort n = 560	Comparison of GP cohort with Professional cohort.
GENDER n (%)					
Male	479 (65.2)	1523 (45.9)	$\chi^2 = 89.7$,	350 (62.5)	$\chi^2 = 1.1$,
Female	255 (34.7)	1792 (54.1)	$p < 0.001$	210 (37.5)	$p = 0.305$
Missing	1 (0.1)	0 (0)		0 (0)	
AGE *years;*			t = 0.299,		t = 2.7,
mean (SD) [Range]	46.5 (8.2)	46.3 (10.9)	$p = 0.77$	45.1 (10.2)	p = 0.06
missing	[29 - 67]	[29 - 67]	CI (-0.71, 0.96)	[29 - 67]	CI (0.4, 2.4)
	0	0		0	
MARITAL STATUS n (%)					
Married	664 (90.3)	2393 (72.2)		459 (82.0)	
Single	4 (6.3)	420 (12.7)	$\chi^2 = 113.3$	55 (19.8)	$\chi^2 = 24.8$
Separated	10 (1.4)	179 (5.4)	$p < 0.001$	14 (2.5)	$p < 0.001$
Divorced	8 (1.1)	185 (5.6)		25 (4.5)	
Widowed	6 (0.8)	138 (4.2)		7 (1.3)	
Missing	1 (0.1)	0 (0)		0 (0)	
SMOKING STATUS n (%)					
Never smoked	586 (79.7)	1085 (32.7)		201 (35.9)	
Ex smoker	116 (15.8)	948 (28.6)	$\chi^2 = 504$	190 (33.9)	$\chi^2 = 220$
Current smoker	31 (4.2)	963 (29)	$p < 0.001$	104 (18.6)	$p < 0.001$
Missing	2 (0.3)	319 (9.6)		65 (11.6)	
ALCOHOL STATUS n (%)					
Drinker	636 (86.5)	2375 (71.6)	$\chi^2 = 20.6$	410 (73.2)	$\chi^2 = 3.4$
Non drinker	98 (13.3)	621 (18.7)	$p < 0.001$	85 (15.2)	$p = 0.065$
Missing	1 (0.1)	319 (9.6)		65 (11.6)	
ALCOHOL STATUS n (%) (MALE)					
Drinker	426 (88.9)	1068 (70.1)	$\chi^2 = 8.6$	245 (70.0)	$\chi^2 = 8.1$
Non drinker	52 (10.9)	211 (13.9)	$p = 0.003$	54 (15.4)	$p = 0.005$
Missing	1 (0.2)	244 (16)		51 (14.6)	
ALCOHOL STATUS n (%)					
(FEMALE)	209 (82)	1307 (72.9)	$\chi^2 = 4.3$	165 (78.6)	$\chi^2 = 0.39$
Drinker	46 (18)	410 (22.9)	$p = 0.034$	31 (14.8)	$p = 0.534$
Non drinker	0 (0)	75 (4.2)		14 (6.7)	
Missing					
ALCOHOL CONSUMPTION n (%)					
Within recommended levels	556 (87.4)	1973 (83.1)	$\chi^2 = 7.1$	350 (85.4)	$\chi^{22} = 0.9$
Above recommended levels	80 (12.6)	402 (16.9)	$p = 0.008$	60 (14.6)	$p = 0.34$
ALCOHOL CONSUMPTION n (%)					
(MALE)					
Within recommended levels	367 (86.2)	813 (76.1)	$\chi^2 = 18.4$	203 (82.9)	$\chi^2 = 1.3$
Above recommended levels	59 (13.8)	255 (23.9)	$p < 0.001$	42 (17.1)	$p = 0.251$
ALCOHOL CONSUMPTION n (%)					
(FEMALE)					
Within recommended levels	188 (90.0)	1160 (88.8)	$\chi^2 = 0.3$	147 (89.1)	$\chi^2 = 0.07$
Above recommended levels	21 (10.0)	147 (11.2)	$p = 0.608$	18 (10.9)	$p = 0.787$

n= number; χ^2 = chi squared; t = independent t test; *p* = significance level; CI = confidence Interval; SD = Standard Deviation.

with the GP responses. A professional / managerial subgroup of NIHSWBS respondents was identified.

Comparisons between the groups in the categorical variables of sex, smoking habits, alcohol consumption, intention to exercise and exercise category were made using chi squared analysis. Age distributions between the groups were compared using an independent t test. Regression analysis was used to determine predictors of exercise category.

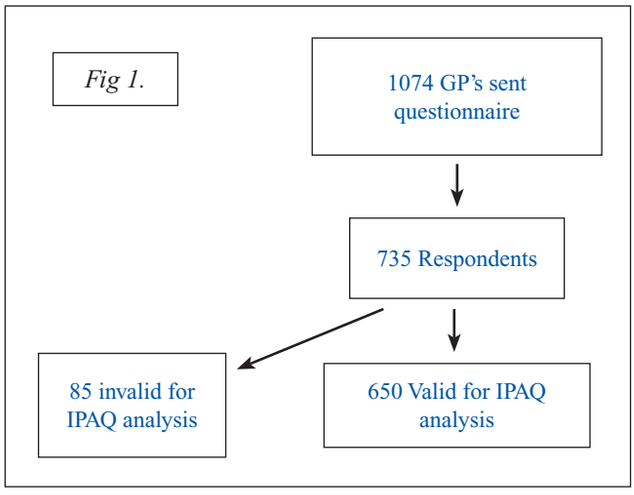
In accordance with strict data processing rules regarding incomplete responses and outlying values[17], some of the returned IPAQ questionnaires were excluded from analysis of the exercise part of the study. Other results reported contain the complete set of replies.

RESULTS:

Of the 1074 questionnaires posted 735 GPs responded (68.4%). There were no significant differences between age and sex distributions of respondents and non-respondents. In the NI population survey data 3315 individuals in the same age range as the GP respondents (29 – 67 years) were identified.

Following exclusion of 85 (11.6%) of the 735 GP responses (adhering to IPAQ data processing rules[17]) the 650 valid responses were analysed regarding physical activity levels (650/1074; 60.5%). On the same basis, 305 (9.2%) cases were removed from the selected NI population cohort, leaving a sample of 3010. Of 560 identified as professional / managerial from the NI cohort, 514 responses were valid for analysis of physical activity. (See Figs 1 and 2).

A significantly smaller proportion of GPs were classified as being inactive (43.4%) than of the total NI population cohort (56.2%) or its professional / managerial subgroup (51.8%) ($p<0.001$) (Table I). Within both the GP cohort and the professional / managerial subgroup there were no significant differences between males and females in their reported levels of physical activity, but within the total NI cohort males reported higher levels of physical activity than females. Comparing differences between groups for males only, GPs reported significantly more physical activity than both the total NI cohort and the professional / managerial subgroup. Female GPs reported significantly more physical activity compared with females from the total NI cohort but



similar to the professional / managerial subgroup. GPs were less likely to report having no intention of taking exercise than either the total NI cohort or the professional / managerial subgroup (4.2% v 21.7% & 12.5% respectively).

Walking was by far the most common physical activity reported by GPs (32%); approximately 10% of GP respondents also reported swimming, gardening, jogging, golf, cycling or going to the gym as forms of leisure-time physical activity.

Regression analysis showed that neither sex, number of sessions worked, having a shower in the practice or date of last BP or cholesterol check could predict a GP respondent's exercise category. Specifically, age did not predict the GPs' exercise category. However, in both the NI population cohort and the professional / managerial subgroup, age was a predictor of exercise category; for every 10 years increase in age among those in the NI general population cohort there was a 20% greater chance of inactivity. For every 10 years increase in age among the professional group there was a 30% greater chance of inactivity.

Table II shows that the proportion of males in the GP cohort (65.2%) was similar to the professional subgroup but was significantly greater than in the total NI cohort (45.9%). In comparison with the general population and the professional / managerial subgroup relatively more GPs were married

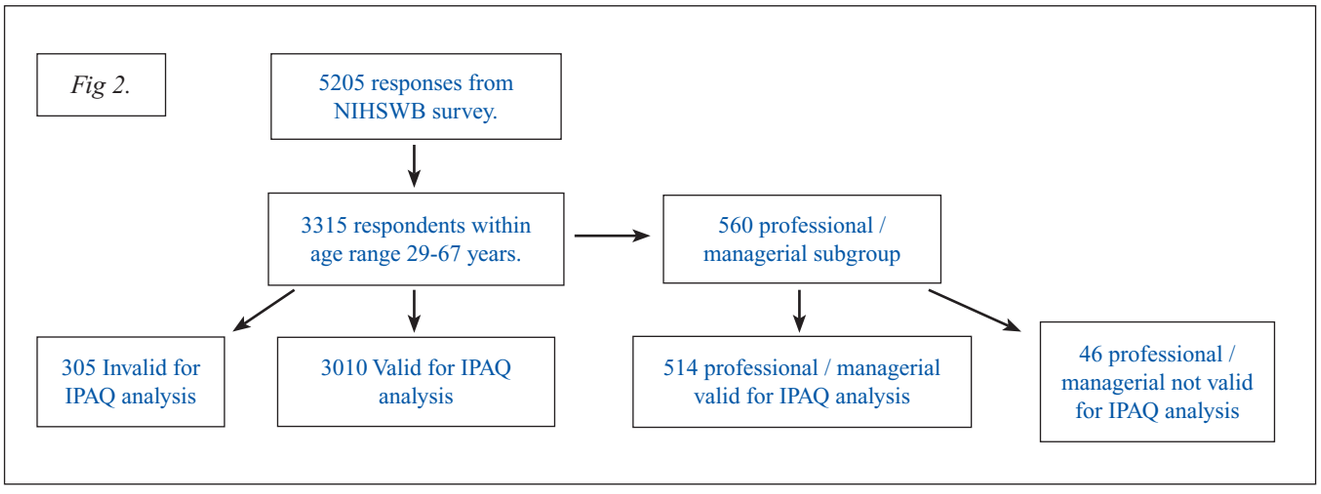


Table III

Comparison of characteristics of total GP cohort and cohort with responses valid for IPAQ analysis.

	Total GP Cohort n=735	GP cohort with Valid IPAQ Responses n = 650	Comparison
GENDER n (%)			
Male	479 (65.2)	432 (66.5)	$\chi^2 = 0.317$
Female	255 (34.7)	217 (33.4)	p = 0.57
Missing	1 (0.1)	1 (0.2)	
AGE *years;*			t = 0.83
mean (SD) [range]	46.5 (8.2)	46.1 (8.0)	p = 0.407
missing	[29 - 67]	[29 - 65]	CI(-0.5, 1.2)
	0	0	
MARITAL STATUS n (%)			
Married	664 (90.3)	587 (90.3)	
Single	46 (6.3)	41 (6.3)	$\chi^2 = 0.07$
Separated	10 (1.4)	9 (1.4)	p = 0.99
Divorced	8 (1.1)	8 (1.2)	
Widowed	6 (0.8)	5 (0.8)	
Missing	1 (0.1)	0	
PRACTICE LOCATION n (%)			
Urban	257 (35.0)	229 (35.2)	
Rural	162 (22.0)	145 (22.3)	$\chi^2 = 0.04$
Urban/Rural Mix	314 (42.7)	274 (42.2)	p = 0.978
Missing	2 (0.3)	2 (0.3)	
No of SESSIONS PER WEEK			
mean (SD)	8.4 (1.84)	8.4 (1.84)	t = -0.01,
[Range]	[1 - 14]	[1-14]	p = 0.989
Missing	10 (1.3%)	7 (1.1%)	CI (-0.5, 1.2)
SHOWER IN PRACTICE n (%)			
Yes	209 (28.4)	179 (27.5)	$\chi^2 = 0.05$
No	521 (70.9)	468 (72.0)	p = 0.82
Missing	5 (0.7)	3 (0.5)	
INTENTION TO EXERCISE n (%)			
No intention	31 (4.2)	28 (4.3)	
Thinking about	93 (12.7)	83 (12.8)	$\chi^2 = 0.157$
Not enough	261 (35.5)	240 (36.9)	p = 0.691
Regular <6/12	27 (3.7)	22 (3.4)	
Regular>6/12	313 (42.6)	271 (41.7)	
missing	10 (1.3)	6 (0.9)	
SMOKING STATUS n (%)			
Never smoked	586 (79.7)	522 (80.3)	$\chi^2 = 0.1$
Ex smoker	116 (15.8)	99 (15.2)	p = 0.991
Current smoker	31 (4.2)	27 (4.1)	
Missing	2 (0.3)	2 (0.3)	
ALCOHOL STATUS n (%)			
Drinker	636 (86.5)	564 (86.8)	$\chi^2 = 0.02$
Non drinker	98 (13.3)	85 (13.1)	p = 0.889
Missing	1 (0.1)	1 (0.2)	
ALCOHOL CONSUMPTION n (%)			
Within recommended levels	556 (87.4)	492 (87.2)	$\chi^2 = 0.1$
Above recommended levels	80 (12.6)	72 (12.8)	p = 0.922
LAST BP CHECK n (%)			
Never	14 (1.9)	11 (1.7)	
< 2 years	545 (74.1)	485 (74.6)	$\chi^2 = 0.478$
> 2 years	144 (19.6)	131 (20.2)	p = 0.924
Not sure	28 (3.8)	21 (3.2)	
Missing	4 (0.5)	2 (0.3)	
LAST CHOLESTEROL CHECK n (%)			
Never	138 (18.8)	127 (19.5)	
< 1 year	239 (32.5)	212 (32.6)	
1 -5 years	228 (31.0)	194 (29.8)	$\chi^2 = 0.3$
> 5 years	116 (15.8)	105 (16.2)	p = 0.990
Not sure	14 (1.9)	12 (1.8)	
Missing	0 (0)	0 (0)	

n= number; χ^2 = chi squared; t = independent t test; p = significance level; CI = confidence Interval; SD = Standard Deviation.

(90.3%), had never smoked (79.7%); significantly more in the GP cohort than the general population reported drinking alcohol (86.5%). However, the proportion who reported drinking above recommended 'safe' levels of alcohol were smaller for GPs (12.6%) than for the general population (16.9%) ($p < 0.001$). Further subgroup analysis indicated that significant differences in levels of reported alcohol consumption between the groups were confined to males.

There were no significant differences in the distribution of the characteristics of the GP cohort before and after exclusion of those with invalid IPAQ data (Table III).

DISCUSSION

Main Findings of Study:

Our study shows that GPs report taking significantly more physical activity than other people of similar age in NI. GPs are also much less likely than the general population to report that they have no intention of doing physical activity.

Whilst reported levels of activity fell with age in the general population, and the professional subgroup, this was not observed among the GPs. The inverse association of physical activity levels with age is in keeping with previous work[18] and was our reason for comparing an age matched sample of the general population with our cohort of GPs.

Our findings confirm reports of previous work which had shown that levels of physical activity are related to social class[9, 10]. However, in relation to their social class peers, GPs in our study were more active, but this finding was only significant in respect of males.

Our study indicates that the number of GPs in NI who currently smoke (4.2%) is much less than that of the general population (29%). In the 1960s, following the emergence of evidence to suggest that smoking might be harmful to health, many doctors stopped smoking. Doll and Hills' landmark studies revealed over 85% of doctors smoked in the 1950s;[19] this figure has since plummeted with approximately 30% smoking in the 1970s[20] and 10% smoking in the 1980s[12]. Doctors appear to have 'led the way' towards adopting a non-smoking lifestyle: in comparison, approximately 40% of the general population smoked cigarettes in the late 1970s[21]. More recent data show that this figure dropped to approximately (27%) in 2000/01[16].

Almost 75% of the GP respondents had their BP checked in last two years and 63% had a cholesterol check in the last five years; this compared with 69% and 52% respectively from a study of GPs in Britain in the early 1990s[12]. This may suggest that GPs' awareness of the value of preventive health care may be increasing. We failed to identify comparative data for the general population.

The relationship between health and physical activity is now well established. With respect to physical activity, our current findings suggest that GPs are in a similar position to 'lead by example' as they have done with smoking. In the face of the growing obesity epidemic in the western world, it is ever more important that health workers assume a leading role in averting the health crisis which will inevitably occur if people do not increase their physical activity.

Strengths of the study

This study's strengths include its size, encompassing an entire region, with 735 of 1074 surveyed GPs (68.4%) responding, and the use of a validated physical activity questionnaire, the IPAQ. We were also able to use raw data from a major lifestyle survey of the general population for comparison. Previous work examining the physical activity levels of doctors' achieved lower response rates than our study. In one mail survey, 47% of 451 hospital doctors responded [11]; in another, 48% of 408 GPs responded to a non-validated questionnaire[12]. The higher response rate which we received may indicate increasing interest from GPs in physical activity.

Limitations of study

Our study is limited in that it measures self-reported activity rather than actual activity. However the IPAQ validation study demonstrates a good correlation between reported and actual activity[13]. GPs may be prone to overestimate their exercise habits precisely because they know the benefits of physical activity and what they should be doing. However, the efforts taken to ensure anonymity of the questionnaires should have minimised this possible source of bias.

CONCLUSION

Our findings show that GPs report healthier lifestyle choices compared to the population. Further studies should examine GPs' actual physical activity habits and explore their barriers to engaging in health enhancing levels of exercise. Previous research has shown that GPs' personal habits can influence their patients.[6] They should be encouraged to 'practise what they preach' and, by their example, as well as their advice, to promote physical activity in the community in which they work.

GPs' reports suggest that many are following healthy lifestyle advice: ways of helping those who intend to become physically active should be explored.

ACKNOWLEDGEMENTS

Northern Ireland Statistics and Research agency. Clinical Research Support Centre, Education & Research Centre, Royal Group of Hospitals, Belfast, Northern Ireland.

Funding was from the Research and Development Office of the Department of Health Social Services and Public Safety (DHSSPS) Northern Ireland, under award scheme for GP research registrars (GPARTS).

Conflict of Interest. All researchers in this study are independent of the Research and Development Office.

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Ulster Med J 2007; **76 (2)** 98-101

Technical Note

CESA – A New Modality for the Difficult Aortic Aneurysm

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Accepted 3 January 2007

INTRODUCTION

A thoracic aortic aneurysm (TAA) is a life-threatening condition with a 20% five-year survival in untreated patients.[1] Rupture is invariably fatal. Surgical repair should be considered when the aneurysm is >6cm in diameter, rapidly enlarging, or impinging on adjacent structures.[1] Open repair, via a left thoracotomy carries significant morbidity and mortality rates.[1-2] More recently, endovascular repair of TAA has become an acceptable alternative to open repair with lower peri-operative morbidity and mortality rates.[3-4] The combination of both open and endografting techniques has further expanded the options for treatment of TAA especially for complex lesions which involve the visceral arteries.[2,5] We present a case of combined endovascular and surgical approach (CESA) for the treatment of a TAA in a patient with a previous open abdominal aortic aneurysm (AAA) repair.

CASE REPORT

The patient is a 64-year-old man who had a previous elective open repair of a 5cm infra-renal AAA in February 1998. At that time he was noted to have an asymptomatic 4cm TAA. He was a smoker of 20 cigarettes/day with a history of mild chronic renal failure, hypertension, and hypercholesterolaemia.

Surveillance computerized tomography (CT) imaging demonstrated fairly slow increments in the size of the aneurysm which commenced in the descending thoracic aorta distal to the origin of the left subclavian artery and continued through the diaphragm to just above the coeliac axis in the abdominal aorta. The aneurysm had increased to 6cm in maximal diameter by June 2002. Open repair of the TAA was deemed inadvisable due to the high risk of mortality in the peri-operative period as well as the likelihood of paraplegia, especially in patients with a previous open AAA repair. By March 2003, the maximal diameter of the TAA had increased to 6.2cm with a top neck diameter of 3.1cm, neck length of 5.0cm, distal neck diameter of 3.0cm and distal aortic diameter of 2.8cm. Following review of his CT films, it was felt that an endovascular thoracic stent would be technically feasible but as the stent would occlude the coeliac axis and superior mesenteric arteries, open bypass would be required to these vessels to preserve the blood supply of the bowel.

A laparotomy and left groin incision were performed to allow access to the previous aortic repair and visceral vessels (Fig 1a) and also to facilitate deployment of the thoracic endograft through the common femoral artery. A 10x8mm Dacron bifurcated prosthesis (Gelsoft Plus®, Sulzer Vascutek Lyd, UK) was used to bypass from the anterior aspect of the previous infrarenal aortic graft to the superior mesenteric artery and coeliac axis (Figs 1b, 2). Intra-operative doppler signals for all anastomoses were good. The limb to the coeliac axis was passed anterior to the pancreas and behind the stomach. The trunks of the coeliac axis and superior mesenteric arteries were then ligated using 2/0 prolene (Fig 1c). Omentum was placed over the aortic grafts and the mid-line wound was closed.

The thoracic stent (Talent®, Medtronic Ave, Watford, UK) was then deployed through the exposed left common femoral artery under careful radiological control (Fig 1c). Three separate endoprostheses were used in total to ensure complete exclusion of the aneurysm with a stent overlap of approximately 50% at each junction site. Proximally, a straight graft with a proximal and distal diameter of 36mm and length of 114mm was delivered followed by the deployment of two tapered distal extension stents with 38mm proximal and 34mm distal diameters and length of 112mm. An intra-operative check angiogram demonstrated satisfactory placement of the thoracic endograft with no evidence of endoleak (Figs 3a, 3b). The left groin wound was then closed. There were no major complications encountered throughout the procedure. He remained in the intensive care unit for 10-days and made slow but steady progress. He was discharged well on day 19.

Almost two-years later, he was admitted as an emergency with chest and abdominal pain. A CT scan confirmed a ruptured thoracic aneurysm arising from a slight dislocation between components of the previous thoracic stent (Fig 4). He underwent emergency endovascular repair where the dislocated grafts were bridged with two further thoracic endografts. Following initial slow progress in the high dependency unit due to a persisting left pleural effusion, he was discharged well on day-16. Since then, he has been well with no further stent-graft nor aneurysm related complications.

DISCUSSION

Endovascular repair of AAA is a widely documented and accepted technique.[1,4] As with AAA stenting, endovascular

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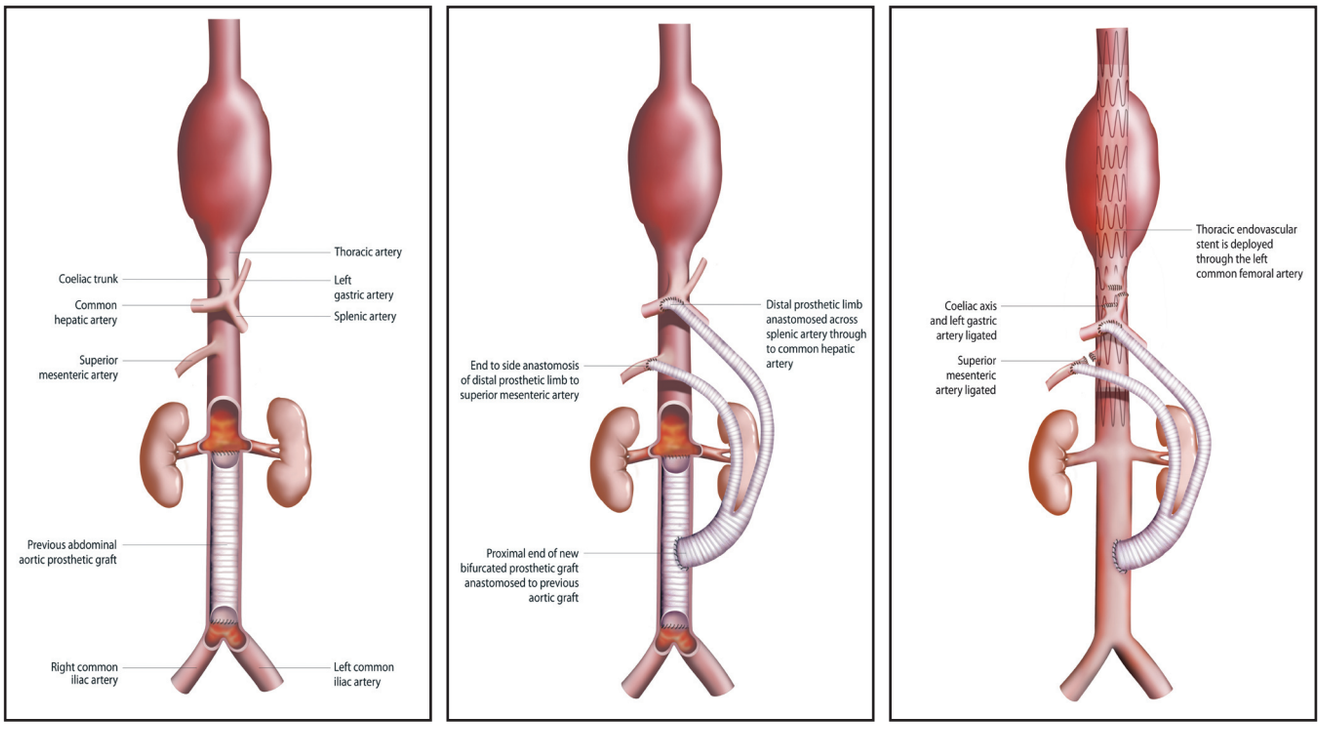
Fig 1.



Stage a) Anatomical representation of the TAA and previous AAA repair.

Stage b) A bifurcated prosthesis is anastomosed to the previous AAA graft and then distally to the superior mesenteric arteries and coeliac trunk vessels.

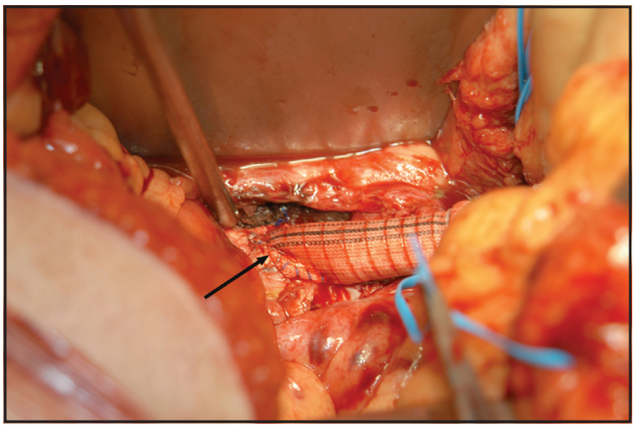
Stage c) The native visceral vessels are clamped and ligated. The thoracic endograft is then deployed to the TAA.

exclusion of TAA's requires relatively straight, normal segments of aorta both proximally and distally for device fixation. When the TAA involves the brachio-cephalic vessels proximally, or the visceral vessels distally, certain difficulties arise due to impingement or exclusion of the native vascular flow by the endograft itself. The native vessels often have to be re-implanted or bypassed elsewhere in the aortic tree. In this case, the TAA commenced below the left subclavian artery and continued distally to just above the coeliac axis. In order to provide an adequate landing zone, both the coeliac axis and superior mesenteric artery had to be covered by the stent graft. This meant that both vessels had to be relocated.

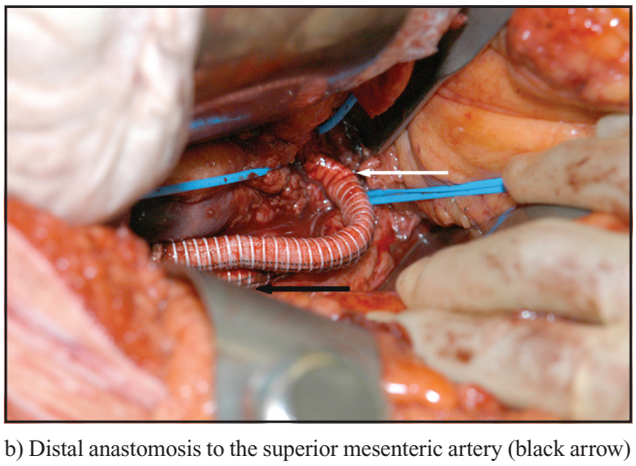
The transabdominal approach facilitated visceral arterial bypass prior to ligation of native vessels without the need for aortic cross-clamping. This resulted in a reduction in the duration of bowel ischaemia. Due to the anatomy of a thoraco-

Fig 2.

Intra-operative images.



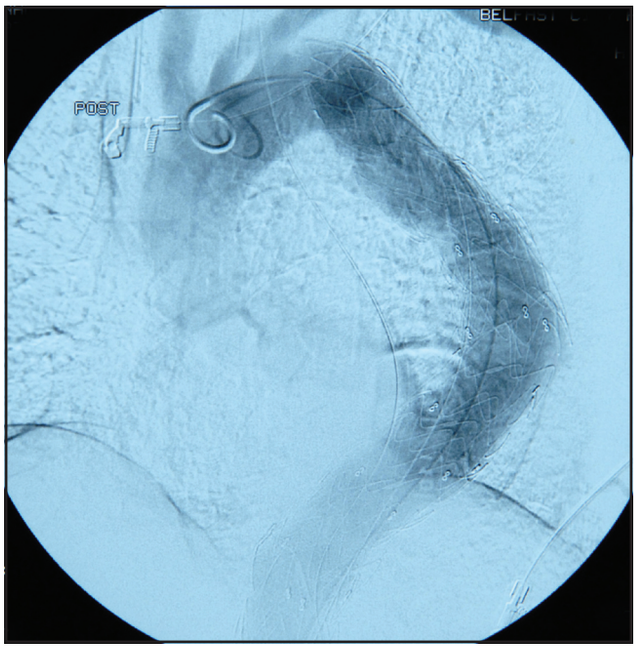
a) Proximal anastomosis to the previous aortic prosthesis (black arrow).



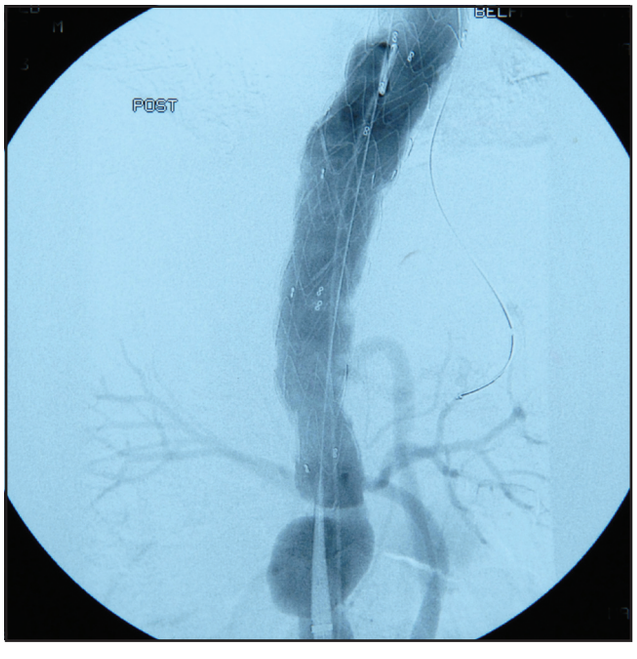
b) Distal anastomosis to the superior mesenteric artery (black arrow) and then to splenic artery across to the common hepatic artery (white arrow).

Fig 3.

An intra-operative check angiogram demonstrated satisfactory placement of the thoracic endograft with no evidence of endoleak.



a) Proximal portion of thoracic endograft deployed distal to the origin of the left subclavian artery.



b) Distal portion of the thoracic endograft extending down to just above the renal arteries. The visceral revascularization prosthetic grafts to the coeliac axis and superior mesenteric artery can also be identified.

abdominal aortic aneurysm, we were not able to perform antegrade bypass grafting to the visceral arteries from the proximal aorta which would have offered a shorter, more direct bypass grafting route. The retrograde approach adopted here was a technically easier option and most importantly avoided the use of supracoeliac aortic cross clamping. Although the long-term safety and durability of retrograde bypass grafting has yet to be proven, early reports are encouraging with retrograde graft patency rates of 98% at 8-months following CESA and 90-95% at 36-months following procedures for chronic mesenteric ischaemia and renal artery stenosis.[5] We also tried to minimise intraperitoneal routing of the Dacron grafts by utilising the retroperitoneal route.

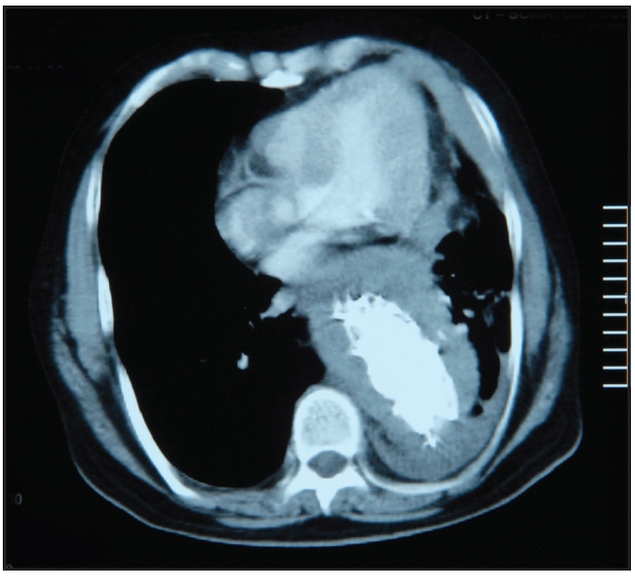


Fig 4.

Computerised tomography scan demonstrating the ruptured thoracic aortic aneurysm arising from a slight dislocation between components of the previous thoracic stent resulting in a left haemothorax.

While peri-operative mortality is dramatically reduced by the use of a stent graft, the endovascular portion of the CESA is not without risk. Vascular injury, device malfunction, and atheroembolic events during device positioning and deployment have all been reported.[6] Longer term studies have also raised concerns regarding the significance of endoleaks and endotension, and aspects of stent durability, including migration, kinking and material disintegration over time.[7] Unfortunately, these complications are not always easily amenable to correction as shown in this case. CESA has also been utilized elsewhere in the aortic tree; aortic arch aneurysm endograft exclusion with bypass grafting of the ascending aorta to the brachio-cephalic trunk and left common carotid artery, and relocation of the iliac artery bifurcation to facilitate endovascular repair of AAA with extensive iliac artery involvement.[8-9]

We have reported a successful outcome for the management of complex aortic aneurysm pathology. With advances in endovascular devices using branched devices it is hoped that future complex TAA's may be treated with minimally invasive techniques alone which would incorporate side branch cannulation and branch graft deployment.[10] However, for this technique to become a viable alternative in the management of TAA, the long-term durability of endovascular endografts has still to be proven.

Acknowledgements: We thank Mr Adrian Knipe, Department of Medical Illustration, Belfast City Hospital for his assistance in the production of the technical figures.

The Authors have no conflict of interest.

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Ulster Med J 2007; **76 (2)** 102-106

Historical Paper

Two Sons of the First Congregation

Hume Logan

Accepted 30 January 2007

Based on the Gary Love Lecture given to a joint meeting of the Ulster Medical Society with the Society for the History of Medicine, 25th January 2007.

The population of Ireland was originally Roman Catholic but was diluted after the Elizabethan campaigns by Anglicans and the Plantation of Ulster by Scottish Presbyterians. While there may have been a Presbyterian church near the North Gate in either Hercules Street or North Street in Belfast, the well documented but later meeting houses were established late in the seventeenth century in Rosemary Street, where the church stands today. Two churches were built after the original one (the First Congregation). The first of these was built because the original could not contain all the congregation and the second because of doctrinal differences. Two of the early ministers of the First Congregation were Samuel Haliday (1720-1739) and Thomas Drennan (1739-1768)

SAMUEL HALIDAY AND FAMILY

The Reverend Haliday, born in 1685, attended Glasgow University in 1701, graduating MA four years later. He moved to Leiden and was licensed in Rotterdam and in 1708 was ordained in Geneva. He became Chaplin to the Scots Cameronian Regiment serving in Flanders and came to Ulster in 1712. Having been Chaplin to Colonel Anstruther's Regiment, he was called to the First Congregation in 1719. Refusing to sign the Westminster Confession of Faith, he lived a life of controversy. He married a wealthy widow and had three sons, one of whom, Alexander Henry born in 1728, became a doctor. (Fig 1).

Fig 1. Alexander Haliday. Reproduced with the kind permission of the owner, currently on loan to the National Portrait Gallery, London.

Where the young Haliday received his early education is not known but it was probably at the hands of the Reverend Drennan. He followed his father and many other Ulstermen to Glasgow University where he matriculated in 1743 and graduated MA, MD in 1751, aged twenty three. This does not mean that he gained his clinic experience in Glasgow, as the first hospital there was built in 1794. Haliday wrote to Cullen from Belfast in 1751 stating that he had been in Paris when "the news of your establishment in the University of Glasgow reached me". This may have been in 1750 when Cullen was appointed Professor of Medicine. The official date given for Cullen taking up the Chair of Medicine is 1751. Haliday's letter is reproduced in a biography of Cullen, but this is only an extract from it. The original is in the University of Glasgow and outlines his undergraduate career and is best recorded in his own words.

" ….. in the beginning of my Education I passed four winters happily and I hope not idly in Glasgow - for the last two you may remember (if time and distance of situation have left you any remembrance of one) I was chiefly engaged in the medical - very under your direction - the Summer between these and the one which succeeded the last I improved as well as I could in the shop of our principal apothecary in this place - the next winter was spent in Edinburgh, where I attended with some care Mr Monroe, Dr Rutherford (both his college and his clinic lectures) and which was of more advantage (in consequence of your advice) Dr Young and the Infirmary - from the Doctor I heard much and in the other saw somewhat of the genuine appearances of disease and the effects of applications - the summer was employed in essays in practice

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and in the reading of practical authors, particularly Hoffman whose writings tho diffuse and ill ordered, I have found much more instructive, than the clear well digested axioms of Boerhaeve - in the beginning of Winter I went to London, where I attended with a pleasure and improvement that well rewarded my care the lectures of Mr Hunter - and for eight months St Georges Hospital - from this I passed to Holland in which place and in Paris half a year was employed as usefully as my situations would allow - on my return to London I renewed my attendance at the hospital, inspected the files of an apothecary and dissected a little; - after some months I had proposed to revisit Glasgow, to conclude my Studies where they at first commenced and assume a character I began to think my self not altogether unqualified for - but the bad state of a tender Mother's Health and an only Sister's concerned with some other circumstances to hurry me home".

Of course, there was a reason for all the detail in the letter as he went on

"And now I wish I could as well excuse the request which is to follow as it will apologise for this long detail of the particulars of my Education - can I have the honour at this distance of taking a degree in my Mother University?"

This was not a matter of sitting an examination as he stated that he "could have obtained a degree on easy terms, but the view of taking an authentic one in Glasgow prevented my applying elsewhere -unforeseen circumstances have forced me to this irregular application here …." It would seem unlikely that Haliday sat any form of examination as he wrote this letter in May 1751 and his MA, MD degrees were awarded the same year. At this time many doctors practiced on the strength of having a certificate stating that they had attended a medical school. Haliday appears to have started practice in Belfast in 1751 where he remained for the rest of his life.

THOMAS DRENNAN AND FAMILY

The Reverend Thomas Drennan was educated in Glasgow. He was assistant to Francis Hutchinson in a Dublin academy until Hutchinson was appointed to the Chair of Moral Philosophy in Edinburgh. He was ordained to the ministry in Holywood in 1731 and moved to the First Congregation in 1736. Like Haliday he did not subscribe to the Westminster Confession. He was to chaperon Anne Lennox in 1741 on a long coach journey at the end of which they agreed to marry. They had nine children only three of whom survived to adulthood. Of these only two are important to this account of medicine and politics in the eighteenth century, the third Nancy, being described as being very quiet and retiring. Martha, or Matty as she was known, was born in 1742 and her brother William in 1754 (Fig 2). They were very close.

William's life has already been documented in detail elsewhere and only an outline follows. His initial education was at the Belfast School in Church Lane. From there he went to Glasgow graduating MA in 1771 aged seventeen. In 1773 he went to Edinburgh to study medicine. From then until his return to Belfast in 1807, some fifteen hundred letters passed between him and Matty and her husband Samuel McTier. The Drennans were an important family in Belfast and Matty knew everything that was going on and relayed it to her brother. After his graduation in 1778 he became very interested in politics and the letters have been very helpful to historians. He also had a friendship with Haliday and the letters are the only source of information about Haliday's medical practice.

Nothing is known about Drennan's activities in Belfast after graduation and setting up practice in Newry in 1782 where he wanted to be an accoucheur. However, his dislike of Newry and his interest in politics caused him to move to Dublin in 1789. He associated with many involved in politics there and was the founder of the Society of United Irishmen. He was tried for sedition in 1794 but escaped conviction. This cooled his enthusiasm for politics and he returned to Belfast in 1807.

Matty herself played a part in Belfast medicine, being present at the founding of the Lying-In Hospital which ultimately became the Royal Maternity Hospital. She was the first secretary of the charity and was succeeded by Mrs Haliday.

THE LETTERS

When the letters started, Haliday had been practicing in Belfast for twenty two years and in 1789 Matty wrote that Haliday's practice in the town had increased due to Ross's death. He did not confine himself to the town having developed a large country practice and Matty later reported that he left the town work to Mattear. Some of his rural work is documented and shows how arduous his life must have been. On one occasion he was in Armagh "attending Lord Chief Baron Burgh who was in a desperate fever", On another occasion he was unable to attend a meeting with Lord

Fig 2. Dr William Drennan MD, 1754-1820. (Artist Robert Home, 1752-1834). Photograph © National Museums Northern Ireland 2006, reproduced with the kind permission of the trustees of the National Museums Northern Ireland. Collection Ulster Museum, Belfast.

Charlemont because he was in Saintfield where "two infants under inoculation would not permit me to attend". This was variolation or inoculation and not vaccination as we know it. When Drennan was seriously ill with typhus in Newry, Samuel McTier wrote that "Dr H was abroad ….. I then sent an express to Dr H asking him to go to Newry as soon as possible". After he arrived on Saturday "he was soon called away 54 miles off" and promised to return on Monday, but it was Tuesday before he turned up. He then insisted on sitting up all night with Drennan as McTier had been up the previous three nights. Drennan was treated with James's Powders and his legs were "blistered" and he recovered.

Other examples of Haliday's rural practice exist and they show how far he travelled, presumably on horseback or in a carriage. Sadly he did not record his feelings nor his treatment of his patients but it is known that he charged one guinea per mile for each Consultation. Fevers of various types, despite their unknown aetiology, seem to have been the most serious illnesses but smallpox and tuberculosis were also common. Drennan recorded that at one time he had "no less than five patients ….. in consumptions which appear very prevalent". A Miss Stapleton who was dying was expected from England and three of her sisters had died of the same condition within two years. Matty also recorded a case which Haliday said was "in a galloping consumption".

The therapy employed seems bizarre today. For chest complaints "a Burgandy pitch plaster of sufficient size to be applied between the shoulders, to be removed once or twice a week and to be reapplied after rubbing the skin beneath in a gentle manner with a flannel". The normal treatment for fevers was James's Powders – one part oxide of antimony and two parts phosphate of calcium - first concocted by Dr James, an English physician. Headaches could be treated by "shaving the head and rub it nightly with flower of mustard until it grows red and warm". Drennan's mother was noted to have had an "issue" cut on her arm. This was an artificial ulcer created anywhere on the body depending upon the symptoms it was being used to cure. They were created either by making an incision large enough to receive one or two peas, or by destroying the skin by caustic. After three days fresh peas were inserted. A linseed poultice could then be applied twice daily until the eschar formed and separated. The wound was then filled with either peas, beans or beads which stayed in place best if put on a thread. There was little surgery at this time but Haliday and a surgeon called Fuller from Belfast were in Newry to inspect a patient's foot and amputation was advised to save the patient's life.

While little is known about this aspect of Haliday's life, we do know that he was considered to be the leading doctor in the town. This is confirmed by his appointment as a consultant to the Belfast Dispensary when it was opened in 1792. Of his other activities much more is known. He was married twice. His first wife was called Martha McCollum and they married in 1754. She was the daughter of Randal McCollum who was said to be well off. Sadly she died in December 1772. Three years later he married Anne Edmonstone when he was aged forty seven. Anne was said to be "affable and unaffected, but no way striking in either looks or behaviour". This assessment was obviously by Matty McTier who was not inclined to flattery. Anne came from an affluent family who lived in Red Hall, Ballycarry, County Antrim. Her father was Campbell Edmonstone, Lieutenant Governor of Dunbarton Castle. They seem to have had a very successful marriage. In his will Haliday after leaving larger interests to her left her "£100 by way of atonement for the many unmerciful scolds I have thrown away upon her at the whist table". And a further sum of £500 "in gratitude for her never given on any occasion ….. any just cause to rebuke or complain of her ……a further sum of £100 as an acknowledgement of her goodness in devoting an hour or two, which she could have so much better employed to amuse me with a game of Picket".

They did not have a family but Haliday educated his nephew (Dr William Haliday) and his niece. Their father, Robert, was the Collector of Charleston in 1773 and was the only one to save the tea in storage rather than destroy it. He was banished to London on a paltry pension at the age of fifty eight. Later his son William was one of the founders of the Belfast Medical Society and was its second president.

THE VOLUNTEERS

When Haliday was at the peak of his career the American War of Independence had some dramatic effects on Ireland. The army had to be withdrawn to fight in America leaving the country vulnerable to invasion by the French. This led to the formation of the Volunteers, an armed citizens army. Haliday was involved but was annoyed that he was not made captain of the Blue Company when it was formed despite having been a lieutenant in an older company. Lord Charlemont commanded the Volunteers and Haliday became his right-hand man. They also became friends and Charlemont stayed with Haliday when he came to Belfast. They had an extensive correspondence of about two hundred letters between 1780 and 1799. This covered many subjects from politics to literature, another aspect of Haliday's character as he also wrote poetry and a play.

The Volunteers were not only an armed force but were highly political and this led to the formation of the Northern Whig Club with Charlemont as president and Haliday as secretary. Their object was to endeavour on constitutional lines to secure for the people an adequate representation in parliament and a proper encouragement of agriculture, manufacture and trade of the country. However, at a meeting of the citizens he spoke against the repeal of the penal laws as he felt that the influence of the priesthood over the minds of the laity should be considerably reduced and that they should be better educated before getting the vote. This was also Charlemont's view but it was not that of the Volunteers nor that of Wolfe Tone. He came to Belfast in 1791 and formed the first Society of United Irishmen. Haliday met Tone and wrote to Charlemont "I thought myself so unlucky of seeing so little of him; professional and other engagements deprived me of the pleasure of meeting him except one day, when his good sense and modest unassuming courage were truly engaging". Despite their opposing views they liked and respected each other.

In a letter written from Larchfield in 1783 Haliday wrote to Charlemont "In fact I have been for these two months, an absolute stranger to leisure and my own town". Despite this he made time for other activities. In 1788 the Belfast Reading Society was formed by fifteen artisans to promote

self improvement and to share the cost of buying books which were expensive. Later there was an influx from the merchants and professional classes including Haliday. The society changed its name to the Belfast Society for Promoting Knowledge. Initially meetings were held in a tavern, later in a private house and then in the White Linen Hall where the City Hall now stands. Finally, the society moved across the street to Donegall Square North as the Linen Hall Library and flourishes on the same site today. The members asked Haliday to be their president. Matty writing to her brother suggested that it was his books they were after rather than himself. He presented the society with three boxes of minerals, reflecting another of his interests. Ultimately he bequeathed his books to the library when he died. While he was president from 1792 until 1798 it is amazing that it is claimed that he never attended a meeting of the society. He resigned in favour of his nephew William in 1800.

Haliday was also interested in education as it is noted that when some inhabitants met to found the Belfast Academy, Haliday was elected as their president. His generosity can be realised in that he gave £30 to the school, an amount only equalled by Waddell Cunningham one of the wealthiest merchants in the town. The school ultimately became the Belfast Royal Academy.

There is little doubt that Haliday was a successful doctor and that this brought its rewards. He made donations to several causes including £100 towards the building of the White Linen Hall. He also took a lease from Lord Donegall for five hundred and forty acres. The rent was £120.16s.0d. and he had to pay a fine of £500. At this time Lord Donegall, who had huge estates in Country Antrim, was very short of money and was forced to raise rents and impose fines to increase his capital. The tenants were unable to afford these prices and only the better off merchants in Belfast could raise the money. The existing tenants responded by houghing or maiming the cattle of the new tenants. In December 1770 one of the perpetrators, David Douglas, was taken and imprisoned in the Belfast barracks. The tenants held a meeting in Templepatrick Presbyterian Church and formed a group called the Hearts of Steel. They decided to arm themselves and march on Belfast and secure the release of Douglas. By the time they got to Belfast they numbered about twelve hundred. At the barracks Douglas's release was refused. As it was a Mr Gregg's cattle which had been attacked they then went to the house of his partner, Waddell Cunningham, at the bottom of Hercules Street. They broke into it and set about breaking up the furniture. Haliday lived not far away in Castle Street and he came out and remonstrated with the mob who took him prisoner. He agreed to go to the barracks and try to get Douglas released and he promised that if he failed he would return and act as a hostage. When the mob returned to the barracks the gates were thrown open by the soldiers who fired on the mob killing five and wounding nine. The mob returned to Cunningham's house and set fire to it. There was therefore a risk of the town being burnt down and so Douglas was freed.

Early in 1802 Matty wrote to her brother that "H declines (I fear) rapidly. Says he feels a rattle in his throat every night and must soon make a moonlight flitting". Drennan replied that when he was in Newry, Haliday had complained of having "an intermitting pulse ……and he thought then it was somewhat mortal, but he long survived that fear". In April Matty wrote that Haliday had an "alarming spot on his leg". The next day both his legs were inflamed. Later she recorded that Haliday played cards and wrote letters the day before he died on the 28th April 1802. He was buried in the New Burying Ground beside Clifton House.

After his death in 1802, Benn wrote of Haliday "Besides the estimation in which Dr Haliday was held for professional talent, he was intimate with and associated with persons of the highest rank in the neighbourhood ……. He was probably the best known and most influential inhabitant of Belfast". Drennan also wrote a eulogy of his friend and mentor and there isn't any doubt that he held him in great regard. When Drennan returned to Belfast in 1807 he lived in a small mud walled cottage which Matty had built in 1783. She called it Cabin Hill. As her husband did not like living out of the town, she sold it in 1789. It was again sold in 1800 when it was bought by Drennan's cousin, Miss Martha Young, who died in 1807 and left Cabin Hill to Matty and a considerable sum to Drennan. It was this legacy which allowed him to retire to the cottage and Matty returned to live in Belfast. Apart from his family, Drennan's main interest was in promoting the Belfast Academical Institution which was founded in 1810 and when it was opened in 1814, he gave the inaugural address. The school became the Royal Belfast Academical Institution and later gave rise to the Belfast medical school.

Osler wrote "the philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow". I hope that we will have the wisdom to emulate and remember those mentioned above.

ACKNOWLEDGEMENTS

I wish to thank the Public Records Office Northern Ireland, the Royal Irish Academy and the library of Glasgow University for their assistance. Also the Department of Medical Imaging in the Ulster Hospital. The author has no conflict of interest.

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Preparing for a medical job 'Down under'

With the cold and wet Northern Ireland winter almost over, many people will have started fantasising about life in sunnier climes. We report our experience of a year spent working in Australia with pointers for those who are planning or dreaming of doing the same.

Preparing to go… Several agencies and hospitals advertise posts in the medical journals. Alternatively, as we did, one may obtain hospital contact details and approach the human resources department directly. The usual process of submitting application forms and curriculum vitae followed with telephone interviews if short-listed… expect calls in the early hours of the morning and be prepared for the surreal experience of taking a cheery Australian consultant through your CV while half asleep! Delighted at having obtained the positions of our choice at a large teaching hospital in Perth, Western Australia we thought the rest would be plain sailing. However, hours were spent obtaining and completing the documents necessary to practise medicine in Australia and it is important to allow plenty of time- we began preparations six months prior to going. A temporary resident visa is required- this can be applied for following offer of a job from an Australian hospital. All the forms needed for the visas and medicals are available online from the Australian immigration department.

On arrival… We would advise if possible, to arrive two weeks before starting work. This allows time to recover from jet-lag, fill out yet more forms and sort out essentials like accommodation, bank account and mode of transport. You must present to the state medical board to get an equivalent of the General Medical Council certificate. Obtain a tax file number to avoid emergency tax.

The job… Australia has an impressive health system with an excellent combination of public and private healthcare. Approximately 60-70% of the population have private health insurance which visibly reduces the strain on the public sector. Waiting lists for investigations and treatments are shorter than in Northern Ireland which makes for a pleasant and rewarding work environment. When we arrived in August, the hospital was in the midst of their winter bed crisis… consisting of two trolley waits in the Emergency Department (A&E)! Most conditions are those typically seen in Western countries with a number of issues particular to the indigenous population (the Aborigines) who have a life-expectancy in the mid-forties. Access to health services is difficult- many of the Aboriginal patients we met lived in remote communities in the outback, some having travelled up to four hours by air to reach hospital. History taking from such individuals was a fascinating experience, particularly social and dietary history- we hadn't been previously aware that witchety grubs were so high in protein or that a certain type of green ant will provide over the RDA of vitamin C!

It had been our ambition since medical school to work and travel in Australia. We found that a certain degree of courage is required to step off the traditional ladder of senior house officer and registrar rotations here in Northern Ireland. However, the experience gained- both personal and professional is invaluable.

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Preparing for a medical job 'Down under'

With the cold and wet Northern Ireland winter almost over, many people will have started fantasising about life in sunnier climes. We report our experience of a year spent working in Australia with pointers for those who are planning or dreaming of doing the same.

Preparing to go… Several agencies and hospitals advertise posts in the medical journals. Alternatively, as we did, one may obtain hospital contact details and approach the human resources department directly. The usual process of submitting application forms and curriculum vitae followed with telephone interviews if short-listed… expect calls in the early hours of the morning and be prepared for the surreal experience of taking a cheery Australian consultant through your CV while half asleep! Delighted at having obtained the positions of our choice at a large teaching hospital in Perth, Western Australia we thought the rest would be plain sailing. However, hours were spent obtaining and completing the documents necessary to practise medicine in Australia and it is important to allow plenty of time- we began preparations six months prior to going. A temporary resident visa is required- this can be applied for following offer of a job from an Australian hospital. All the forms needed for the visas and medicals are available online from the Australian immigration department.

On arrival… We would advise if possible, to arrive two weeks before starting work. This allows time to recover from jet-lag, fill out yet more forms and sort out essentials like accommodation, bank account and mode of transport. You must present to the state medical board to get an equivalent of the General Medical Council certificate. Obtain a tax file number to avoid emergency tax.

The job… Australia has an impressive health system with an excellent combination of public and private healthcare. Approximately 60-70% of the population have private health insurance which visibly reduces the strain on the public sector. Waiting lists for investigations and treatments are shorter than in Northern Ireland which makes for a pleasant and rewarding work environment. When we arrived in August, the hospital was in the midst of their winter bed crisis… consisting of two trolley waits in the Emergency Department (A&E)! Most conditions are those typically seen in Western countries with a number of issues particular to the indigenous population (the Aborigines) who have a life-expectancy in the mid-forties. Access to health services is difficult- many of the Aboriginal patients we met lived in remote communities in the outback, some having travelled up to four hours by air to reach hospital. History taking from such individuals was a fascinating experience, particularly social and dietary history- we hadn't been previously aware that witchety grubs were so high in protein or that a certain type of green ant will provide over the RDA of vitamin C!

It had been our ambition since medical school to work and travel in Australia. We found that a certain degree of courage is required to step off the traditional ladder of senior house officer and registrar rotations here in Northern Ireland. However, the experience gained- both personal and professional is invaluable.

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Ulster Med J 2007; **76 (2)** 107-108

Case Report

Diverticular Abscess Presenting as a Strangulated Inguinal Hernia: Case Report and review of the literature.

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Accepted 22 December 2006

ABSTRACT

Potentially life threatening diseases can mimic a groin hernia. We present an unusual case of diverticulitis with perforation and a resulting abscess presenting as a strangulated inguinal hernia. The features demonstrated were not due to strangulation of the contents of the hernia but rather pus tracking into the hernia sac from the peritoneal cavity. The patient underwent sigmoid resection and drainage of retroperitoneal and pericolonic abscesses. Radiological and laboratory studies augment in reaching a diagnosis. The differential diagnosis of inguinal swellings is discussed.

Key Words: Diverticulitis, diverticular perforation, diverticular abscess, inguinal hernia

INTRODUCTION

The association of complicated inguinal hernia and diverticulitis is rare[1]. Diverticulitis can present as left iliac fossa pain, rectal bleeding, fistulas, perforation, bowel obstruction and abscesses. Our patient presented with a diverticular perforation resulting in an abscess tracking into the inguinal canal and clinically masquerading as a strangulated inguinal hernia. The management warranted an exploratory laparotomy and drainage of pus.

CASE REPORT

An 86 year old woman presented to the emergency department with a long standing history of reducible left groin swelling which had become irreducible, painful and erythematous. She noted nausea, anorexia and increasing abdominal pain. She had no previous history of any surgery or trauma and was on warfarin for atrial fibrillation.

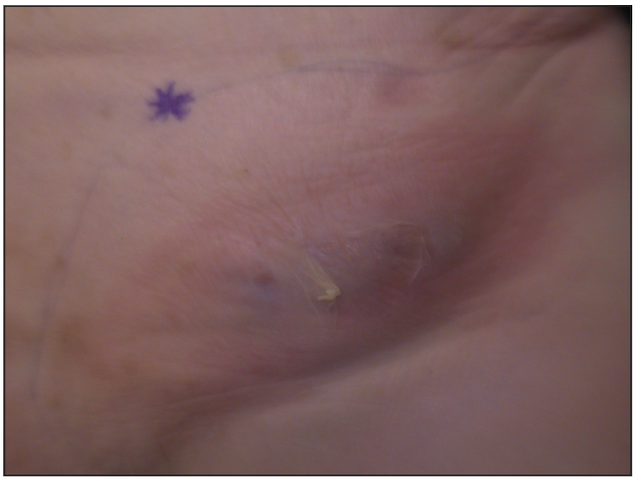

Fig 1. Erythematous and indurated left groin area

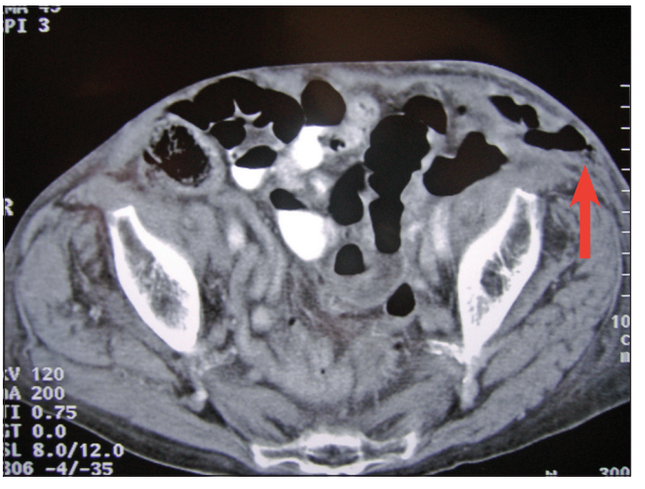

Fig 2. CT scan showing inflammatory changes with stranding of the subcutaneous fat in the left groin and a large bowel diverticulum

On admission, she had a tachycardia (pulse 102 beats/min) and a temperature of 37.5^{O}C. Blood pressure was 130/69 mmHg. On examination the abdomen was soft with a swelling in the left groin that was nonfluctuant, erythematous, indurated and tender (Fig 1). There was no peritonitis. Digital rectal examination revealed tenderness anteriorly. Blood laboratory values were unremarkable with the exception of a raised CRP of 137 mg/l (normal <10 mg/l)and leukocytosis (13,000/mm^3). No intra-abdominal free air was identified on an erect chest X-ray. CT scan (Fig 2) of the abdomen showed bilateral inguinal herniae, with marked inflammatory changes with stranding of the subcutaneous fat on the left side. The differential diagnosis included an irreducible small bowel hernia without obstruction and herniation of the sigmoid colon with associated diverticular abscess.

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A lower midline laparotomy was performed. Findings showed sigmoid diverticulitis complicated by perforation and a paracolonic abscess. The abscess tracked along the round ligament through the inguinal canal and into the subcutaneous space of the left lower quadrant, and was associated with a plug of indurated inflamed omentum into the inguinal canal. The pus was drained and after a wash out, a standard Hartmann's procedure was performed. The inguinal hernia was not repaired at this stage. The patient continued on IV antibiotics (cefuroxime and metronidazole). Pus cultures were positive for *K. pneumonia* and *B. fragilis.* The post-operative course was complicated with respiratory tract infection and a confusional state. Pathology showed a perforation in a sigmoid diverticulum with histological examination confirming diverticular disease with diverticulitis and peridiverticular abscess formation and a perforation. The patient responded to antibiotic treatment along with other standard chest management and had a slow recovery.

DISCUSSION

A wide variety of pathological processes and diseases present as atypical inguinal hernia. We present this unusual case of diverticulitis with perforation. The abscess formed tracked along the round ligament through the inguinal canal and presented clinically as a strangulated inguinal hernia. Appendicular abscesses[2] and appendicitis[3] have been reported on the right side in the hernial sac. The presence of an appendix within an inguinal hernia is not uncommon and is labelled an Amyand hernia[4].

Enlarged lymph nodes, lipomas or abscess of the psoas muscle[5] can present as an inguinal swelling. Patients with no evidence of bowel obstruction clinically and radiologically, presenting with a painful inguinal swelling have a risk of significant extra-abdominal and intra-abdominal disease processes. An infected hip prostheses abscess[6], a subcutaneous fungal abscess[7], pancreatic pseudocyst[8], leaking abdominal aortic aneurysm[9], and peritonitis[10] can present as an atypical inguinal hernia. In females leiomyoma of the round ligament[11], endometrial carcinoma[12], ovarian cysts[13] and Bartholins cysts[14] are reported. In males, torsion of an undescended testis[15], hydrocele and sarcoma of the spermatic cord[16,17] can present as an inguinal swelling. Sarcoma[18], lymphoma[19], and metastatic carcinoma from ovary, gastrointestinal tract, prostate and mesothelium[20] have been confused with the presentation of inguinal hernia. We could not find any reports of complicated diverticulitis to present as a strangulated hernia in patients with pre-existing inguinal hernia.

CONCLUSION

We report a case of perforated sigmoid diverticular abscess, on physical examination and radiographic evidence thought to be a strangulated inguinal hernia. Careful history taking, physical examination and a CT scan of the abdomen and pelvis should help reach a diagnosis, as it is important in planning the management especially in elderly patients with co-morbidities. Thus radiological evidence of incarceration, signs of bowel obstruction and local signs of inflammation should help direct the differential diagnosis. The proposed treatment remains surgery and drainage of pus and resection of the diseased bowel. The main conclusion is that an appearance of a tender red irreducible hernia may not always be due to strangulation of the contents but also due to inflammation of the hernia secondary to intra-abdominal pathology such as generalised peritonitis or abscess formation.

The authors have no conflict of interest.

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Ulster Med J 2007; **76 (2)** 109-111

Case Report

Primary Mediastinal Synovial Sarcoma

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Accepted 23 November 2006

ABSTRACT

Synovial sarcoma occurs predominantly in the soft tissues of the extremities, but is exceedingly rare in the mediastinum. It has overlapping histological and immunophenotypic features with other tumours in the differential diagnosis. We report a case of a patient who had an incidental finding of such a tumour. Because of the rarity of this tumour in the mediastinum, optimal therapy is unknown and the prognosis remains guarded.

Key Words: mediastinal tumour, sarcoma

INTRODUCTION

Synovial sarcoma is a malignant neoplasm predominantly affecting soft tissues of the extremities of adolescents and young adults[1]. It occurs in less than 10% of patients over 60 years old, in which this diagnosis is often not considered[2]. Its' occurrence as a primary tumour in the mediastinum is rare and was first described in the medical literature in the mid 1990's[3]. Herein, we report a further case of a mediastinal sarcoma that required a pneumonectomy to excise completely. We utilised positron emission tomography and computed tomography (PET-CT) to aid in the staging.

CASE HISTORY

A 59 year old male smoker presented to his local casualty department with non specific abdominal pain. During his workup, a chest X-ray was performed which revealed a large mass in the left thoracic cavity, adjacent to the mediastinum (Fig 1). Computed tomography (CT) scan revealed a 12.4cm mass within the left upper zone of the chest. It was closely related to the brachio-cephalic vein and aortic arch, but there was a clear plane of cleavage. However as the mass progressed inferiorly, it appeared to be in close contact with the main pulmonary artery and the left pulmonary artery.

A flexible bronchoscopy was subsequently performed which demonstrated extrinsic compression of the left upper lobe bronchus. However, bronchial washings were negative for malignant cells. To gain a tissue diagnosis, we performed a left anterior thoracotomy which also allowed us to examine the mediastinum for resectability. This revealed the tumour to be free from the visible lung but adherent to the mediastinum. Histopathological analysis found it to be a poorly differentiated sarcoma. PET-CT scan was performed to exclude any metastatic disease. This demonstrated an 18F-Fluorodeoxyglucose (18F-FDG) avid mass with a standardised uptake value (SUV) of 16 with no other foci that may represent metastatic disease (Fig 2).

At thoracotomy, the mass was seen arising from the left hilum, adherent to the left pulmonary artery, left superior pulmonary vein, phrenic nerve and adjacent pericardium and required an intrapericardial pneumonectomy and resection of the latter two structures to achieve complete resection. Histopathological analysis revealed a biphasic synovial sarcoma. The primary site for this tumour was uncertain as the tumour was located in the lateral portion of the mediastinum, close to both the pleura and pericardium. The patient made an uneventful recovery and at 18 months post-operative follow-up was disease free and his quality of life had returned to normal.

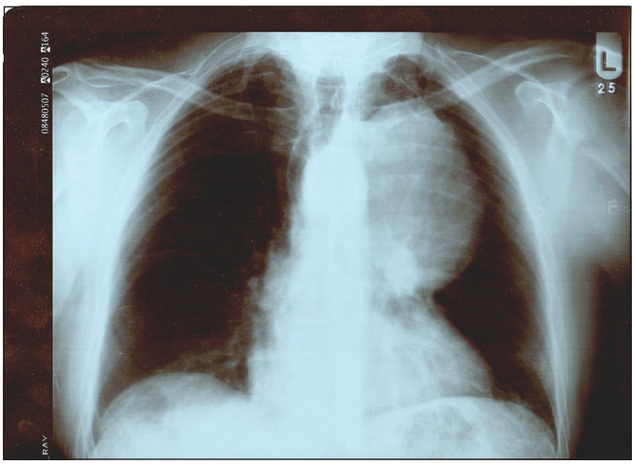

Fig 1. Chest radiograph demonstrating a mass abutting the mediastinum within the left hemithorax.

PATHOLOGY

The tumour measured 13 x 9 x 6cm and was adherent to the hilar surface of the left lung. Sectioning revealed a uniform consistency and it was sharply demarcated from the lung parenchyma. Histologically the tumour was composed of spindle cells and epithelioid cells (Fig 3) although the spindle cells were predominant. Numerous mitotic figures (more than 4 per 10 high power field) were seen and there were focal areas of necrosis. Immunohistochemistry demonstrated strong positivity for Vimentin, Cytokeratins, and focal positivity for EMA. Mesothelial markers (CK5/6, Calretinin) and

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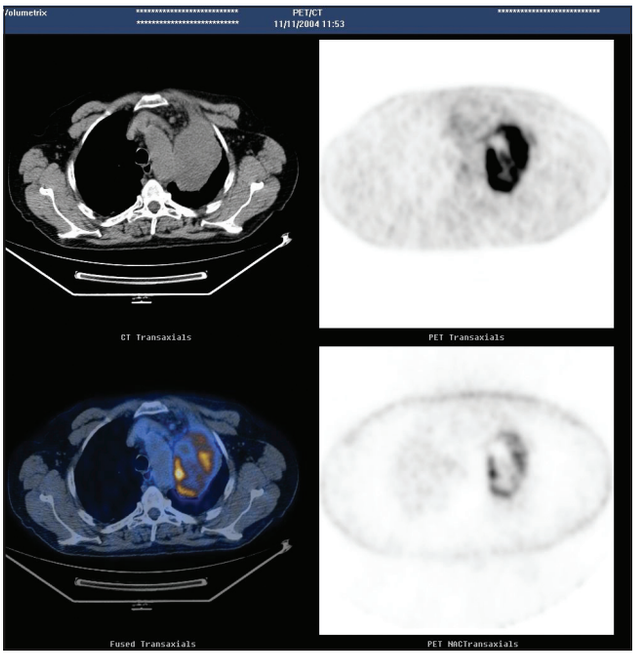

Fig 2. Transaxial image showing tumour with plane of cleavage from arch of aorta. Small volume of pre-vascular/ superior mediastinal nodes on CT are not FDG avid.

primary pulmonary tumour marker (TTF-1) were negative. These findings would be consistent with a biphasic synovial sarcoma.

DISCUSSION

The mediastinum is host to a vast array of both primary and metastatic neoplasms, the differential diagnosis of which is extensive and depends upon the mediastinal compartment involved, clinical history, presentation, and age of the patient. The case illustrated demonstrates the diagnostic difficulty encountered when the patient's age and tumour location are taken into account, as synovial sarcomas are rare mesenchymal neoplasms that primarily affect the deep soft tissues of the extremities and predominates in adolescents and young adults[1]. Although synovial sarcoma has been reported to metastasise to the mediastinum, its occurrence as a primary neoplasm in this location is rare and has only recently been recognised[3]. Patients have presented with dyspnoea[4], chest pain[1], cardiac tamponade[5] and as an incidental finding[1].

Classically, synovial sarcoma is a biphasic tumour composed of spindle shaped fibroblast-like cells and epithelioid cells, but the majority are actually monophasic spindle cell in type. A poorly differentiated variant composed of small round cells has also been described.

The differential diagnosis for thoracic synovial sarcomas includes mesothelioma, fibrosarcoma, malignant peripheral nerve sheath tumour, smooth muscle tumours, thymoma, blastoma, and sarcomatoid carcinoma[6]. However, the diagnosis can be difficult to achieve in an unusual location, overlapping histological and immunohistological features, or if a small sample size is present[6]. Immunohistochemistry can be very helpful. Synovial sarcomas are positive for Vimentin, EMA, Cytokeratins, CD99 (~60%) and S100 (~30%)[7]. The

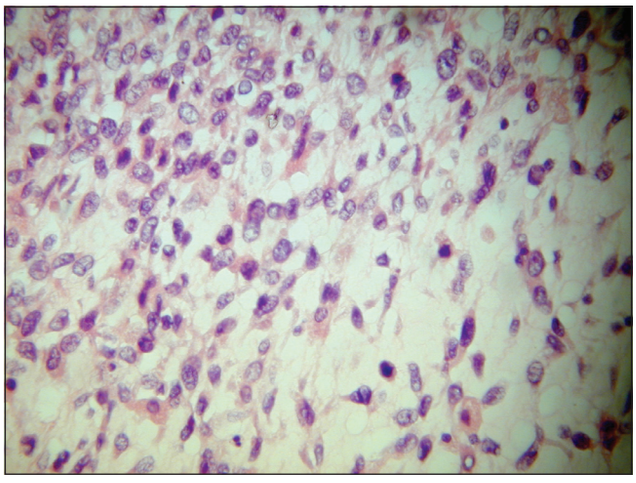

Fig 3. Histology demonstrating spindle and epithelioid cells.

availability of molecular genetic identification (fluorescent in situ hybridization or polymerase chain reaction) of the t(X;18) has improved diagnostic specificity as this translocation is found in over 90% of synovial sarcomas[1]. This translocation involves the SYT gene on chromosome 18 and either the SSX1 or SSX2 gene on the X chromosome[1].

Accurate staging of the disease is important for appropriate patient management and requires the evaluation of the primary tumour and assessment for distant disease. Magnetic resonance imaging (MRI) has been the traditional imaging tool for assessment of soft tissue masses, but more recently soft tissue sarcomas are well recognised as showing increased 18F-FDG uptake in Positron Emission Tomography (PET)[8].

PET-CT combines the strengths of two imaging modalities, exploiting the recognised greater sensitivity of CT in demonstration of small volume lung metastases (sensitivity, specificity 100%, 96.4% vs. 86.7%, 100%) and enhancing 18F-FDG PET imaging by allowing precise anatomical localisation of functional abnormalities[8]. MRI frequently struggles to differentiate the inflammatory and fibrotic changes which occur following surgery and adjuvant therapy from recurrent disease, whilst 18F-FDG PET allows accurate differentiation of locally recurrent disease from healing/post-surgical change[8]. Combined PET-CT imaging is likely to become the imaging modality of choice for follow-up of patients with these rare tumours.

Broad surgical resection is the cornerstone of therapy. Complete resection of the tumour was the overwhelming factor in determining survival in a review of primary mediastinal sarcomas[9]. Radiotherapy is recommended with positive margins[10]. The place for chemotherapy of this tumour is not well defined, and in none of the other case reports was preoperative chemotherapy given[5]. Combination of adriamycine and ifosfamide has been used as an adjuvant therapy and for recurrences[5]. Prognosis used to be poor with survival lasting two months[4], but with aggressive multimodal therapy, survival up to 14 years has been documented[5].

In summary, though mediastinal sarcoma is a rare entity, if aggressively treated with complete resection and or multimodal therapy with intensive follow-up, the survival of such patients can improve.

The authors have no conflict of interest.

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Letters

Cholethorax following Percutaneous Transhepatic Biliary Drainage

Editor,

We report the case of a 51 year old man who developed the unusual complication of a bilious pleural effusion, or 'Cholethorax' following percutaneous transhepatic biliary drainage.

Case Report: A 51 year old man with locally advanced gastric adenocarcinoma presented with painless jaundice one year following the completion of palliative chemotherapy. Laboratory investigations revealed a bilirubin level of 299 µmol/L with AST 117 U/L, ALT 134 U/L, GGT 2447 U/L, ALP 2159 U/L and an ultrasound of abdomen confirmed the presence of biliary obstruction. Percutaneous Transhepatic Cholangiography (PTC) was arranged as the presence of a gastric tumour precluded an approach using Endoscopic Retrograde Cholangiopancreatography (ERCP). The right hepatic duct was cannulated and contrast injected, demonstrating a complicated stricture of the common bile duct. An internal-external biliary drain was then inserted across this stricture to decompress the biliary tree and the position of the drain is shown in figure 1. Three days after the PTC our patient complained of severe right sided pleuritic chest pain and shortness of breath. A chest x-ray revealed right basal atelectasis and provisional diagnoses of a lower respiratory tract infection and possible pulmonary embolus were offered.

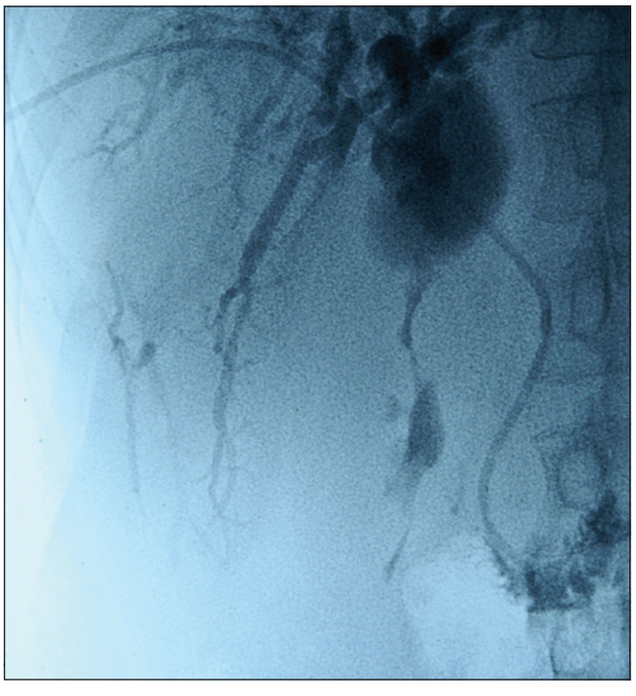

Fig 1.

Over the next 48 hours the patient became increasingly dyspnoeic, with signs of a right sided pleural effusion on examination, and so a repeat chest radiograph was carried out (fig 2). The output of bile into the drainage bag had dramatically decreased and the bilirubin level had risen further to 387 µmol/L. A pleural aspiration was performed which yielded dark brown pleural aspirate with a bilirubin level of 766 µmol/L (fig 3).

A diagnosis of a bilious pleural effusion (Cholethorax) as a complication of percutaneous transhepatic biliary drainage was made. The insertion of a 28F chest drain and rapid drainage of the bilious pleural fluid provided immediate relief of the shortness of breath and pleuritic chest pain. A further PTC was carried out urgently and three self-expanding metal stents were inserted across the complicated biliary stricture to provide adequate biliary drainage.

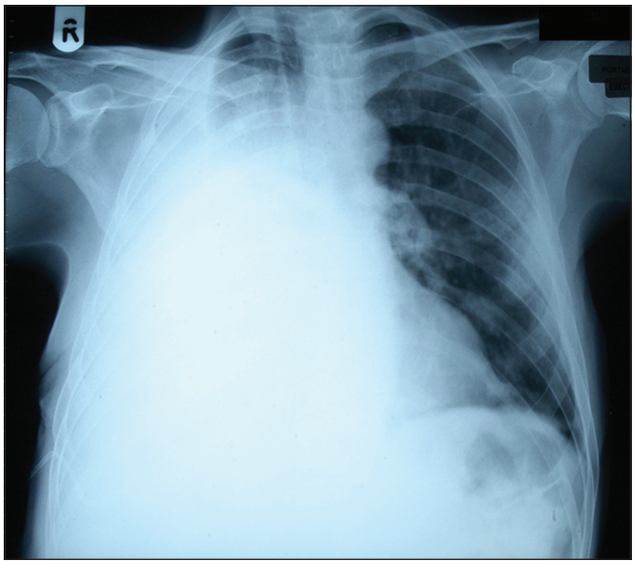

Fig 2.

Discussion: PTC and biliary drainage is used for the management of malignant biliary obstruction in cases where ERCP is inappropriate or has been unsuccessfully attempted. It involves the percutaneous cannulation of either hepatic duct followed by placement of a biliary drain to decompress the biliary tree and subsequent insertion of a stent during the initial procedure or a number of days later. During biliary cannulation it may be necessary to traverse the pleural cavity to gain access to either hepatic duct. An internal-external biliary drain is inserted consisting of a pig tail drain with a hole at the tip to allow the bile to exit into the duodenum and a number of side-holes along the distal length. These side-holes should be placed inside the common bile duct (Fig 1) to allow entry of the bile which then drains internally into the duodenum or externally into a drainage bag.

In our patient's case the drainage catheter became dislodged with the tip remaining in the right hepatic duct while the side-holes formed a direct communication with the pleural cavity. This occurred due to the trans-pleural approach taken during the PTC and as a result bile rapidly drained into the pleural cavity causing a 'Cholethorax'. Bile is an intense chemoirritant and so extensive pleural inflammation was established which also allowed the chest drain to be removed relatively quickly as it essentially caused a pleurodesis

Fig 3.

to occur. Bile also provides a good medium for bacterial growth and so infective sequelae often occur in the setting of a cholethorax.

Biliary pleural fistulas and the formation of bilious pleural effusions are known complications of hepatic trauma[1,2], parasitic liver disease[3] and development of a subphrenic abscess in the setting of biliary obstruction. Iatrogenic causes include biliary stent migration[4], radio-frequency ablation[5] and following cholecystectomy[6] and liver biopsy[7] However, it is the increasing use of percutaneous biliary drainage which has lead to the greatest number of cases.[8-10] For a Cholethorax to arise disruption of the pleural space needs to have occurred and this may not necessarily be obvious during the procedure. Rapid thoracentesis, correction of the cause of the fistula, adequate analgesia and the treatment of infective sequelae are essential in the management of this group of patients.

The authors have no conflict of interest

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Diffuse sclerosing variant of papillary thyroid carcinoma – a rare cause of goitre in a young patient

Editor,

Papillary thyroid carcinoma is the most common thyroid malignancy. We report a case of a rare variant - diffuse sclerosing papillary thyroid carcinoma (DSPC).

Case History: An 18 year old girl presented with a smooth symmetrical goitre. She was clinically euthyroid and had no palpable cervical lymph nodes. Thyroid function tests and anti-thyroid peroxidase level were normal. Ultrasound scan of thyroid showed marked nodular enlargement of the entire gland in keeping with a multinodular goitre. A hypoechoic 1cm nodule was identified at the right lobe which was found to be 'cold' on radio-isotope scanning. A fine needle aspiration of this 'cold' nodule was reported as papillary carcinoma.

She was booked for total thyroidectomy. At surgery she had an enlarged thyroid, with a gross appearance in keeping with a thyroiditis or lymphoma. Frozen section confirmed papillary carcinoma. The gland was hard and gritty. Several local lymph nodes were also excised. Post-operative recovery was uneventful.

Sectioning revealed a diffusely firm, white, gritty gland (fig 1). Histopathology showed this to be the rare diffuse sclerosing

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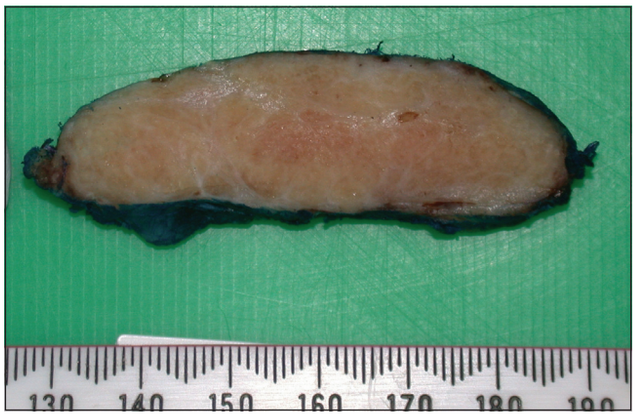

Fig 1. Sclerotic hemisection of thyroid lobe

variant of papillary thyroid carcinoma. Scattered islands of tumour tissue, squamous metaplasia, stromal sclerosis, heavy lymphoplastic infiltrate and abundant psammoma bodies were found diffusely throughout both lobes and through the capsule (fig 2). All excised lymph nodes contained metastatic carcinoma.

She underwent radioablative therapy followed by replacement levothyroxine. There was no residual uptake on subsequent 123-Iodine isotope scanning.

Discussion: First described in 1985, diffuse sclerosing papillary carcinoma of the thyroid (DSPC) is a rare variant malignancy, recently reported to account for 0.8% of papillary thyroid carcinomas.[1,2] Patients present with a diffuse goitre and are mostly clinically euthyroid, but can also be hypothyroid or hyperthyroid. It occurs most frequently in young females and may be mistaken clinically for benign disease particularly thyroiditis.[3-5] Most patients have lymph node metastases at the time of diagnosis and lung metastases are common.[3] Cerebral metastases have also been reported.[6]

The presence of several pathological characteristics is diagnostic: diffuse firm enlargement of the thyroid gland, scattered islands of papillary carcinoma, extensive lymphatic permeation and lymphocytic infiltration, squamous

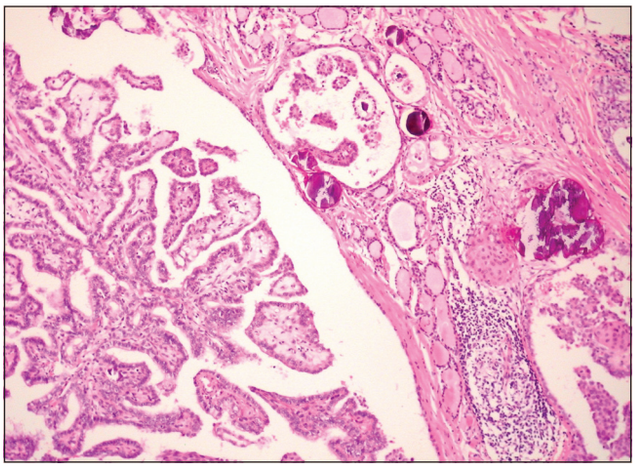

Fig 2. Papillary carcinoma, with psammoma bodies and squamous metaplasia. Sclerosis and chronic inflammation, to right of field. (x 200)

metaplasia, sclerosis and numerous psammoma bodies.[7] Detection of abundant psammoma bodies on ultrasonography may provide pre-operative evidence of DSPC.[4] This could facilitate improved surgical planning for a technically challenging thyroidectomy.

Early studies suggested that DSPC had a poorer prognosis than classical papillary carcinoma due to its aggressive nature with frequent lymph node and distant metastases at the time of presentation. It had also been reported that eradication required a more aggressive therapeutic approach.[3] However, more recent studies suggest that DSPC patients have a similar prognosis and that the treatment should be that for classical papillary thyroid carcinoma i.e. radical surgery, radio-iodine ablation and/or external radiotherapy.[2,8]

There are potential pitfalls which may delay the diagnosis of DSPC. In this case, the clinical presentation, biochemical, serological and initial radiological findings were all indicative of benign pathology. FNA indicated malignancy leading to surgery demonstrating its importance in the diagnosis of DSPC. As metastases are frequently present it is therefore important to consider this rare malignancy when investigating a goitre in a young patient.

The authors have no conflict of interest.

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A case of primary lung malignancy presenting as pericardial effusion with associated localised Epstein-Barr virus infection or persistence.

Editor,

Acute pericarditis and pericardial effusion has many causes including infections, malignancy, collagen vascular disease, autoimmune diseases, uraemia, myocardial infarction, trauma, surgery, medications and hypothyroidism. We report a rare case in which pericardial fluid was positive for both malignant adenocarcinoma cells and PCR positive for Epstein-Barr virus.

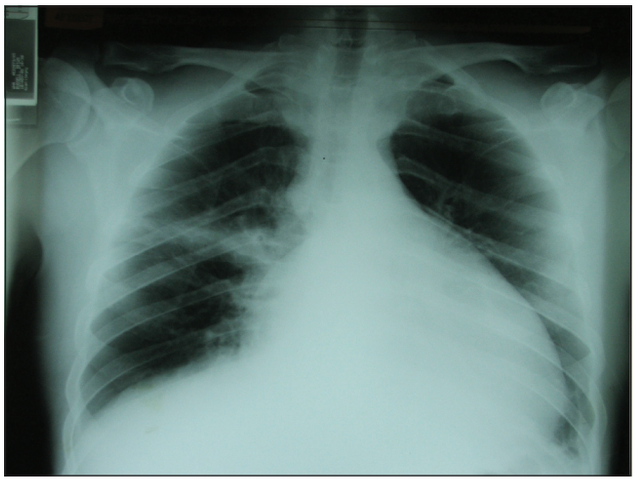

Fig 1.

Case report: We report the case of 44 year old male mechanical engineer admitted with two weeks history of lethargy, malaise, vomiting, breathlessness and two episodes of syncope. There was no previous history of cardiorespiratory disease and he was a non smoker. On examination he was tachycardic, hypotensive and had elevated jugular venous pressure. On auscultation heart sounds were muffled with no murmur or pericardial rub heard. Chest X-ray showed cardiomegaly, (Fig 1), whilst ECG showed sinus tachycardia with no significant ST or T wave changes. A transthoracic echocardiogram showed large pericardial effusion with right atrial and ventricular collapse (Fig 2). These features suggest he was in cardiac tamponade. A pigtail catheter was inserted and 1550ml of frank haemorrhagic fluid was drained subxiphoidally.

Pericardial fluid was analysed as per guidelines for diagnosis and management of pericardial diseases of European Society of cardiology. Pericardial fluid was positive for Epstein-Barr virus on polymerase chain reaction while polymerase chain reaction for Epstein-Barr virus from leucocytes in circulation and IgM antibodies for Epstein-Barr virus antigens were negative, consistent with localised pericardial presence of Epstein-Barr virus[1].

Further study on pericardial fluid revealed malignant epithelial cells with morphology suggestive of adenocarcinoma. Immunohistocytochemistry was positive for CK-7, CEA, TTF1, EMA, and weakly positive for CKS, CK-6, and Ber EP4 and negative for HMBE1, PSA, HMB 45 and CK-20. In summary TTF-1 and CK-7 being positive was highly specific

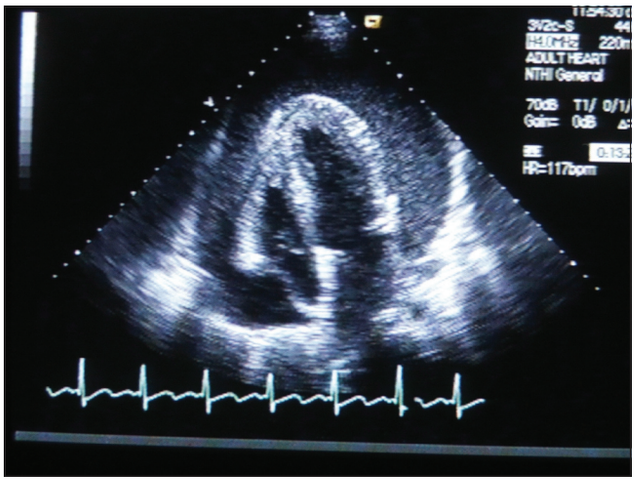

Fig 2.

of lung primary[2]. TTF-1 is a lineage marker for tumour arising from peripheral airway or alveolar epithelium and has no prognostic relevance[3].

Chest X-ray after therapeutic drainage of pericardial fluid showed two opacities in right middle and lower zones. A computerised tomographic scan of the chest and abdomen revealed marked right hilar lymphadenopathy and a further nodal mass just below the right carina. A 1.7cm speculated mass was seen in the right upper lobe adjacent to the horizontal fissure with a little fluid in the fissure and surrounding consolidation. There were bilateral pleural effusions and further pleural-based lesion in the right lower lobe. Based on clinical and radiological findings the tumour was staged T1 N1 M1. An incidental finding of the presence of pulmonary thromboembolic disease bilaterally extending into 3rd pulmonary division was also seen and hence the patient was started on a therapeutic dose of low molecular weight heparin. The patient was referred to oncology for further treatment

Discussion: Pericardial inflammation and effusion due to Epstein-Barr virus infection is rarely reported. There are a few case reports of Epstein-Barr virus causing adenocarcinoma lung especially in Asian populations[4]. Malignant pericardial effusion and localised presence of Epstein-Barr virus can be explained either by malignancy secondary to Epstein-Barr virus infection[5,6] or due to co-existing infection, thus making this a very rare case. It has been proposed that viral load estimation from malignant cell and non-malignant cell would have proved the causative role of Epstein-Barr virus[4]. As identification of causative role of Epstein-Barr virus has no implication in treatment or prognosis tissue biopsy and viral load estimation was not attempted.

The authors have no conflict of interest

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Merkel cell carcinoma of the cheek: Diagnosis in an elderly woman

Editor,

Merkel cell carcinoma (MCC) is an uncommon primary neuroendocrine skin tumour. It is commonly seen in the elderly, on the sun exposed areas which can mimic benign or less malignant skin tumors. We report a case of Merkel cell carcinoma of cheek in an elderly woman which was initially treated as a boil. This highlights the importance of considering this tumour in the differential diagnosis of head and neck skin lesions as it is fatal if not diagnosed and treated early.

Case History: A 93 year old woman was referred, with a left cheek swelling, progressively increasing in size over a period of two to three months. An initial clinical diagnosis of boil necessitated the administration of two courses of antibiotics by her GP, before attending the general surgical clinic. On examination a single, firm, non-tender, purple pink swelling with superficial central ulceration was noted on the left cheek, measuring about 4x4cm size with well-defined margins and normal surrounding skin (Figure). The histology of a biopsy from an ulcer edge was consistent with Merkel cell carcinoma. Immunohistochemistry confirmed the diagnosis. Unfortunately this patient died two months after the diagosis.

Discussion: High index of suspicion is needed to diagnose some of the rare skin lesions. Merkel cell carcinoma of the skin is one of those uncommon, aggressive, neuroendocrine, cutaneous tumour most commonly found in head and neck region. It is a rare neuroendocrine tumour of the skin accounting for less than 1% of cutaneous malignancies, usually presents as red, purple or violaceous firm painless nodule or plaque. It is often mistaken for more common skin tumours because of its rarity.

Diagnosis can be made with histology alone and electron microscopy is encouraged as histologically it can resemble many other neoplastic processes. Immunohistochemistry is required for the definitive diagnosis of Merkel cell carcinoma. In our case malignant cells stained positive for CAM 5.2, CK-20 and chromogranin and negative for S100 and LCA (leukocyte common antigen).

Surgical treatment is the corner stone of the treatment. Wide local excision with a clearance margin of 3-5 cm is commonly recommended[1-4]. It is widely accepted that patients with regional node metastasis should undergo lymph node dissection. Adjuvant radiation therapy is generally recommended for primary site and lymph node basin in stage I and II disease. It may also be used as the only treatment for patients who are not fit for any surgical resection. Chemotherapy is generally reserved for the stage III disease. And no chemotherapeutic protocol has been able to achieve a significant increase in survival rate[3]

Conclusion: Some distinctive features of presentation are

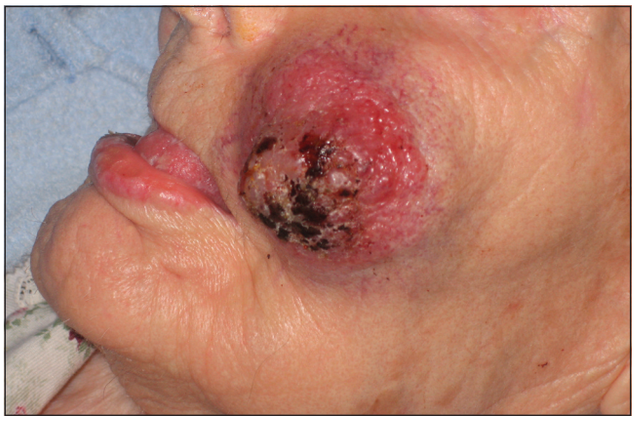

Fig 1.

red, violaceous, intradermal nodule in sun exposed areas. High index of suspicion is needed at first presentation as it frequently proves lethal despite various multimodal therapies if not diagnosed early. It is clear from the available data that early diagnosis and wide local excision will prolong the survival.

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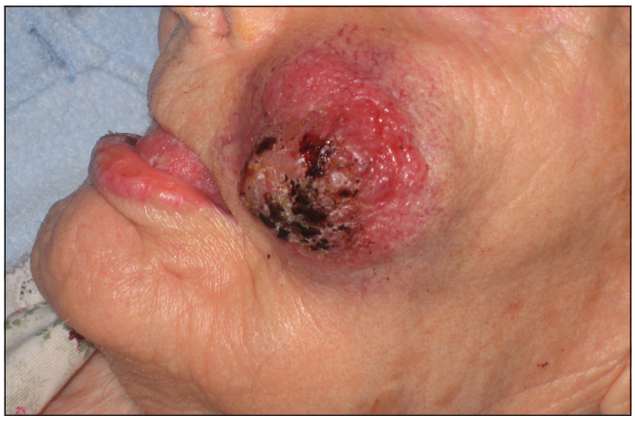

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An Unusual Cause Of Pyrexia Of Unknown Origin In An 81 Year Old Lady

Editor,

We report a rare cause of pyrexia of unknown origin. An 81-year old woman presented to hospital with left hip pain following a fall. On admission, there was reduced range of movement of the left hip but no other abnormal findings. Initial investigations were normal and she was managed with analgesia and low dose enoxaparin. She was a retired missionary nurse who had worked in Africa for most of her life. Her past medical history included episodes of malaria and schistosomiasis.

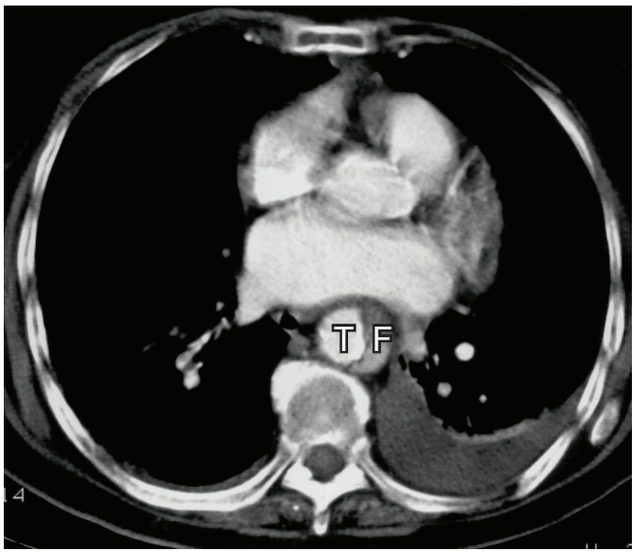
Five days after admission she developed a temperature of 38^0C. Clinical examination was normal except for bruising over her left hip. Haemoglobin fell from 12g/dl on admission to 7g /dl, although there was no overt blood loss and she remained haemodynamically stable. It was suspected that she had bled at the site of injury, however an isotope bone scan excluded a hip fracture. Her C-reactive protein (CRP) was elevated at 320 mg/l (normal <10 mg/l) and, as dipstick urinalysis showed blood and protein, she was treated for a possible urinary tract infection.

Over the ensuing weeks unremitting low-grade pyrexia continued. Other than lethargy and anorexia there were no specific symptoms. Repeated physical examinations were normal. There was no growth on repeated blood and urine cultures. A search for acid-fast bacilli was negative. Serological tests for atypical bacteria, viruses and autoimmune causes of her pyrexia were negative. Multiple blood films for malarial parasites were negative. Chest radiographs, an abdominal ultrasound scan and an abdominal computed tomography (CT) scan were unremarkable. No vegetations were identified on a transthoracic echocardiogram. A transoesophageal echocardiogram was not performed at this stage as it was thought unlikely that the patient would tolerate the procedure due to agitation.

An empirical course of intravenous antibiotics followed by a trial of anti-tuberculosis therapy were administered without a significant response.

After 40 days of pyrexia we remained concerned that infective endocarditis had not definitively been excluded. A transoesophageal echocardiogram was performed. This demonstrated a previously unsuspected thoracic aortic dissection that was delineated further on a CT scan of chest (Figure). It arose at the level of an aberrant right subclavian artery and terminated at the level of the coeliac axis. It was not suitable for surgical intervention and the patient was managed with careful blood pressure control (systolic blood pressure <120 mmHg). She spontaneously defervesced after 52 days of pyrexia. Her CRP normalised and following a period of rehabilitation she returned home.

Discussion: Aortic dissection usually presents as an emergency, most often associated with tearing chest pain[1]. However approximately 15% can remain almost clinically silent[2]. Although one third of patients with aortic dissection may experience a transient increase in temperature[1], prolonged pyrexia as the dominant presenting clinical sign is extremely rare[3]. The pyrexia is thought to result from tissue destruction in the aortic wall and the release of endogenous pyrogens in



Computerised tomography of chest demonstrating thoracic aortic aneurysm (T= true lumen, F=false lumen)

the aortic haematoma[4]. The febrile episode may last anywhere between five and eleven weeks and is often accompanied with a rise in inflammatory markers and a normochromic, normocytic anaemia[5].

In this case the unusual presentation of the dissection along with the confounding factor of previous residence in Africa delayed the diagnosis. This reminds physicians investigating PUO to remain open-minded as not all conditions present themselves as classically as the textbooks would have us believe.

The authors have no conflict of interest.

*Kim Sinnamon[1], *Registrar*

M Ivan Wiggam[2], *Consultant*

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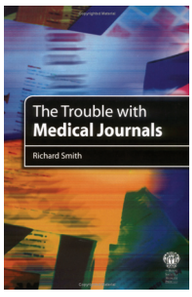
Book Reviews



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The only trouble with Richard Smith, for 13 years Editor of the British Medical Journal, is that he writes well but tends to repeat himself. Editors, and ex-editors, are a small group in the medical world, but we like to think we have been influential. This book is a series of stories of Richard Smith's interaction with prospective authors, medical researchers of all sorts, the authorities of the BMA and the public at large. In between these well told stories are his thoughts and concerns for the future of medical journals. After leaving the BMJ he went off to Venice, sat in a palazzo and unburdened himself of all his editorial worries.

In his own words "medical journals have many problems and need reform: over-influenced by the pharmaceutical industry, too fond of the mass media, neglectful of patients. Peer review, the process at the heart of journals and all of science is deeply flawed. The scientific community has not responded adequately to the problem of fraud. And the whole business of medical journals is corrupt because owners are making money from restricting access to important research, most of it funded by public money".

This is heady stuff, but with his racy style and continuous name dropping, any of us who have read medical journals over the years can feel at ease with his thoughts. He ranges over the broad field of medical and scientific publishing, not restricted to the BMJ. We all have our own views on the MMR vaccine crisis, or the tobacco industry, or cancer research, and he is not afraid to be outspoken about these and many other topics that interact with medical journals. He keeps coming back to the substantial profits made by the publishers, who do not have to pay the authors, nor the hapless peer reviewer, and contribute no added value to the educational process. He would like all medical knowledge to be freely distributed throughout the world. Some of it is, but the process is still complex.

The Ulster Medical Journal is well down the list in terms of impact factor, and does not envisage lawsuits or high financial deals – we even have difficulty in getting any support at all from "big pharma". But we do fulfil a purpose – local, academic, informative, and above all to provide a platform for those of us who live and practice medicine in Ulster, to say what we are doing in a formal and ethical manner. The journal is the biggest expense to the Ulster Medical Society, and cannot be said to make a profit. But I think it will go on coming through our letter boxes two, or even three times a year, in well printed paper format, with the familiar blue cover, for a long time in the future. The e-mail and the internet may facilitate urgent matters and take the place of the public meeting and the telephone, but we still like to read. Maybe the local journal will survive when the big players succumb to globalization.

Another way of reacting to this well informed diatribe is to join the opposition, become a medical publisher, and make your fortune! Brendan Bracken, a well known pre-war politician with Irish roots and Churchillian connections had arrived in London penniless after the first world war, but managed to buy the now defunct "Practitioner" for £50,000 in 1928, which became the foundation of his financial empire, culminating in the ownership of the Financial Times and a safe seat in Westminster.

This book is a good read: you can take it lightly, in short chapters, but at the end you will be better informed as well as entertained, both as a reader and as a potential author. You may even decide to join the iconoclasts and cancel all your journal subscriptions!

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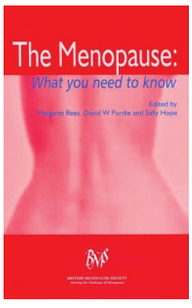


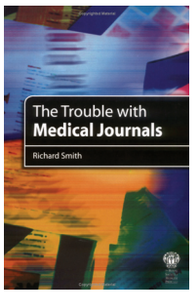
The Menopause : What you Need to Know. Eds: Margaret Rees, David W Purdie & Sally Hope. Royal Society of Medicine Press, London. June 2006. 176pp. £10.95. ISBN: 1853156728.

The British Menopause Society published the 4th Edition of its excellent handbook for health professionals, Management of the Menopause in January 2006. This companion volume has been revised and updated and is aimed at "the people who actively have to face the menopause and its consequences", namely the patients. This small volume, of just over 100 pages, covers a wide range of issues relating to women's health prior to, during, and after the menopause. The information is unbiased, non promotional and up-to-date. The recent publications from numerous studies on hormone replacement use, and the reaction to these by the media, have generated confusion, if not even hysteria in both the public and some members of the medical profession. The chapter on benefits, risks and controversies goes a long way to addressing the present state of knowledge in the most simple terms. There is a useful chapter on alternative and complementary therapies, which not only discusses the advantages but also the dangers of some of the so-called and commonly used herbal remedies.

Where possible medical language has been avoided, but detailed definitions of words used by health professionals are given. So often a book of this nature is patronizing, but not this one. Doctors can not only recommend this small book, but they should be aware that women who read it will have gained a great deal of knowledge, and this will result in searching questions during a consultation. There are useful sources of information at the end of each chapter, including journal, book and website references; the latter, if sourced, may make an interview even more taxing!

William Thompson

Book Reviews



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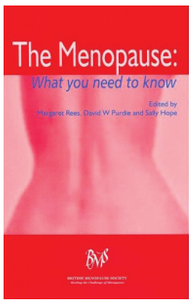

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William Thompson

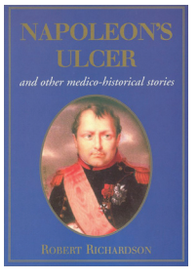
Get Through Accident and Emergency Medicine. Amy Herlihy. Royal Society of Medicine Press, London. October 2006. 140pp. £22.50. ISBN: 1853156949

Most MRCP and MRCS Part 1 candidates would be advised to invest in a Sainsbury's shopping trolley if they decide to venture to their local university bookshop in pursuit of a relevant MCQs textbook. The shelves of these stores creak from the burden of the wide selection of texts. The unfortunate MCEM / MRCS A&E candidate will be left with growing anxiety and the knowledge that there are very few suitable MCQs textbooks. "Get Through" aims to bridge this gap and help you prepare for your exams.

The book covers a wide range of topics, from paediatrics to toxicology, and the book's strength lies in its relevance to day to day practice. The various questions address many clinical scenarios we come across on run-of-the-mill, shop-floor work. The book's stated main focus is revision for Part 1 examinations, however the MCEM part 1 syllabus is heavily based in the realms of anatomy, patho-physiology, microbiology, biochemistry, etc., with only 5 out of a possible 50 questions relating to clinical medicine. The book does try to address this imbalance with a chapter on anatomy, however MCEM candidates will probably find limited relevance to the content of their Part 1 exam.

The book is ideally suited to candidates preparing for 2nd Part exams or MRCS A&E MCQ, where there is a greater emphasis on clinical topics. It certainly would be a useful revision tool to highlight areas for further study. One area of concern that may confuse and will certainly frustrate candidates is the number of incorrect answers in the book. Hopefully this is a problem that will be addressed on further prints.

Paul D Faulkner & Ruth Spedding



Napoleon's Ulcer (and other medico-historical stories). Robert Richardson. Quiller Publishing, London. October 2006. 192pp. £14.95. ISBN: 1904057969

I was lured into reviewing this book under false pretences. All that was mentioned in the request was the most famous gastric ulcer in history – surely a gastroenterologist would be the ideal candidate to review such a book? With no more information than the first line of the title, I naively agreed. The nicely presented package arrived resplendent with a glossy cover endowed with a portrait of the great man and embossed with the headline title in bold gold lettering. Only then did the first question simmer in my sub-conscious: Why the sub-title '*and other medico-historical stories*'? The reputable book editor of this esteemed journal mentioned nothing other than gastric ulceration!

Let us begin with the ulcer, which takes up the introductory chapters of the book. I confess that I had limited knowledge of Napoleon's predicament prior to this review and I have emerged much the wiser (or at least better informed). However, not for the last time in this review process, I found myself confused. Was I reading a detective story requiring a solution? Or was it being presented as a clinical case history for medical analysis? Or was it a fantasy based on speculation? I struggled to know which role the author wanted it to fulfil. What I did enjoy in these early chapters was the information conveyed about the state of knowledge at that time regarding ulcer disease. They did not have to worry about breath tests and helicobacter pylori.

Just as I was engaging with Napoleon and finding myself speculating about whether or not he had H. pylori, Napoleon is gone. Not just dead and dissected but by page 41 of 226, his presence left this scene of time; or at the very least the pages of this book. And guess what comes next?

One turns over the page anticipating more on Napoleon or perhaps his doctor (who is to feature later), or some treatise on other famous ulcers or anything but the menopause. The *menopause*? Yet that is the non-sequitur that "sequiturs". Hence the second question I have with this book: What is its purpose? How does it hang together? What is the common thread? Where are we going? (Four questions, I know…)

But back to the story of the menopause. Here we find such useful comments from history as "woman is a pair of ovaries with a human attached" (Virchow) and Galen's view that menses were simply the natural blood-letting necessitated by overeating. Here we begin to see the virtue of the book. It is a book full of quotes and anecdotes to be used in appropriate circumstances, dropped into the conversation to impress the dinner party, thrown out in lectures to medical students to maintain interest.

If you were looking for an unusual angle on your chosen field of medical expertise, the chances are you will find it in this book. Provided of course your chosen field is one of the eclectic topics covered within it. Having said that, it is hard to envisage the use of either of the above quotations in any circumstance that would not result in a lynching of the utterer.

However the fact that Roman sailors only cut their hair during a storm and that French physiologists injected themselves with canine testicular extract in the pursuit of eternal youth must have value and interest to some discerning readers.

For an enjoyable historical read, the chapter on Larrey is the most enlightening. In this chapter a historical tale is told that engages the reader and leaves him admiring a multi-talented but flawed man. That is a good "medico-historical" chapter that fulfils the promise of the book's subtitle. However that chapter only highlights my third question: Is this book really "medico-historical" as it claims? Chapters such as those on blood have more to do with mythology than history. Other chapters on hair, death and transplantation lean towards psycho-analysis and philosophy. Mind you, I am still not sure about the castration complex and its link with hair.

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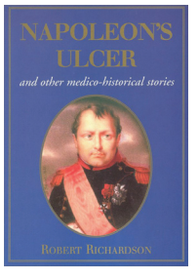

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consciousness: What is the purpose of this book? What is it trying to be?

Only when we come to the last page of the book do we learn the secret. The page that solves the riddle comes after the book has ended, after the index, and at the end of a series of pages advertising books by the same author. Finally, an answer to the purpose of the book; finally a link that binds the apparently un-associated! The solution is a novel previously written by the author; a novel that spans all the epochs referred to in this tome; a novel in which the hero visits the historical characters of this book. This current book is the back-text of that novel. Perhaps next time I will be asked to review the novel.

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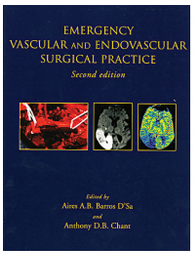
Emergency Vascular and Endovascular Surgical Practice, 2nd Ed. Aires A.B. Barros D'Sa, Anthony D.B. Chant. Hodder Arnold, London. October 2005. 592pp. £155. ISBN: 0340810122



I congratulate Barros D'Sa and Chant in producing an excellent book which brings together the pathophysiological, administrative, therapeutic, radiological and surgical aspects involved in the management of a wide spectrum of emergency conditions, that may be encountered by all physicians with an interest in vascular and related specialties. The book is ingeniously divided into subsections, with each theme elegantly presented.

It provides some basic facts in the provision of emergency vascular services and treatment outcomes in the UK, USA and Scandinavia. It also supplies the reader with knowledge on the pathophysiology of vascular conditions and the complications that may develop in the management of some of these conditions. The risk assessment and the medico-legal minefield involved in the management of these patients are also discussed.

The section on Acute Cerebrovascular Syndromes gives a good synopsis on acute ischaemic strokes and their management, in particular the timing and role of surgical intervention, a subject upon which many vascular surgeons are still hesitant. This section is followed by another well put together section on acute lower limb ischaemia and diabetic feet. This gives an excellent overview on surgical and endovascular options and the possible problems that may be associated with intervention. However, chapter 18, "Acute Ischaemia Secondary to Occult Prosthetic Graft Infection", is just slightly difficult to read because of the many complex algorithms. Nonetheless, it covers an arduous subject commendably. The rest of the book embraces magnificently catastrophes, injuries and emergencies of the arteries and veins in the thorax, abdomen and peripheries. It provides the reader with wealth of information on the aetiology, pathophysiology and the various medical and conventional surgical options necessary for dealing with these conditions.

I have no doubt this book will be a valuable asset in any private or institutional library. The authors have managed to put together a book on the diverse emergency vascular conditions encountered by vascular clinicians, including some rare conditions which, although not typically seen in Northern Ireland, nonetheless have presented at our doorsteps, and will no doubt challenge our capabilities and resources at some stage in our careers. This is definitely a very good reference and guide book for vascular surgeons at all levels.

Chee Soong

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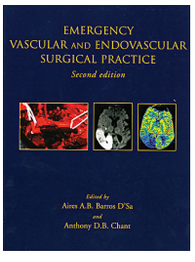
Brian Johnston

Emergency Vascular and Endovascular Surgical Practice, 2nd Ed. Aires A.B. Barros D'Sa, Anthony D.B. Chant. Hodder Arnold, London. October 2005. 592pp. £155. ISBN: 0340810122



I congratulate Barros D'Sa and Chant in producing an excellent book which brings together the pathophysiological, administrative, therapeutic, radiological and surgical aspects involved in the management of a wide spectrum of emergency conditions, that may be encountered by all physicians with an interest in vascular and related specialties. The book is ingeniously divided into subsections, with each theme elegantly presented.

It provides some basic facts in the provision of emergency vascular services and treatment outcomes in the UK, USA and Scandinavia. It also supplies the reader with knowledge on the pathophysiology of vascular conditions and the complications that may develop in the management of some of these conditions. The risk assessment and the medico-legal minefield involved in the management of these patients are also discussed.

The section on Acute Cerebrovascular Syndromes gives a good synopsis on acute ischaemic strokes and their management, in particular the timing and role of surgical intervention, a subject upon which many vascular surgeons are still hesitant. This section is followed by another well put together section on acute lower limb ischaemia and diabetic feet. This gives an excellent overview on surgical and endovascular options and the possible problems that may be associated with intervention. However, chapter 18, "Acute Ischaemia Secondary to Occult Prosthetic Graft Infection", is just slightly difficult to read because of the many complex algorithms. Nonetheless, it covers an arduous subject commendably. The rest of the book embraces magnificently catastrophes, injuries and emergencies of the arteries and veins in the thorax, abdomen and peripheries. It provides the reader with wealth of information on the aetiology, pathophysiology and the various medical and conventional surgical options necessary for dealing with these conditions.

I have no doubt this book will be a valuable asset in any private or institutional library. The authors have managed to put together a book on the diverse emergency vascular conditions encountered by vascular clinicians, including some rare conditions which, although not typically seen in Northern Ireland, nonetheless have presented at our doorsteps, and will no doubt challenge our capabilities and resources at some stage in our careers. This is definitely a very good reference and guide book for vascular surgeons at all levels.

Chee Soong