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Editorial

Mark My Words

I have previously espoused this view, but it seems to your editor that medical specialties can be viewed using the lexicon of Physics. At one end of the spectrum we find Relativity (The world of the very large - like my own specialty, Radiology) and at the other end, the world of the very small: Quantum Mechanics. In this edition, we consider as our review article, another of the 'quantum' subjects: Immunology. David Edgar is to be congratulated on producing such a well-written and lucid article, on what can be a vastly complicated and perplexing subject. His review on immunology gives the reader a synopsis of current thinking on this central subject.

Principal aspirations of a general journal, like ours, should be education and diversity. In this edition we consider subjects as varied as Sclerosing Cholangitis Overlap Syndrome; visual assessment in children with neurological disorders; the impact of the Emergency Nurse Practitioner; the history of Tuberculosis and it's tangential orbit with one of Ireland's greatest literary dynasties. Also, editor emeritus, Patrick Morrison, works the neat trick of seamlessly melding ancient and modern mythology with the unveiling of genetics' latest contribution to our increased understanding of gigantism.

Another innovation within this edition is 'Grand Rounds'. The concept of Grand Rounds is anything but new, of course. What I envisage for it is a portal or forum aimed directly at non-specialists, doctors in training, and medical students. This edition's inaugural paper is, 'The optimal management of Peripheral Vascular Disease for the non-specialist' by Mark O'Donnell et al. I would hope that this feature speaks directly and cogently both to those approaching examinations, as well as those in established clinical practice.

I am pleased to say that, thanks to the hard work of our tireless sub-editor, Mary Crickard, the experiment with social networking continues and I hope you will follow us on Facebook and Twitter (UMJ_Belfast). It is perhaps worth restating that all of our previous editions are available, free, on line via the Ulster Medical Society, (www.ums.ac.uk/journal). I would be delighted, as always, to receive your thoughts and ideas for these and future directions (editor@umj.ac.uk).

It gives one perspective and is a somewhat sobering thought to appreciate that it is the privilege of the Journal editors to have an obituary within these pages. I knew him as Dr Gibson for many years, and as Mark, latterly. One day, we were having a conversation about albatrosses, as one did with Mark, and I was blathering on about the Rime of the Ancient Mariner. I had, and loved, an audio version from the *Nation's Favourite Poems*, read by John Nettles. Lovely, murmured Mark. By any chance, had I heard the Richard Burton version? I hadn't? Ah. The following day, there it was, sitting unobtrusively on my desk. The Welsh wizard was as magnificent as had been advertised. Mark was a very courageous man who bore his illness and met his fate with grace and courage. Among his many attributes, he had a profound but quietly-kept faith. Hiding, as it were, his light under many bushels. I hope, in repose, that he might approve of this slice of Coleridge[1]:

Oh sleep it is a gentle thing
Beloved from pole to pole
To Mary Queen the praise be given
She sent the gentle sleep from Heaven
That slid into my soul.

It is an extraordinary coincidence that I would eventually like Mark, become editor of the Ulster Medical Journal. The link editorially, between us, is Patrick Morrison. I owe a great debt of thanks to Patrick and also to his co-author, Stanley Hawkins, for rising manfully to the task of preparing Mark's obituary. In doing so, with determination and great discipline, they have distilled a life into one short page. To sum up a life's aggregate with its achievements, disappointments, aspirations, joys and heartaches is no easy business. However, not your obituary this, Mark: my words.

As the new decade begins, it's not unusual to evaluate, assess and take stock. Searching for perspective can be challenging, living, as we do, on what Douglas Adams described as the *unfashionable* western spiral arm of the galaxy[2]. Almost twenty years ago (February 14th, 1990) the astrophysicist and cosmologist Carl Sagan persuaded NASA engineers to turn Voyager 1 around, some four billion miles from earth, for, as it were, a last peek over its shoulder, as it exited our planetary solar system[3]. His purpose was to give us a unique perspective of our place in space. As he wrote himself, the earth appeared merely as "a mote of dust, suspended in a sunbeam." I would urge you to make the time, to take the time, to enjoy Sagan's audiovisual masterpiece, 'Pale Blue Dot'. It's four minutes long.

(www.youtube.com/watch?v=jhGKwo6-Lce).

That accomplished, and feeling cosmologically small enough, we can return to work. On behalf of the editorial team, in our mote of the unfashionable western spiral arm, may I wish you and yours a blameless 2011.

Live long and prosper, and don't panic[2].

Barry Kelly
Honorary Editor

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LIST OF REFEREES FOR 2010

We pass on our sincere thanks to all of our referees for 2010.

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Improvement in services for patients with rare diseases

Dr Fiona Stewart, Consultant in Medical Genetics, Belfast City Hospital

The Society for Mucopolysaccharide Diseases and the Primary Immunodeficiency Association in partnership with the Belfast Trust have undertaken an exciting new venture in Northern Ireland to improve services for families with these rare groups of diseases. They have appointed an all-Ireland advocacy support worker who will provide support for families both North and South of the border.

Mrs Alison Wilson has been appointed to the post. She has spent the last two years studying for an MSc in Genetic Counselling at Cardiff University. She will spend four days a week undertaking her advocacy/support role and one day a week working for the Northern Ireland Regional Genetics Service as a genetic counsellor. The MPS Society provides support for families with diseases including Hurler, Hunter Sanfilippo, Morquio, I–cell, fucosidosis and Fabry disease. The PIA covers diseases such as hereditary angioedema, hypogamma-globulinaemia, Wiskott Aldrich and many more.

Expert medical care is provided for these disorders in the regional centres. However, families affected with these disorders face many problems. These include accessing appropriate care packages and equipment, dealing with the benefit system and the education system and making the complexities of their conditions known to the health and social care professionals with whom they have contact.

The role of the advocacy support worker is to provide expert information and advice to MPS/PIA sufferers, their families and carers on issues relating to the non-clinical management of individuals affected by primary immunodeficiencies or MPS and related diseases. They also provide an active listening service to enable individual sufferers, their families and carers to speak about, reflect on and make fully informed decisions in respect of the meeting of their needs. This service includes an out of hours service, which operates every day of the year. Finally, they work in partnership with individuals and families and impart skills and knowledge to promote self advocacy.

If you have patients or families with these disorders and feel that they may benefit from the help of the advocacy support service, Alison may be contacted via the MPS Society at 0845 3899901 or via the Regional Genetics Service, based at Belfast City Hospital.

Primary Immunodeficiency Association

Supporting people with and promoting awareness of primary immunodeficiencies and disorders of the immune system

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Society for Mucopolysaccharide Diseases

The Society for Mucopolysaccharide Diseases (the MPS Society) is a voluntary support group founded in 1982, which represents from throughout the UK over 1200 children and adults suffering from mucopolysaccharide and related lysosomal storage diseases including Fabry disease, their families, carers and professionals. The Society is a registered charity entirely supported by voluntary donations and fundraising. The Society has the following aims:

- To act as a support network for those affected by MPS & related diseases
- To bring about more public awareness of MPS & related diseases
- To promote and support research into MPS & related diseases

Society for Mucopolysaccharide Diseases

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Obituary

J Mark Gibson MD FRCP FRCPI (1953-2010)

Stanley Hawkins, Patrick Morrison

John Mark Gibson was born, in London, on Easter Sunday, 5 April 1953. His father, John Gibson was Professor of Mental Health at Queen's University Belfast and his mother Emily, had been a nurse in London during the Blitz. Mark grew up in South Belfast, and attended the Royal Belfast Academical Institution. Excelling academically, his diverse extracurricular activities included playing the double bass, cycling and steam trains. As a teenager he joined the City of Belfast and Northern Ireland Youth Orchestras and it was through music that he met his wife, Frances Dillon. For twenty-five years he would be leader of the bass section of the Belfast Studio Symphony Orchestra.

Mark read medicine at Trinity College Dublin and after house jobs in Dublin he returned to Belfast. Whilst working at Claremont Street Hospital, and in the Neurology unit at the Royal Victoria Hospital Belfast, he decided to specialise in that field. From 1980 until 1982, he worked in Southampton as registrar to the QUB graduate Dr Philip Kennedy, and between 1982 and 1985, he undertook his MD research on Parkinson's Disease with Professor Chris Kennard.

In 1988, he was appointed consultant neurologist to the Royal Victoria, Belfast City and Altnagelvin Hospitals. He is fondly remembered in Altnagelvin not just for his crucial clinical contribution but also for his arrival and departure, in all weathers, by bicycle and train. Deeply committed to the principles of the NHS, he eschewed private practice.

Mark developed a sub-specialty interest in the study of movement disorders, particularly in Parkinson's Disease (PD) and Huntington's Disease (HD). In Belfast City Hospital he secured funding for, and initiated, a multidisciplinary clinic, the main focus of which was PD. Mark, as medical advisor, worked closely with the Parkinson's Disease Association and his wife Frances, a senior Speech and Language Therapist was the Belfast representative on the Association's board for several years.

Mark devised novel methods for recording eye movements. With Alan Collins and Dr Canice McGivern, he modified a dental chair with an improvised head clamp and a set of LED lights. This 'Heath Robinson' apparatus worked well and was used to study patients with ocular motor abnormalities including HD, and the pre-symptomatic HD carriers that had been identified by Patrick Morrison.

His multidisciplinary clinic provided a unique opportunity to perform systematic research into movement disorders, and resulted in landmark publications on PD. He helped define the ocular motor pathophysiology of HD on a large series of affected and presymptomatic cases. Mark had exacting personal standards, quietly disapproving of the 'salami slicing' of data, which he deplored.

Mark, as postgraduate trainer, played an important role in the development of postgraduate Neurology throughout Ireland. With Professor Michael Hutchinson in Dublin, he developed a monthly day-release scheme with a defined curriculum. Mark was also very active in the Association of British Neurologists, representing the interests of Northern Irish neurologists.

As Ulster Medical Journal editor for ten years, he nurtured the academic careers of many young doctors. On occasion, guiding the novice author to produce the publication-worthy text could be challenging but he remained considerate, patient and courteous. Authors during that period will recall helpful annotations written with characteristic green or brown fountain pen ink. Mark introduced the now familiar A4 Journal format. His editorial work for the journal was recognised by the Ulster Medical Society with the rare honour of the awarding of an Honorary Fellowship of the Society in 2005.

A voracious reader, Mark also had a catholic taste in literature and enjoyed sharing recommendations with friends and colleagues. An enthusiastic advocate of the 'Quo Vadis' desk and pocket diaries, he found such 'old technology' trusty and reliable. Frequently during a conversation, he would produce his trusty diary and scribble a few notes for future reference.

Mark loved and was beloved of his close and extended family. When, in 2006, he became ill and later when he endured a bone marrow transplant, he drew great comfort from them. Despite imperfect health, he returned to work but after a further year, he retired, choosing to spend more time at home with his family and on many restorative trips to the family caravan at Rosbeg in County Donegal. During this period, and despite grave illness, significant publications by him continued to appear in international journals.

On 25th September 2010, aged fifty-seven, Mark died at home. In the week before he died, he arranged and planned his funeral service, sparing those close to him. The inspirational memorial service was held at Fisherwick Presbyterian Church, Belfast where he had been a faithful member of the congregation. There was music, sadness and reflection but also glimpses of Mark's intelligent and gentle sense of humour. He is survived by his wife, daughter Amy and son Laurence.

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Review

Clinical Immunology

J David M Edgar

Accepted 31 October 2010

Clinical immunology has developed very significantly as a speciality over the last twenty years, as has the understanding of the immunological basis of many diseases and the development of immunological therapies. Indeed it is difficult to think of a speciality that has not developed an "immunological dimension" in this time.

The purpose of this mini-review is to update the non-specialist reader on the basic immunological mechanisms which underlie an effective immune response and the clinical disorders which results when the processes are deficient or disordered. The basic science description is, of necessity limited in scope and detail. Further explanation of the basic cellular and molecular mechanisms involved in immune defence can be found in recent textbooks[1,2].

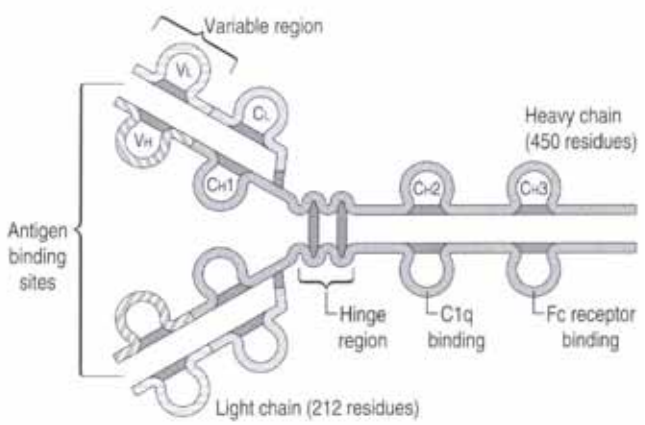

Fig 1. The basic structure of IgG1. The n terminal end of the heavy and light chains is the variable region responsible for antigen binding (Fab). The Fc region is responsible for complement (C1q) activation and binding to cell surfaces via Fc receptors.

Innate and adaptive immunity

Innate immune defences are the body's constant, unchanging defence against infection. These are non-specific and include physical components such as skin, mucous membranes, gastric acid, nasal cilia etc as well as phagocytic cells and proteins of the complement system. In contrast, the **adaptive** immune system includes lymphocytes and immunoglobulin (antibody) molecules which share characteristics of **specificity** and **memory**. The components of the adaptive system recognise and are stimulated by specific fragments of microorganisms termed **antigens** (from *Anti*body *Gen*erating). When antigens are appropriately presented to lymphocytes by specialist **antigen presenting cells** (APC: see below), they generate antigen specific T cells and B cells that develop to produce antibody molecules.

There are five isotypes of immunoglobulin, or antibody, molecules: IgG, IgM, IgA, IgD and IgE. All five share a basic "Y- shaped" structure (Figure 1) although IgM and IgA tend to exist in pentameric or dimeric forms. IgG is the major isotype present in serum, IgA has a crucial role at mucous membranes and IgM is the isotype that dominates the primary antibody response to first encountering a foreign antigen. IgD molecules function as cell surface receptors and IgE, whilst important in protection from parasitic infection is most notable in western societies for its role in allergic or type 1 hypersensitivity disease.

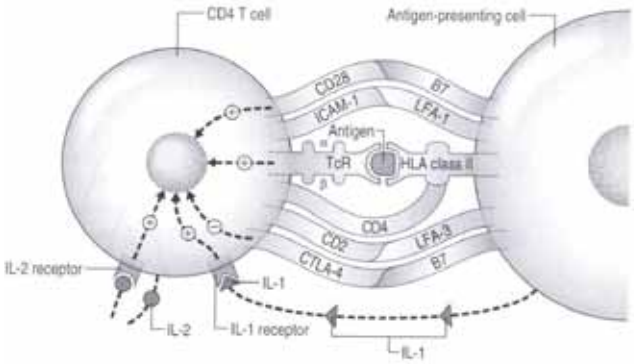

Fig 2. Activation of CD4+ T cells. In addition to antigen recognition via the T cell receptor(TCR), a range of cell surface molecules and soluble cytokines deliver additional positive (+) or negative (-) signals. Interleukin 2 (IL-2) secretion activates both the secreting T cell (autocrine) and it's near neighbours (paracrine)

The normal peripheral blood lymphocyte population comprises 70-90% T cells; 5-10% B cells and 1-10% natural killer (NK) cells. These are all derived from lymphoid stem cells in the bone marrow. Lymphocyte subsets are defined by their expression of surface markers termed CD antigens (CD: cluster of differentiation). T cells are classified by their cell surface markers as CD3+, with the helper subset (Th) defined as CD3+CD4+ and the cytotoxic subset (Tctx) as CD3+CD8+. There are also a number of regulatory T cell subsets which are described below. B cells are CD19+ and

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NK cells CD16+CD56+.

Immature T cells emerge from the bone marrow and undergo maturation during their passage through the infant's thymus gland. During that maturation, T cells with specificity for "self antigens" are deleted and only those with appropriate reactivity to foreign antigens complete their passage to the peripheral circulation. This is one of the "central" mechanisms of inducing "self-tolerance" and preventing autoreactivity against self antigens.

The process of developing specific immunological responses to microorganisms involves elements of both the innate and adaptive immune systems. Innate cells with phagocytic function recognise and engulf (phagocytose) invading microorganisms. Once phagocytosed, the microorganisms are broken down into short amino acid sequences which ultimately stimulate an immune response through a process of **antigen presentation** to lymphocytes (Figure 2).

Mature T cells recognise antigenic fragments/ peptides, only when they are *presented* to them bound to one of the **major histocompatibility complex (MHC)** molecules (MHC Class 1 or 2). MHC molecules are coded for by a discrete area on the short arm of chromosome 6 and have central roles in enabling the body to distinguish the recognition of self from non-self molecules. **MHC Class 1** molecules are expressed on all nucleated cells, whereas **MHC Class 2** are only expressed on specialist **antigen presenting cells (APC).** Each type of MHC molecule binds antigen fragments and presents these to their respective T cell subset. **CD4+ Th** cells only recognise antigen presented in the context of **MHC Class 2** molecules whilst **CD8+ Tctx** cells only recognise antigen fragments in the context of **MHC Class 1** molecules. The specific binding of the T cell receptor to antigen presented in the peptide binding groove of the MHC molecules leads to cellular activation. There are a also a number of non-specific co-stimulatory cell surface molecules that serve to enhance the binding and influence the nature of the cellular activation (Figure 2). The fact that T cells only respond effectively when antigen is appropriately presented is termed **MHC restriction**, and it is important to understand as it relates to the major functions of the two main cellular subpopulations. **CD4+Th** cells are central co-ordinators of the immune response, only being activated by specialist APC cells. **CD8+Tctx** cells are effectors, and therefore must be capable of recognising infection or malignant transformation of any nucleated cell in the body.

CD4+ Th cells stimulate B cells both by direct cell surface interaction but also by the secretion of cytokines. Cytokines are low molecular weight polypeptides that act to provide inter cellular signals. Most are known as **interleukins** (meaning that they effect communication between white blood cells) and are numbered in the order in which they were discovered. So, **interleukin 2 (IL-2)** is an important activator of T cells and was discovered before **interleukin 8** (**IL-8)** which has an important role in recruiting neutrophils. Cytokines may affect the cell that produced them (autocrine effect) or other cells in their immediate vicinity (paracrine effect) but generally have little influence on cells at distant locations (endocrine effect).

The interaction of **APC, CD4+ T cells and B cells** is central to the adaptive response to pathogens resulting in primary and secondary antibody responses (Figure 3). The first or primary exposure to a microorganism is characterised chiefly by production of antigen specific IgM , however on secondary exposure, memory B cells are stimulated and high levels of protective IgG are produced. It is that highly specific, high titre IgG that provides long term protection.

Table 1:

UK Immunisation Schedule (www.immunisation.co.uk)

2 months:

- Diphtheria, tetanus, pertussis (whooping cough), polio and Haemophilus influenzae type b given as a 5-in-1 single jab known as DTaP/IPV/Hib
- Pneumococcal infection

3 months:

- 5-in-1, second dose (DTaP/IPV/Hib)
- Meningitis C

4 months:

- 5-in-1, third dose (DTaP/IPV/Hib)
- Pneumococcal infection, second dose
- Meningitis C, second dose

Around 12 months:

- Meningitis C, third dose
- Hib, fourth dose (Hib/MenC given as a single jab)

Around 13 months:

- MMR (measles, mumps and rubella), given as a single jab
- Pneumococcal infection, third dose

3 years and 4 months, or soon after:

- MMR second jab
- Diphtheria, tetanus, pertussis and polio (DtaP/IPV), given as a 4-in-1 pre-school booster

Around 12-13 years:

- Cervical cancer (HPV) vaccine (girls only): three jabs given within six months

Around 13-18 years:

- Diphtheria, tetanus and polio booster (Td/IPV), given as a single jab

65 and over:

- Flu (every year)
- Pneumococcal

T cell regulation

It is important that once an immune response is initiated, there are mechanisms to control and/or limit reactivity to prevent

uncontrolled or inappropriate immunological activation and potentially harmful inflammatory reactions. In terms of responses to microorganisms, the destruction and eradication of the microorganism itself is an important mechanism for "switching off" an immune response.

Within the population of **CD4+ Th** cells there is further differentiation into different functional subpopulations which have various regulatory functions. **T helper 0, 1 and 2 (Th0, Th1 and Th2)** subdivisions are defined by their preferential patterns of cytokine secretion and their differing influences on ultimate nature of the immune response to a pathogen. **Th0** differentiate into either **Th1** or **Th2**. The **Th1** cytokines are IL-2, IL-12 and IFN-γ favouring a cellular immune response whilst the **Th2** cytokines, favouring an antibody response, are IL-4, IL-5, IL-6 and IL-10. There is mutual suppression between these two dominant patterns of cytokine secretion such that, once a response has become committed in either direction, this pattern will tend to be maintained (Fig 4). The secretion of IL-4 and IL-5 tends to promote eosinophilia and IgE production and therefore Th2 responses are associated with type 1 hypersensitivity reactions and allergy. Other clinical examples of the consequences of **Th1/Th2** response include the response to protozoal and mycobacterial infection. In lepromatous leprosy, there is a dominant **Th2** response to the mycobacterium, which results in poor cytotoxic killing, high microbiological load and poor granuloma formation. In contrast, in granulomatous disease, there is a dominant **Th1** response, potent cytotoxic response with localisation of microorganisms within an inflammatory granuloma and a consequently low mycobacterial count. There are other direct clinical consequences of this understanding of T cell functions. In some specific primary immunodeficiency states, there is an inability to mount effective **Th1** type responses because of deficiency in either interferon γ or IL-12 secretion or responses. In such patients, replacement or supplementary treatment with interferon can be life saving. In other clinical situations e.g. multidrug resistant tuberculosis or eradication of non-tuberculous mycobacteria from the bronchiectatic lung, adjunctive interferon γ therapy can be similarly effective through boosting of the **Th1** response.

The concept of "central tolerance" has already been mentioned, however "peripheral tolerance" also occurs as a means of maintaining control of potentially autoreactive lymphocytes[3]. The population of **CD4+CD25+** (CD25 is the IL-2 receptor and is a marker of "activated" T cells) regulatory cells are also important in controlling self reactive responses and abnormalities in this population may predispose to autoreactivity and autoimmunity[4,5].

The **Th17** population is relatively recently described cell subset also thought to be involved in development of autoimmunity, particularly multiple sclerosis, diabetes, psoriasis and Rheumatoid arthritis[6]. **Th17** are probably developmentally distinct from **Th1** and **Th2** cells and they preferentially produce cytokines IL-17, IL-21 and IL-22. Their pro-inflammatory functions may indicate an important role in protective immunity at mucosal sites and they are thought to be down regulated by both **Th1** and **Th2** subsets[7,8].

Immunology of the newborn

The newborn infant is immunologically immature and depends on its innate immune defences and passively acquired maternal immunoglobulin G (IgG). Newborn infants, particularly those born prematurely, who have not had adequate transfer of maternal immunoglobulin in the last trimester of pregnancy, are therefore vulnerable to developing infection.

Maternally acquired IgG binds specifically to the wide range of microorganisms already encountered by the mother and is a form of **passive immunity**. It provides immediate wide-ranging protection until the natural process of antigen exposure has stimulated the production of endogenous antibody by primary and secondary responses. The half life of IgG is approximately 3 weeks *in vivo* and typically, maternally derived immunoglobulin levels will wane and fall so that the newborn reaches an ***immunological nadir*** of serum immunoglobulin levels between 3 to 6 months of age. At this stage the infant is most vulnerable to infection. If the production of immunoglobulin is abnormally delayed, the infant can develop ***transient hypogammaglobulinaemia of infancy (THI)***, which may require treatment with immunoglobulin replacement therapy should significant infection occur. It is crucial that **THI** is differentiated from one of the potentially life threatening **Primary Immunodeficiency Disorders** (PID: see below) that typically present in the first year of life. **THI** is therefore a diagnosis of exclusion.

Infant Immunisation

The UK immunisation schedule (Table 1) has been developed to protect the population from common infectious disease with potential for significant morbidity and mortality. The schedule is under regular review and is updated as new vaccines are developed. For most infectious agents, a series of vaccine doses is required, given at intervals, to generate a high level of protective antibodies. Underlying this is the concept of the primary and secondary antibody response of the adaptive immune system (Figure 3). Individual vaccines vary in their immunogenicity and the dosing and booster schedules are therefore individually determined to maintain appropriately high protective antibody levels.

Immune deficiency

Development failure of immune system components, or breakdown in its control can lead to the development of a wide range of ***primary immune deficiencies (PID)***. Figure 5 indicates how immune deficiencies arise as a result of failure of development or depletion of T cells at different stages of development (ontogeny). Whilst many PID present in childhood, they can present at any age in life and can affect individual components of the immune system e.g. immunoglobulin molecules[9], complement components[10], neutrophils[11] or lymphocytes or they can be combined deficiencies affecting both lymphocyte and immunoglobulin numbers and levels[12].

The most common PID are those characterised by deficiency of immunoglobulins (IgG, IgA or IgM). The most common type of antibody deficiency is ***common variable immune deficiency (CVID)***. CVID usually presents in children or young adults with a prolonged history of recurrent upper and lower respiratory tract infections, although it may also

present with autoimmune disorders affecting the GI tract, haematological or endocrine systems. An important aim for CVID patients is to establish the diagnosis and commence treatment before recognised complications of the disorder e.g. bronchiectasis have developed. A UK wide audit in 1996 suggested that the average diagnostic delay for such patients was of the order of 7 years, however anecdotally we know the delay can be much longer for individual patients[13,14]. Commencement of immunoglobulin replacement therapy by either the intravenous (IvIg) or subcutaneous (ScIg) routes is highly efficacious in reducing the number of infections and therefore preventing the development of complications[15]. IvIg and ScIg are usually lifelong treatments and may both be self administered at home after appropriate patient training. In Northern Ireland we currently have data on 218 patients with PID. 151 of these receive immunoglobulin replacement, around 80 of whom are treated at home (Table 2).

TABLE 2

Patients on treatment for Primary immunodeficiency & auto inflammatory syndromes in Northern Ireland, 2010

Common variable Immune deficiency (CVID)	93
C1-inhibitor deficiency	27
X-linked agammaglobulinaemia (XLA)	22
Other hypogammaglobulinaemia	14
Specific antibody deficiency	11
IgG subclass deficiency/IgA deficiency	9
Wiskott-Aldrich syndrome	4
Autoimmune polyendocrinopathy and chronic ectodermal dysplasia (APECED)	4
Severe combined immune deficiency (SCID)	4
Ataxia Telangectasia	4
Good's syndrome	3
Interferon gamma receptor deficiencies (IFNgR1 def)	3
X-linked Hyper IgM (XHIGM)	3
Hyper IgD syndrome	3
Autoimmune lymphoproliferative syndrome (ALPS)	3
Chronic mucocutaneous candidiasis (CMC)	2
Chronic granulomatous disease	2
Complement deficiencies	2
Idiopathic CD4 cytopaenia	2
Schnitzler syndrome	1
Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked (IPEX)	1
X-linked lymphoproliferative disease (XLP)	1

One of the few "immunological emergencies" and the most serious PID is ***severe combined immune deficiency (SCID)***. SCID usually presents during the first months of life. Affected infants are characterised by failure to thrive, recurrent bacterial, viral and/or fungal infections and there may be additional features including diarrhoea, rashes and liver dysfunction caused by **graft versus host disease** as well as morphological abnormalities. Graft versus host disease occurs in this context when functioning maternal lymphocytes transfer to the newborn at birth. The infant's immune system is unable to eradicate these and instead these maternal lymphocytes go on to proliferate and attack skin, liver and gut, resulting in a syndrome very similar to that seen after bone marrow transplantation. The acronym SCID

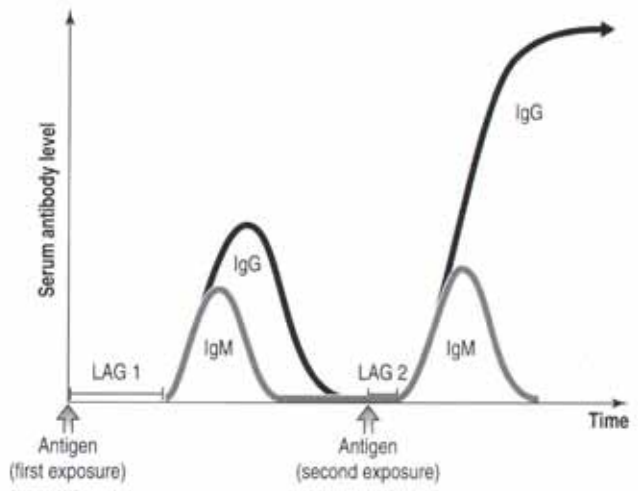

Fig 3. Primary and secondary antibody responses typify the adaptive immune response to antigen. Memory cells generated from the primary response become rapidly activated upon re-exposure to the same antigen.

can erroneously suggest a clinical presentation so severe and so rare, that an average paediatrician is unlikely to encounter the condition. This is however not the case and whilst SCID is rare, as is the case for other PID, it is almost certainly under diagnosed. There may be several factors contributing to the under diagnosis of SCID. Affected infants may initially appear relatively well, with perhaps frequent attendances related only to symptoms of relatively mild viral infection, diarrhoea or oral/perineal thrush. Identification of infants at high risk of SCID is therefore difficult, but one should have a higher index of suspicion if the parents are from a cultural background in which first cousin marriage is common (e.g. the Indian subcontinent). It should be emphasised that children with SCID do not typically have *absent* lymphocytes and/or immunoglobulins. Rather, their lymphocyte and

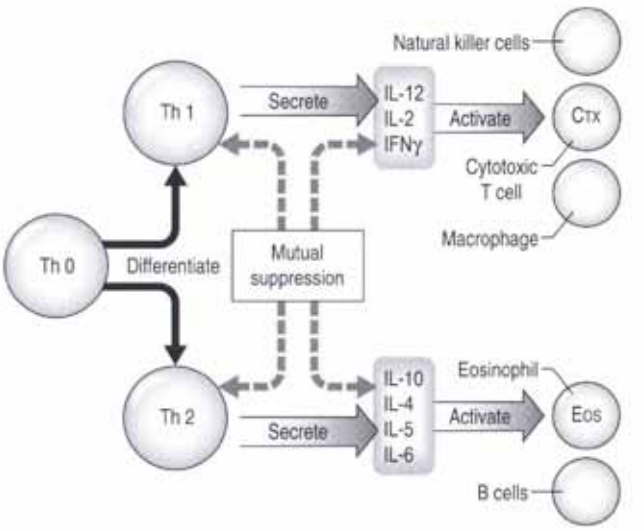

Fig 4. T cells differentiate along two major axes depending on their pattern of cytokine secretion. To give T helper 1(Th1) cells, which tend to promote cellular responses, and T helper 2 (Th2) cells whch tend to promote antibody production and IgE mediated responses. Th1 and Th2 cells are mutually suppressive. The distinction between these two subpopulations is not absolute in humans.

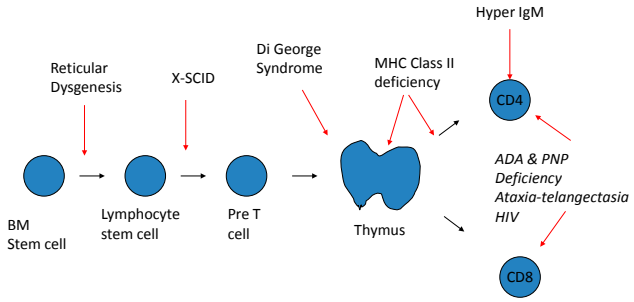

Fig 5. T cell development and Immunodeficiency

immunoglobulin levels are well below normal age-related reference ranges. A useful guide is that any child with a total lymphocyte count of <2.8 x10^9/L should be investigated for SCID, although a normal lymphocyte count does not exclude the diagnosis. We assess children for SCID on a regular basis and probably make the diagnosis at least once every year. If diagnosed early and managed appropriately, including early bone marrow transplant, long term survival from the disorder is currently of the order of > 85%.

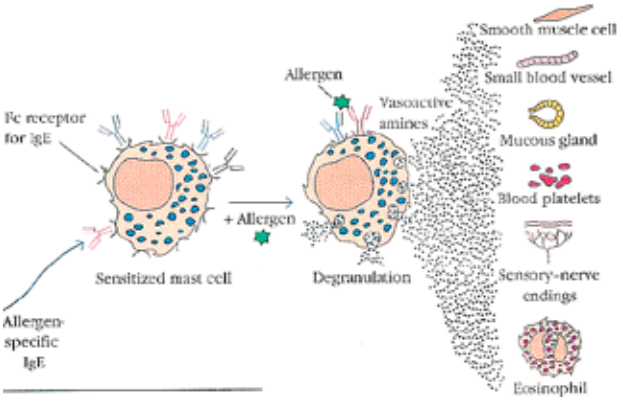

Fig 6. Antigen cross links specific IgE molecules on the surface of Mast cells causing degranulation and release of multiple mediators including histamine, heparin, platelet activating factor and leukotrienes. These mediators cause different symptoms depending on the anatomical site of release.

Under diagnosis is a major problem for patients with PID. There is also significant geographical variation in perceived prevalence across the UK which is probably at least partly explained by the patchy provision of immunology services. In Northern Ireland there were approx 25 patients diagnosed with PID in 1996, and this has risen to over 200 patients in 2010. This relentless annual rise in the number of diagnosed cases shows no signs of abating.

Whilst the most severe conditions require bone marrow transplantation[16], others are managed with regular immunoglobulin replacement therapy, enzyme replacement therapy, cytokine treatments or prophylactic antibiotics. Many of these disorders are on the basis of single gene defects and PID have been the candidate conditions in which much of the success in clinical trials of somatic gene therapy has been achieved.

Understanding of the prevalence of PID across the UK is limited and this is currently being addressed through the establishment of a UK-PID registry under the auspices of the UK primary immunodeficiency network (www.ukpin.org.uk). Servers for this project went live in 2009 and already approx 1300 out of an estimated 5000 patients have been registered. Across Europe, the linked database of the European Society for Immune Deficiency (http://www.esid.org/statistics.php) established in 2004 has details of over 12,000 PID patients.

Allergy

Allergic disease is a much more common clinical problem than PID and a source of considerable workload in primary care, organ based specialities (eg ENT, dermatology & respiratory medicine) as well as clinical immunology services. The spectrum of allergic disease seen in specialist allergy clinics includes potentially life threatening anaphylaxis, drug and venom allergy and complex multisystem allergic disease. A particular problem is the patient with chronic urticaria and /or angioedema of uncertain aetiology and that will be specifically addressed below.

TABLE 3:

Gell & Coombs classification of hypersensitivity

Type of Reaction	Effector Mechanism	Clinical Disorder
I	IgE, Mast cells	Allergic rhinitis, urticaria, angioedema, anaphylaxis
II	IgG directed at cell surface bound antigen	Transfusion reactions, acute graft rejection, Graves disease, Myasthenia Gravis, goodpasture's syndrome
III	Immune complexes	Cryoglobulinaemia, post-streptococcal glomerulonephritis, systemic lupus erythematosus
IV	CD4+ lymphocytes	Delayed type hypersensitivity, contact eczema, granulomatous reactions

Is the rise in allergic disease real?

It is sometimes suggested that the apparent rise in allergic disease is due to greater awareness and hence increased rates of diagnosis. However there is a well documented rise in the prevalence of allergic disease in "westernised" societies, but not in most of the less industrialised regions including Africa, India and South East Asia. Why should this be the case? It is recognised that societies with a high prevalence of allergy tend to have smaller family sizes, lower rates of infectious disease in infancy, higher rates of immunisation and greater degrees of domestic cleanliness. The ***Hygiene Hypothesis*** suggests that all of these factors lead to a decreased rate of microbial turnover at the infant's mucosal sites and that this in turn promotes abnormal immunological responses to antigens encountered, be they inhaled (pollens, animal dander, house dust mite) or ingested (foods)[17,18]. Allergic disease is

therefore characterised by the presence of antigen specific IgE to (usually) innocuous antigen and is the end result of a disordered immune response.

What is the cellular basis for allergy?

As already stated, Th2 cytokines, in particular IL-4 & 5 tend to promote IgE mediated responses to antigens. Once produced, antigen (or allergen) specific IgE binds via specialised receptors to the surface of mast cells. When later exposure to the allergen occurs, the IgE molecules are cross linked causing mast cell degranulation and the release of histamine and other mediators (leukotrienes, heparin, platelet activating factor etc) into the local tissue (Figure 6). These mediators have a wide range of effects and depending on the site of allergen exposure and location of mast cells activated, the resulting symptoms may include eg: rhinitis, conjunctivitis, urticaria, angioedema, vomiting, diarrhoea or anaphylactic shock.

Clinical Allergy

The increasing prevalence of allergic disorders represents a great challenge to the health service. Most medical practitioners have little or no formal training in allergic disease, however they are aware of the potentially severe nature of some allergic reactions. Paediatricians have historically taken an interest in food allergy and in Northern Ireland there is now a network of paediatricians with an interest in allergy, with at least one consultant in most of our hospitals.

The spectrum of allergic disease is wide; however the underlying mechanisms are common to most. The term *allergy* is widely misused in the popular press to refer to any adverse reaction. However in this context, allergy means Type 1 hypersensitivity (from the Gell & Coombs classification: Table 3)

Urticaria

Urticaria is caused when mast cells are activated in the epidermis. It is commonly described as resembling "nettle stings" and is typically raised and intensely itchy (Figure 7). It may occur as part of an acute allergic reaction or be a chronic problem, occurring on an almost daily basis for at least 6 weeks (***chronic idiopathic urticaria / CIU***). In patients with CIU it is very rare to identify an allergen and extensive laboratory investigation of such patients is not usually recommended. Management is usually with prolonged courses of non-sedating oral antihistamines, often at 3-4 times the recommended dose, to obtain complete suppression of the rash. Several variants of CIU occur, including autoimmune urticaria, urticarial vasculitis and physical urticarias. Good guidance is available on their diagnosis and management[19].

Angioedema

Angioedema is a non-dependent, non-pitting swelling that can affect any part of the body but frequently affects the perioral and periorbital regions, tongue, genitalia and peripheries such as the hands and feet. It can also occur internally causing laryngeal oedema or acute intestinal obstruction. Mast cell activation in the deep dermis is the usual cause; however in addition to histamine release, increased generation or reduced degradation of bradykinin is thought to be a key causative factor. Angioedema and urticaria commonly occur in the same person either as part of an acute allergic reaction or in approximately 40% of people with CIU. Management of the latter group is the same as for CIU. Approx 10% of "CIU patients" have chronic angioedema but no urticaria. Two important variants exist which are distinct in terms of both aetiology and treatment. Angiotensin converting enzyme inhibitors (ACEi) can cause potentially life threatening angioedema and the history is not typical of an allergic mechanism. In such patients, angioedema usually occurs after prolonged ACEi treatment, the swelling is not related in time to taking the medication and in some people, swelling may persist for some time after withdrawal of the drug. Anyone presenting with angioedema whilst taking an ACEi, must have alternative anti hypertensive drugs prescribed. There is a smaller but well described risk of angioedema with the Angiotensin II receptor blocking drugs and therefore alternatives such as calcium channel blockers and Beta blockers are preferred if possible.

TABLE 4

Factors associated with fatal nut reactions

- **Being away from home**
- **Eating food from commercial sources**
- **Not carrying rescue medication**
- **Alcohol**
- **Age: Between 15-25**
- **No deaths < 13 years (one series)**
- **Asthma**
  - **Excessive reliance on β2 agonists for asthma control**
  - 12 of 13 cases of fatal and near fatal reactions
  - 24 of 25 fatalities had asthma

Partial deficiency of the complement control protein C1 esterase inhibitor (C1-inh) also leads to recurrent angioedema in genetically affected individuals. Although C1-inh deficiency causes a loss of control of the activation of the classical complement pathway, it is via its indirect effect on bradykinin metabolism that angioedema occurs.

These patients are at risk of sudden death due to laryngeal oedema after intubation or dental treatment. They also suffer regular peripheral swellings and are frequently treated with either the prophylactic androgens danazol or stanozolol or the antifibrinolytic tranexamic acid. Acute laryngeal oedema requires administration of intravenous C1-inh concentrate. The angioedema of C1-inh deficiency does not respond to anti-histamines, corticosteroids or epinephrine.

There are approx 27 patients with C1-inh deficiency in Northern Ireland and these families are well defined and have management plans that include the possession of C1-inhibitor concentrate at home for emergency use. However it

is important to note that in approx 33 % of new cases, there is no suggestive family history and the diagnosis rests on identifying typical angioedema, usually without urticaria and on testing, serum complement C4 levels are usually low as are levels of C1-inh enzyme. The diagnosis of C1-inhibitor deficiency is not uncommonly made late, in adulthood and therefore should be considered in any patient presenting with otherwise unexplained angioedema usually without urticaria.

TABLE 5

Management advice for nut allergy

(i) A nut free environment at home

(ii) *Oral antihistamine for:*

a. Inadvertent / presumed nut exposure
b. Minor reactions: skin rash, non-life threatening angiodema
c. pre-medication

(iii) *Injectable adrenaline for*

a. life threatening airway obstruction (includes severe asthmatic symptoms)
b. anaphylactic collapse

(iv) *Warning device/card*

(v) *Emergency contacts in mobile phone: ICE (In case of emergency) / SOS*

(vi) *Support information*

a. www.anaphylaxis.org.uk
b. www.allergyni.co.uk
c. www.epipen.co.uk

Anaphylaxis

The term **anaphylaxis** originally indicated a state of susceptibility to severe allergic reactions and it was derived from *ana* (against) and φύλαξις *phylaxis* (protection). *Anaphylactic reactions* are now defined as "severe, life-threatening, generalised or systemic hypersensitivity reaction". The usual defining clinical characteristics are significant airway obstruction or hypotension, but clinical features may include a sense of impending doom, urticaria, angioedema, abdominal pain, vomiting or diarrhoea. The route of exposure, dose and nature of the allergen as well as coexisting conditions such as asthma or infection and concomitant medications e.g. Beta blockers may all affect the dominant clinical features. It is crucial that medical practitioners recognise anaphylactic reactions and treat them promptly to ensure the best chance of survival[20]

The underlying pathophysiology is the systemic activation of mast cells throughout the body. In the clinical diagnosis of allergic reactions this may be confirmed by the measurement of serum mast cell tryptase levels at the time of reaction (and 2 and 24 hours later). Formal protocols exist both locally and nationally for the structured investigation of anaphylactic reactions e.g. during anaesthesia[21]

Food allergy

Food allergy is often misunderstood and its prevalence overestimated. There is often confusion between food allergy and intolerance. True food allergy is common in early infancy with cow's milk protein, egg white, wheat, shellfish, peanuts and tree nuts being common allergens. Diagnosis of food allergy in infancy rests on the typical clinical features, supported by specific IgE skin or blood testing. Most infants eventually outgrow their food allergies with the notable exception of peanut and tree nut allergy.

Peanut & tree nut allergy

Peanut and tree nut (e.g. brazil, cashew & hazel nuts, walnuts, almonds, pistachio etc) allergy came to the attention of the medical community in the UK in the late 1980's and early 1990s. Initially, it was thought to be a rare condition, but the prevalence of peanut allergy rose significantly in the 1990s such that now approx 1:75 pre-school children is said to be affected in the UK. There is great public awareness of the issue of peanut allergy both because of the precautions now taken e.g. in schools and commercial food suppliers and the small number of deaths that have occurred and received much media attention. Approximately 50% of peanut allergy sufferers will also report reactions to tree nuts. Some people are allergic to tree nuts but not peanuts, but the prevalence is not well defined and almost certainly varies between different tree nuts. Peanuts are in fact legumes and some peanut allergy sufferers will also react to cross reacting legumes including beans and peas.

What are the defining characteristics of peanut allergy?

Peanut allergy is often first noticed in infancy or early childhood, although onset can be at any age. It is usually a prolonged allergy, with sensitivity lasting into adulthood. Although there are published reports that up to 20% of affected children may outgrow this allergy this is not generally reflected in current clinical practice in the UK. For the most part we advise that one should assume peanut allergy is effectively a lifelong condition. It is recognised that there is a spectrum of severity of reactions with some individuals being exquisitely sensitive, reacting even to the smell of peanuts whilst others may be able to consume a small amount of peanut before reacting. The fact that severe reactions can be triggered by small amounts of nut antigen in some people causes great anxiety for patients and their families.

Allergic reactions to nuts are almost universally of very rapid onset. Typically the individual will spit out the offending food or vomit. Reactions often involve angioedema of the perioral region, tongue or larynx with resultant respiratory difficulty. People with asthma will often experience wheeze. Hypotension can be profound.

A popular misconception is that allergic reactions typically increase in severity over time and e.g. with peanut allergy that there is an inexorable increase in severity and that severe anaphylaxis will ultimately be unavoidable. This is not the case. In most people, if the circumstances and degree of exposure to allergen are similar, the reaction tends to be stereotypical. However there are a number of factors associated with increased risk of severe reactions and these are listed (Table 4). It is however important to emphasise that

the vast majority of patients with peanut and nut allergy, who have been properly assessed at a specialist clinic, practice careful nut avoidance and have an effective management plan in place which includes rescue medication, manage their condition very effectively[22]. A summary of our management advice for patients with peanut allergy is also provided (Table 5).

Although the potential severity of peanut allergy is widely recognised, deaths are fortunately rare. National audit data for the UK indicates that there are on average 2.6 deaths per year caused by peanut or tree nut allergy.[23,24]

Desensitisation

Desensitisation (or allergen immunotherapy) is a therapeutic strategy which is aimed at reducing the degree of allergic sensitisation of an individual patient. The basic approach is that the patient is exposed to minute amounts of the substance to which they are allergic on a regular basis, often over a prolonged period, typically three years. The result is that by regular, low dose exposure to allergen, the harmful IgE mediated allergic response is largely "switched" to an IgG (usually IgG4) protective response[25]. Allergen may be administered subcutaneously (SCIT), orally (OIT) or sublingually (SLIT). Pollen SCIT was widely practised in general practice the UK in the 1970s and 1980s however there were 17 deaths reported to the regulatory authorities and as a result, desensitisation is now highly regulated and restricted to specialist centres. In retrospect, it is felt that the deaths were at least in part due to inappropriate selection and monitoring of patients. It is worth noting that desensitisation has remained widely practiced in Europe and North America and is an effective therapeutic strategy[26,27]. Delivery of SCIT is however burdensome for both patients and doctors in terms of time commitment and precautions required. This is a major factor limiting its delivery in the UK. The advent, in 2007 of a licensed product for grass pollen SLIT (Grazax, ALK-Abello) has transformed delivery of grass pollen desensitisation. In our service, we have treated well over 100 patients in that time with good clinical effect on their hay fever symptoms and very few side effects. It is anticipated that OIT and SLIT will continue to be developed for a wider range of allergens. Recent trials from UK and North America provide encouragement that this may be an effective strategy for the management of nut allergy in the future[28,29].

Autoimmunity

Autoimmune reactions and diseases indicate that in certain circumstances, the normal immunological control mechanisms which are outlined above become defective. A number of mechanisms are thought to be responsible for this abnormal reactivity to "self-antigens". These include cross reactivity, molecular mimicry, provision of T cell epitopes, release of sequestered or cryptic antigens, failure of T cell regulation and anti-idiotype responses. The classical association between group A streptococcal infection and rheumatic heart disease is an example of "cross reactivity" in which the streptococci express antigens that are structurally similar to self antigens on cardiac muscle. Antibody and T cells specifically generated against the streptococcal antigen therefore cause damage to the structurally similar self proteins.

At a molecular level, the concept of "molecular mimicry" is also postulated. It is known that short molecular sequences (e.g. 5-amino-acid sequences) are commonly shared between microorganisms and self proteins. It is thought that both these mechanism may contribute to the development of autoreactivity. The potential linkage of foreign proteins (e.g. drugs or chemicals) to self proteins provides another mechanism for bypass of normal immunological control. B cells binding to the self-non-self complex have the potential to process and present the non-self component to T cells reactive to the foreign proteins. Thus it is possible for T cells to deliver inappropriate helper signals to B cells binding the self component, stimulating an autoimmune reaction. This is known as "provision of T cell epitopes". Furthermore, some self antigens are not normally exposed to cells of the immune system and are said to be "sequestered", e.g. lens proteins from the eye. Tissue damage can release such antigens and allow an immune response to occur e.g. after traumatic damage to one eye, the release of proteins can cause autoimmune damage to the other – **sympathetic ophthalmia**.

Cryptic antigens are those that are only released during the normal turnover of body proteins by antigen presenting cells. Because they are not normally expressed, tolerance does not develop and their release can allow the generation of autoimmune responses. It is likely that cryptic epitopes are normally only released in low concentrations; however coincidental factors such as infection or inflammation may be necessary to initiate the autoimmune response. T cell regulation has already been mentioned and a failure of T cell regulation (or suppression) has long been postulated as a mechanism for the generation of autoreactive responses. The balance of cytokines secreted in the microenvironment is important in influencing the nature of an immune response to a microorganism is therefore thought that the balance of T cell cytokine secretion in humans may be important in influencing autoimmune responses. Finally, the antigen binding sites of antibody molecules are known as **idiotypes** and it is possible that during a normal response to infection, a "second wave" of **anti-idiotype antibodies** is generated, directed not against the microorganism, but against these idiotypic sites, thereby generating auto antibodies

Two specific diseases highlight the importance of maintenance of central tolerance and effective regulatory T cell mechanisms[30,31]. In **Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dysplasia syndrome type 1 (**APECED Type 1) there are mutations in the autoimmune regulator gene (AIRE) on chromosome 21. These mutations lead to failure of apoptosis of autoreactive T cells and the consequent development of autoimmunity. Patients with **IPEX** (Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked) syndrome harbour mutations in the forkhead box P3 (FOXP3) gene in regulatory T cells, which leads to severe autoimmunity and immune deficiency.

In clinical terms, it is important to distinguish between those autoimmune reactions, (that may occur as a consequence of infection, surgical procedures, drug treatment or increasing age and are characterised by the detection of autoantibodies in blood) and autoimmune disease.

Autoreactivity may only be temporary; indicating that the immune system can regain control of autoreactive lymphocyte

clones after the "external insult" has been withdrawn. Autoimmune reactions are much more common than autoimmune disease. The detection of autoantibodies in blood, even in an unwell patient, does not therefore necessarily mean that the patient is suffering from an autoimmune disease, e.g 10% of the population over 70 years of age have detectable antinuclear antibodies in serum. Autoimmune disease is said to be present only when tissue damage and symptoms occur and autoreactive antibodies or T cells are detected.

Autoantibodies may be primary or secondary. Primary autoantibodies are rare in clinical practice and are defined as directly causing disease. Examples include the anti-TSH receptor antibody in Graves' disease, the anti-acetylcholine receptor antibody in Myasthenia gravis or the anti-voltage gated calcium channel blocking antibodies in Lambert Eaton Myasthenic syndrome. Secondary autoantibodies occur as part of an autoimmune process, may be associated with specific disease (and be diagnostically helpful), but do not directly cause disease. Examples of secondary autoantibodies include antinuclear antibodies in systemic lupus erythematosus and antimitochondrial antibodies in primary biliary cirrhosis.

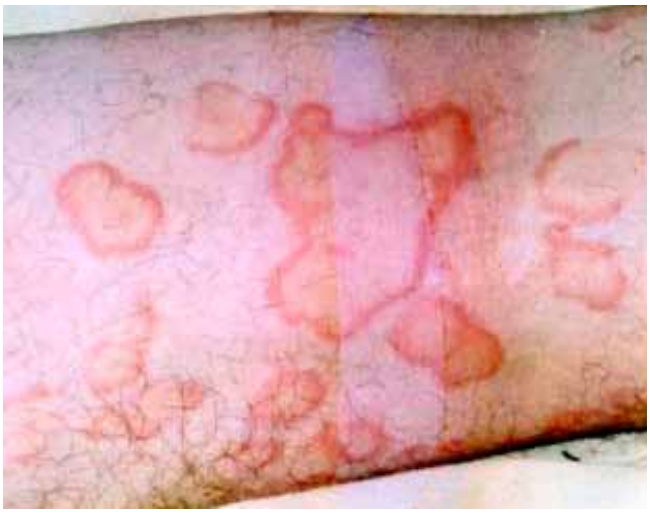

Fig 7. Typical urticarial lesions

Auto inflammatory disease

A further group of clinical conditions, characterised by disordered immunological responses, is gaining increasing attention. These conditions are typically characterised by regular fevers, lymphadenopathy, rashes, joint pain, mouth ulcers etc. They are often referred to as **Periodic Fevers,** and our understanding of their pathogenesis and treatment has increased rapidly over recent years[32]. Several have very specific genetic causes and respond exquisitely to therapeutic immunological intervention. **Familial Mediterranean Fever (FMF)** is one of the best known of these conditions and is characterised by recurrent fever, serositis (abdominal, chest or joint pain), typically beginning before the age of 18 years. It is caused by a mutation in the MEFV gene which encodes the protein pyrin, which normally acts to indirectly inhibit production of the inflammatory cytokine IL-1. Acute attacks are managed with analgesic and anti-inflammatory drugs and the long term administration of colchicines reduces the frequency and severity of attacks. **TNF Receptor Associated Periodic Syndrome (TRAPS),** previously known as **Familial Hibernian Fever (FHF)** (as affected patients seemed to share Irish ancestory,) is associated with mutations in the TNF Receptor gene (TNFRSF1A). It has similar clinical features to FMF, but patients respond very well to treatment with the decoy TNF receptor, etanercept. A number of other periodic fever syndromes exist; including hyper IgD syndrome (HIDS) and Muckle Wells/Familial Cold Urticaria syndrome (associated with mutations of MVK and NLRP3 genes respectively). In a number of these patients, specific immunological intervention with drugs such as the IL-1 antagonist Anakinra is proving particularly effective[33].

CONCLUSION

This mini-review has outlined the basic components of the immune system and how they work together to generate normal effective immune responses. I have also highlighted how the response may be defective through deficiency, over-reactivity (allergy) and dysregulation (autoimmune/ autoinflammatory diseases). Constraints of space dictate that each area has been touched on only superficially and therefore further suggested reading sources are listed for those who wish to explore these issues further.

The field of primary immune deficiency has been revolutionised by the identification of single gene disorders which have assisted in disease classification and led to specific success in gene therapy. Allergic disease is also increasingly well understood in terms of basic science and it seems likely that we are on the threshold of a series of new developments in the area or desensitisation which should bring enormous benefits to patients. The combination of increased understanding of basic immunological inflammatory mechanisms and the development of novel therapeutic agents continues to deliver new effective treatments for immunologically mediated conditions that were once thought to be untreatable.

For the clinician interested in the application of basic science to the investigation and treatment of a wide range of different diseases, affecting both paediatric and adult populations, it is difficult to think of a more exciting area of medicine.

The author has no conflict of interest.

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Paper

Evaluating distinctive features for early diagnosis of primary sclerosing cholangitis overlap syndrome in adults with autoimmune hepatitis

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LIST OF ABBREVIATIONS:

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; AST, aspartate transaminase; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyl transpeptidase; HAI, hepatic activity index; IAHG, international autoimmune hepatitis group; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LFTs, liver function tests; MRC, magnetic resonance cholangiography; OLS, overlap syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibody.

ABSTRACT

Aims: Overlap syndromes constitute a significant proportion of autoimmune liver disease. Our aim was to describe our cohort and evaluate practical methods of correctly diagnosing autoimmune hepatitis / primary sclerosing cholangitis overlap syndrome as early as possible clinically.

Methods: 118 autoimmune hepatitis patients were screened for cholestatic liver function tests. 24 patients with cholestatic liver function tests were investigated for possible primary sclerosing cholangitis by clinicopathological review and magnetic resonance cholangiography. Retrospectively, potential predictors of autoimmune hepatitis / primary sclerosing cholangitis overlap syndrome were compared with a control group.

Results: Overlap syndrome was diagnosed in twelve (50%) of 24 autoimmune hepatitis patients with recent cholestasis. The cholestatic group had a lower AST (p=0.012) and International Autoimmune Hepatitis Group (IAHG) score (p=0.102), and higher IgM (p=0.002) at disease presentation. More patients in the cholestatic group developed ulcerative colitis (p=0.138).

Conclusions: Identifying AIH / PSC overlap syndrome at diagnosis is often difficult. Certain clinical and biochemical features should alert the clinician. All patients with AIH, and biochemical cholestasis should be investigated with MRC.

Keywords: Autoimmune hepatitis; overlap; primary sclerosing cholangitis.

INTRODUCTION

Autoimmune liver disease largely comprises autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). The understanding, definition, and treatment of autoimmune liver disease has changed since first described during the 1950s. Narrower case definitions and improved treatment have resulted from increased clinical awareness, enhanced by biochemical, serological, histological, and radiological techniques[1,2].

Since the 1980s, "overlap syndromes" (OLS) of autoimmune liver diseases have been described. OLS indicates a variant form of autoimmune liver disease with characteristics of AIH and PSC or AIH and PBC. The patient may present with features suggesting OLS, or develop them during the course of an initially "pure" autoimmune liver disease. Accurate categorisation and characterisation of overlap syndromes requires a high index of suspicion during evaluation of clinical, biochemical, immunological, histological and radiological features. Patients with OLS have a different disease course and require specific therapy. Compared to 20 years ago, overlap syndromes are more frequently diagnosed [3], and have been the subject of several recent clinical reviews[2,4,5]. Recognising OLS early offers optimum disease management to individual patients. Clearly defining OLS, rather than only utilising pure diagnostic categories of

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autoimmune liver disease, offers an opportunity to assess pathogenic mechanisms and develop treatment strategies.

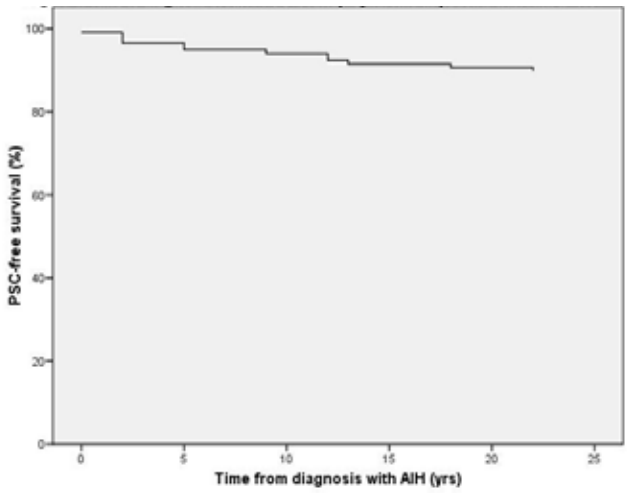

Fig 1. Time to diagnosis of AIH / PSC 'overlap' syndrome in patients with AIH. n-118

A useful tool in the study of autoimmune liver disease has been the International Autoimmune Hepatitis Group (IAHG) 'score' for AIH. This scoring for AIH was introduced in 1992 [6] and subsequently revised in 1999 [7]. The IAHG score has been validated by prospective review [8], and found to have high sensitivity (98%) and moderate specificity (60-80%) for a diagnosis of AIH [9]. These IAHG criteria have not been designed or validated for OLS. However the criteria have enabled clinicians to compare cohorts of patients, and objectively study other liver diseases for features of AIH.

In cohorts of patients with AIH, the incidence of AIH / PSC OLS is described between 7% [10] and 10% [11]. In cohorts of patients with PSC, the incidence of AIH / PSC OLS has been described as 7% [12], 8% [13], 17% [14], and 54% [15]. The variation in prevalence rates may be attributed to different patient inclusion criteria and methods of screening for disease. Study analysis reveals that some retrospective studies suffer from incomplete data, poorly defined patient groups, and variation of the criteria used for diagnosis.

The clinical importance of early diagnosis, the improved quality and availability of Magnetic Resonance Cholangiography (MRC), and the variation of disease prevalence between previously published cohorts suggest a need for further investigation,. This study seeks to define the epidemiology of AIH / PSC OLS retrospectively in a cohort of patients with AIH, and to determine which investigations should be rationally employed to improve diagnosis.

METHODS

Patient selection

118 patients attending the Liver Clinic in a large, teaching hospital with a diagnosis of autoimmune hepatitis, were included in the study. The initial diagnosis was based on clinical presentation, biochemistry, immunoglobulins and autoantibody profiles and, where a liver biopsy was performed, histology. Follow-up since initial diagnosis ranged from 2 to 26 years [median 12 years].

TABLE 1:

Clinical and laboratory characteristics at clinical presentation of AIH patients who developed cholestatic LFTs and a control AIH group

Characteristic	Cholestatic group (n=24)	Control group (n=25)	p-value
Female (%)	14 (58)	15 (60)	1.000
Age at presentation	40.2 (±15.6)	43.4 (±15.7)	0.503
AST (u/L)	271 (±338)	722 (±692)	**0.012**
ALP (u/L)	463 (±528)	263 (±180)	0.084
IgG (g/dL)	21.0 (±12.0)	20.8 (±11.5)	0.990
IgM (g/dL)	2.47 (±1.44)	1.42 (±0.78)	**0.002**
ANA or SMA (titre ≥1:40)	15	12	0.365
AMA (titre ≥1:40)	2	0	0.488
Alcohol intake <25g/day	23	22	0.600
Other autoimmune disease	1	4	0.349
Diabetes Mellitus	4	5	1.000
Ulcerative Colitis	6	2	0.138
IAHG score	8.3 (±6.0)	12.6 (±4.9)	0.102

Values are mean (±standard deviation), or categorical frequency

Study design and patient data

Those patients presumed to be at greatest risk of AIH / PSC OLS on the basis of biochemical liver function test (LFT) pattern were selected from the cohort. LFTs from the last three clinic visits were reviewed to identify all patients with cholestatic LFTs (defined as above normal ranges: GGT> 58 U/l and ALP >120 U/l). Our choice of 'cut-off' for "persistently elevated ALP or GGT" is based on previously described AIH cohorts[3]. This "cholestatic LFT group" comprised 24 patients, who subsequently underwent biliary tract evaluation by MRC, if not already performed. A radiologist (P.E.) reviewed each MRC specifically for features of PSC. Results were graded as "consistent with PSC", "suspicious of PSC", or "no evidence of PSC".

In an effort to identify distinguishing features possibly predicting OLS at the time of original diagnosis of AIH, we retrospectively compared the baseline characteristics of this cholestatic group with control patients. 25 control patients were randomly sampled from the remaining AIH cohort and matched by gender and age (±5 years). This group did not undergo evaluation by MRC.

For each patient in the study and control groups (total n=49), the IAHG score was calculated for the time of initial presentation. According to IAHG criteria[6,7], a pre-treatment aggregate score of >15 is 'definite AIH', and 10 – 15 is 'probable AIH'. Any diagnosis of ulcerative colitis was recorded, given the association with PSC.

Where available, slides from a liver biopsy performed at initial presentation i.e. before treatment, were blindly reviewed by two liver pathologists independently (M.L., M.G.) for well-described features of hepatitis or biliary disease modified from previous studies[16,17]. Depending on the variable in question, either a two-tier (0 or 1) or three-tier (0, 1 or 2) scoring system was employed. Necroinflammatory activity and fibrosis were scored according to the familiar modified Knodell hepatic activity index (HAI) system on scales of 0-4 or 0-6 [18]. For any features included in the histological component of the IAHG scoring system, the definitions used by the IAHG were followed where possible. Specifically, these describe "biliary changes" as "bile duct changes typical of PBC/PSC and/or a substantial periportal ductular reaction with copper/copper-associated protein accumulation".

Statistical analysis

The Mann-Whitney test (for continuous, non-parametric data) was used to compare the cohort with the control group. The two-tailed Fisher's exact test (employed because of the small sample size) was used to compare categorical variables. The Gamma test for concordance or discordance of ordinal variables was used to compare each patient group for degree of histological features. p-values <0.05 were considered significant. SPSS (Chicago, IL. USA. Edition 15.0, 2007) was used for statistical analysis.

TABLE 2:

Pathological features of pre-treatment liver biopsy at diagnosis of AIH in patients who subsequently developed cholestatic LFTs compared to AIH control group

Characteristic (%)	*Cholestatic group (n=10)*	*Control group (n=15)*	*p-value*
Granulomatous cholangitis (%)	1 (10)	0 (0)	0.400
Lymphocytic cholangitis (%)	2 (20)	1 (7)	0.426
Neutrophilic cholangitis (%)	0 (0)	2 (13)	0.500
Concentric periductal fibrosis (%)	0 (0)	1 (7)	1.000
Ductopenia (%)	3 (30)	1 (7)	0.267
Substantial periportal ductular reaction (%)	6 (60)	6 (40)	0.124
Copper-associated protein deposits (%)	5 (50)	2 (13)	0.132
Cholate stasis (%)	2 (20)	1 (7)	0.543
Canalicular cholestasis (%)	1 (10)	5 (33)	0.289
Biliary changes (IAHG defn) (%)	4 (40)	2 (13)	0.175
Predominant lymphoplasmacytic infiltrate (%)	6 (60)	9 (60)	1.000
Liver cell rosetting (%)	2 (20)	5 (33)	0.659
Severe interface hepatitis (%)	2 (20)	6 (40)	0.232
Confluent necrosis (%)	2 (20)	7 (47)	0.439
Moderate/severe spotty necrosis (%)	3 (30)	8 (53)	0.626
Marked portal inflammation (%)	1 (10)	4 (27)	0.453
Modified HAI fibrosis staging score (mean?)	2.5 (±2.2)	1.3 (±1.3)	0.221

Values are mean (±standard deviation), or categorical frequency

RESULTS

The clinical and laboratory characteristics from the time of diagnosis of the cholestatic group of AIH patients (n=24) and the matched control AIH group (n=25) are summarised in Table 1. The cholestatic group had a lower AST (p=0.012), higher IgM (p=0.002), and lower IAHG score (p=0.102) at presentation compared to the control group. The other parameters recorded were similar for both groups.

Only 10 of the 24 patients with cholestatic LFTs (including four of the 12 overlap cases), and 15 of the 25 patients in the control group, had an initial liver biopsy which was available for review. Therefore statistical evaluation of histology data was limited. Of the histological features assessed (Table 2), ductopenia, substantial periportal ductular reaction, copper-associated protein deposition, and overall 'biliary changes', as defined by IAHG criteria, occurred more frequently in the cholestatic group and hepatitic features were more prominent in the control AIH group, but none of the changes reached statistical significance.

In our cohort, 12 (50%) of AIH patients with cholestatic LFTs had features of PSC on MRC. At the time of initiation of this study, eight cases of AIH had already been reclassified as AIH / PSC overlap syndrome. During the course of this study, four more patients with cholestatic LFTs were demonstrated to have cholangiographic features consistent with or suspicious of PSC.

Comparison of the AIH / PSC OLS group (defined by abnormal MRC), the cholestatic LFT group (with normal MRC), and the control AIH group, showed a similar duration of clinical follow up (mean 11.2 years, range 2-28 years). Rates of clinical remission, relapse, liver failure requiring transplantation, or death, were similar between each of these three groups.

DISCUSSION

This study showed that, of 24 patients who were identified from a cohort of 118 AIH patients by the development of cholestatic LFTs, one half (12/24) had features of PSC on MRC evaluation, indicating a diagnosis of AIH / PSC OLS. A retrospective comparison of this cholestatic group with a control population at the time of presentation, was performed in an attempt to identify important early predictive features for developing OLS. At time of original diagnosis of AIH, patients in the cholestatic group had lower transaminases, higher serum IgM levels and a greater incidence of ulcerative colitis. IAHG scores were lower than the control group. In our cohort, no other clinical or pathological differences between the two groups were statistically significant.

Many groups have studied patients with autoimmune liver disease. Abdamlian et al.[11] prospectively studied 79 patients with a clinical diagnosis of AIH. They found that 10% had definite or probable PSC on MRC. Predictors of PSC were younger age at diagnosis, elevated alkaline phophatase at diagnosis, elevated bilirubin at time of MRC, and greater lobular activity on initial liver biopsy. Gheorghe et al.[10] studied 82 patients with AIH. Only eight of this group underwent ERCP (based on a cholestatic biochemical or histological profile), of which seven were positive for features of PSC. Therefore at least 7% of their AIH cohort had features of AIH / PSC OLS. Our finding that at least 12 (10%) of 118 AIH patients developed AIH / PSC OLS is consistent with these studies. The most comprehensive descriptive epidemiology of autoimmune liver disease prevalence and categorisation comes from Czaja et al.[15], who retrospectively reviewed 225 patients with any autoimmune liver disease. Of the 225 patients, 18% were reclassified as having OLS. 14 of 26 patients with PSC (54%) were found to have features of AIH and PSC.

Four large studies have reviewed patients with cholangiographically-proven PSC for features of AIH (assessed by IAHG criteria[7]). Kaya et al.[12] (n=211) reported 1.4% of PSC cases had 'definite' AIH and 6% had 'probable' AIH. Floriani et al.[14] (n=41) found 17% with AIH, van Burren et al.[13](n=113) found 8% with 'definite' AIH, and Boberg et al.[4] (n=114) found 2% with 'definite' and 33% with 'probable' AIH.

The pathogenesis, time of disease onset, and sequence of progression of AIH / PSC OLS is poorly understood[5],[19],[20]. Retrospective analysis of the initial diagnosis is usually impossible because most patients do not have both cholangiography and liver biopsy performed at time of diagnosis of AIH. McNair et al.[21] presented five cases of AIH / PSC OLS. Two had 'pure' AIH at diagnosis, which transformed into AIH / PSC OLS subsequently. Three had concurrent features of AIH and PSC at presentation. Abdo et al.[22] reviewed 91 patients with AIH. Six patients (7%) subsequently developed cholangiographically-proven PSC. This included three patients with a previously normal cholangiogram, performed after the initial diagnosis of AIH. Gregorio et al.[23] prospectively studied children attending King's College Hospital liver clinic (London, UK) with

a diagnosis of AIH (n=28) or PSC (n=27). All patients underwent biopsy and cholangiography at presentation. Of the 27 patients with PSC, 14 (52%) had 'definite' and 13 (48%) 'probable' AIH by IAHG scores. One patient with 'pure' AIH and normal cholangiography at presentation, subsequently developed cholangiographically-proven PSC. As discussed by these and other authors, it appears that some cases of 'pure' AIH, with no features to indicate AIH / PSC OLS at diagnosis originally, subsequently can transform into AIH / PSC OLS[21,22].

The main weaknesses of this study are the small number of patients and incomplete data. Clinical notes for baseline data at diagnosis were not always available due to the long duration of follow-up. Many cases did not have a liver biopsy performed and some liver biopsies were unavailable or uninterpretable. MRC scanning is clearly preferable to ERCP from a patient perspective, but may cause claustrophobia, which prevented MRC in one case. MRC has a sensitivity of 82 to 91% and specificity of 85 to 98% [24,25], when compared to the 'gold standard' ERCP for the diagnosis of PSC. The sensitivity of MRC has improved due to better availability and quality of MR scanning. 'Small duct' PSC (biochemical and histological features of PSC, but normal cholangiography) will not necessarily have been identified by our investigations. Angulo et al.[26] identified 18 patients (5.8%) from their PSC cohort (n=309), with 'small duct' PSC. Only 25 AIH patients, out of our cohort of 118, underwent cholangiography. Therefore, the prevalence of AIH / PSC OLS may be even greater in our cohort.

This is the first study to examine whether an earlier diagnosis of AIH/PSC OLS could be made in patients with an initial clinical diagnosis of AIH. Our study reiterates the finding of other groups: a significant minority of patients diagnosed with AIH will eventually turn out to have AIH / PSC OLS. There are no clinical, biochemical, serological or histological findings which strongly predict this development. Therefore, we recommend that MRC should be performed in every case of AIH where there is an elevation of ALP and GGT, following a poor transaminase response to corticosteroids. In the event of a normal MRC, liver biopsy should be considered to look for small duct disease. The frequency with which MRC should be performed and whether MRC would reveal cases of AIH/PSC OLS in AIH patients with normal ALP and GGT remain to be determined.

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Paper

The Impact of Emergency Nurse Practitioners on Referrals to a Tertiary Hand Trauma Service: A Pilot of Referral Quality Scoring System

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ABSTRACT

Hand injuries account for 2000 referrals to the Northern Ireland plastic surgery trauma service each year. Emergency nurse practitioners are increasingly utilised to assess and manage minor injuries and independently refer patients to the hand trauma service. This paper uses a newly developed scoring system to assess the impact of varying grades of referring practitioner on the quality and appropriateness of referral.

INTRODUCTION

Hand injuries account for 20% of cases treated in accident and emergency departments [1]. Following the introduction of United Kingdom waiting time targets, more A&E departments have instituted emergency nurse practitioners (ENP) in an attempt to target minor injuries [2]. As a result, increasingly, hand injuries are being assessed by ENPs and referred to tertiary hand trauma services. The Royal College of Nursing (RCN) states there is 'a lack of definition of the role of advanced nursing practitioners' but the accepted legal advice is that practitioners must be judged by the standard of the post, not the person filling the post. The pressure on tertiary care emphasizes the need for appropriate referrals, in order to minimize the need for further investigation and subsequent delays in instituting definitive treatment [3].

In Northern Ireland, the majority of hand injuries are referred to the Plastics and Maxillofacial Service based at the Ulster Hospital, Dundonald. The hand trauma service is based on a daily trauma clinic, which manages approximately 2000 patients per year. This is a 'one stop shop' where patients are assessed, prepared for and proceed to theatre, with the aim of reducing the need for in-patient stay. To this end, telephone referrals are received and patients triaged to attend a trauma clinic, usually within 24 hours. Standard advice on the initial management is issued routinely to all grades of referrers, regarding wound dressings, antibiotics and fasting times.

Due to the increasing workload, there is an ever greater reliance on the quality of history taking, examination and initial management undertaken in accident and emergency departments to ensure appropriate referral and efficient use of scarce plastic surgery resources. An efficient referral process relies on 3 components: history, examination and initial management, accurately taken and appropriately recorded; the appropriateness of the referral to an emergency trauma service; and outcome of the trauma clinic episode. The outcome can be objectively recorded, while appropriateness is the subjective opinion of the receiving clinician. However, no audit tool currently exists that allows the quality of hand trauma referral to be objectively graded and used to analyse trends either between groups or over time. It could be presumed that a high quality referral would be deemed appropriate for management in trauma clinic and in the majority of instances lead to an outcome of surgical intervention or follow-up at hand clinic.

This study pilots a method of generating a Hand Injury Quality Referral score, relating this to the appropriateness of the referral and episode outcome, and analyzing trends across the grades of referrers.

METHOD

Data was prospectively collected from 100 patients attending the trauma clinic. This was collected between October and April with 50 consecutive patients in each group to allow time for adequate induction for rotating junior doctors.

Those with severe hand injuries requiring immediate transfer were excluded. All other patients were discussed in advance with the referring practitioner by telephone, given standard advice in accordance to departmental guidelines on initial management and subsequently assessed at the trauma clinic within 24 hours.

The data was collected on a standardised proforma, taking the information from the referral documentation (either a referral letter or A&E 'flimsy') and supplemented with patient questioning if necessary. Data was collected on elements of the history, examination and initial management which combined to generate the Hand Injury Referral Quality score and was calculated by the authors, independent of the receiving surgeon who was blinded to this process. The outcome of the patient episode and appropriateness of the referral as judged by the receiving surgeon was also recorded.

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The details on the Hand Injury Quality Referral score are presented in Table 1, and were calculated by an independent scorer.

Table 1.

Hand Injury Quality Referral Score The maximum score possible is 23. However this can be adjusted for individual injuries and local protocol and allowances for variations in injuries and different practices can be made. For example, a closed injury would be allocated 1 for each of the elements of wound management and antibiotics to allow for direct comparisons between varying injury patterns.

History and Examination Elements (1 point for each recorded on referral)	**Initial Management Elements (1 point for each completed)**
Mechanism of injury	Relevant imaging
Date of injury	Hard copies
Excluded other injuries	Wound washout & closure
Past medical history	Wound dressing
Drug history	Antibiotics
Allergies	Analgesia
Hand dominance	Tetanus
Site	Fasting status
Side	
Neurological status	
Perfusion status	
Functional loss	
Accurate description	
Total: /15	Total: /8

RESULTS

ENPs generated 52% of referrals followed by SHO equivalent grades (32%) and registrars (11%). We separately recorded 5% of referrals as 'Doctor' as the grade of medical staff was not clarified. The mean, range and 95% confidence intervals for the Hand Injury Quality Referral Score did not show significant differences between referral groups, although the widest range of scores were observed in the ENP group. The majority (73%) required surgical intervention while 15% of all referrals were discharged immediately with no planned follow-up. The ENP group most frequently referred patients who were subsequently discharged (22%) but the difference across referring groups was not statistically significant. Overall 17% of total referrals were deemed to be inappropriate.

Of those referrals deemed inappropriate by the receiving surgeon, 70% were generated by ENPs, which was statistically significant (p=0.042). Drug history was the most poorly recorded (24% of referrals), and a high proportion of patients did not receive antibiotics (18%), have their tetanus status clarified (26%) or receive information about fasting (40%).

DISCUSSION

ENPs refer more patients to our service than all medical grades combined which is a recent phenomenon as only referrals from doctors were previously accepted. Hand Injury Quality Referral scores across the referring grades were not found to be significantly different. Using this new scoring system, referrals from ENPs can be considered to be as complete and accurate as those from any grade of doctor, which is in keeping with the literature[4]. ENP referrals were more likely than other groups to be judged as inappropriate by the receiving surgeon and more likely to be immediately discharged without need for surgical intervention or subsequent follow-up at an outpatient clinic. Overall, accepting referrals from ENPs is clinically justified and they are providing a safe service equivalent to medical staff. However, as a group they would benefit greatly from feedback to highlight the elements of a good quality referral, such as antibiotic and tetanus administration. Due to the long tenure in such posts, targeted training is likely to yield discernible benefits. By using the Hand Injury Quality Referral Score changes in referral patterns can be monitored effectively and used to target training in hand injuries.

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Paper

Multidisciplinary assessment of vision in children with neurological disability

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ABSTRACT

Introduction There is no consensus as to the best method of assessing vision in children with neurological disability. There are a variety of tests and approaches that can be used. It is important to look at models of assessment that identify the visual diagnosis and provide appropriate feedback and explanation to parents, carers and educational professionals.

Methods This study reports on the results of comprehensive visual assessments of fifty children with neurological disability over a three year period. It focuses on the feedback from families and professionals after the assessment report was disseminated.

Results The majority of families and professionals strongly agreed that a specialist assessment was needed in this population. Parents and professionals particularly valued the written report which provided guidance on appropriate visual material including advice relevant to education.

Conclusion This study highlights the importance of specialist teams engaging with local child development services and indicates how partnership working can potentially be emotionally supportive as well as developmentally beneficial.

INTRODUCTION

There is no consensus as to the best method of assessing vision in children with neurological disability. There are a variety of tests and approaches that can be used.[1-3] It is therefore important to look at models of assessment that clearly identify the visual diagnosis which encompasses the ophthalmic diagnosis and visual characteristics and how to provide appropriate feedback and explanation to parents, carers and educational professionals doing so in a holistic way that takes into account the other medical diagnosis and specialist needs the child may have. In assessing the utility of such a service we not only need to look at the effectiveness with which a visual diagnosis is obtained after an assessment but also the perceived utility of such an assessment by those individuals caring for and educating the child. Evidence suggests that developmental intervention in the form of visual promotion may benefit even those children with severe or profound visual impairments.[4] Studies show that children with visual impairment demonstrate delayed development in other areas due to the lack of visual stimulus. This may impact greatly on the child with other neurological difficulties.[5;6]

Parents and carers have an important role in visual assessment. The visual skills inventory paper published in 2007 by McCulloch and colleagues found when parents were asked focused questions on their child's vision their responses correlated well with visual ability.[7] This model provides practical assistance for clinicians trying to plan appropriate assessment tools and may result in a more efficient process. Parental involvement is also likely to heighten awareness of the child's visual abilities and may assist in preparing them for a diagnosis of visual impairment. The assessment of visual acuity and function in the paediatric neurodisability population is a complex process, which may require testing by a number of professionals and using various strategies before a reliable conclusion can be drawn about the child's visual ability. There is little in the literature on communicating with families about a diagnosis of visual impairment. One team described various methods of meeting parental needs around this time using strategies such as a dedicated key worker. [8] Studies demonstrate the widespread use of asking parents to provide information on their experience of health service provision for children with disabilities.[8-11] The use of questionnaires has been demonstrated to be effective and valid in a number of settings.[8,11,12] This study reports parental and professional evaluation of a pilot visual assessment clinic with the use of some open ended questions and free text as a means of identifying areas of good practice or dissatisfaction.[13]

The pilot clinic focussed on visual assessment in children with neurodisability. Research on adults with learning problems showed they are fifteen times more likely to have a visual impairment than the rest of the population.[14] Woodhouse

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demonstrated that the more severe the learning disability the more likely it was for visual acuity to be reduced, findings mirrored by the paediatric literature.[1,15,16] The adult literature provides the basis for choosing tests of visual acuity that might be applicable in the neurologically disabled childhood population with numerous studies on testing techniques.[15-17] One of the aims of visual testing is to establish how well an individual's visual system can resolve detail, this is known as their visual acuity. This is a quantitative measure and is usually tested using standardised charts e.g. Snellen with specialised printed targets called optotypes. In the paediatric population these standardized charts have been adapted to include symbols that are recognisable by young children. In young infants unable to identify symbols more opportunistic techniques are needed and tests of preferential looking were developed to try and gauge infant acuity. It is possible to measure the electrical response of the brain to visual stimuli. Visual evoked potentials (VEP) provide a non-invasive, objective measure of visual function which reflects the activity of the visual pathway from the retina to the visual cortex[18] VEPs are generated using standardised flash and pattern stimuli and can be used to assess visual impairment and visual acuity in infancy. It is important to recognise that VEPs merely assess the integrity of the visual pathway. 'Seeing' implies resolution, recognition and conscious perception. Children with complex neurodisability are more likely to have conditions such as nystagmus, central scotomas and poor fixation as well as disorders affecting muscle tone and epilepsy. All these conditions can impair the VEP quality, making acuity assessments more difficult. Success rates vary with this form of visual testing from 50-91% in children with complex neurodisability. [1]

Useful vision requires an ability to focus the eye through a field of vision and to detect variation of depth and colour. The ability to focus the eye (accommodation) can be assessed objectively using refractive techniques that do not rely on patient participation.[19] Visual fields can be tested by conventional direct confrontation techniques or more opportunistic techniques such as Stycar balls.[15,20,21] All of the techniques and tests described can be used to help build an impression of what a child with a neurological disability can see. The assessment process undertaken in the pilot clinic used a variety of tests administered by a team of clinicians experienced in the field of paediatric neurodisability. We report on the experiences of parents and professionals who used the service describing their opinions of the clinic setting, assessment process and the final clinical report.

METHODS

Setting

The pilot visual assessment clinic took place in Northern Ireland over a three year period from 2003-2006. The clinic took place in the Royal Hospital in Belfast. Dedicated facilities are present for paediatric visual assessment including acuity testing and retinoscopy. There is on site access to electrophysiological testing in the hospital. A multidisciplinary team approach was adopted for the pilot clinic. The team was lead by a senior academic optometrist, supported by two academic optometrists with expertise in the assessment of vision in children with neurological problems (JJ, KS, JMcC). Other team members included a paediatrician with expertise in neurodevelopment, an orthoptist, a teacher of the visually impaired (MS) and a clinical scientist with expertise in electrophysiology (CW). The role of the principal author (CL) was as an observer reflecting and reporting on the process.

The sample population consisted of 54 children. This was a convenience sample based on the total number of children seen within the period in which the clinic was funded. Children under the age of sixteen years who had a neurological impairment and a suspected visual impairment were eligible. All children recruited were resident in Northern Ireland and were under the care of a community paediatrician and/or in 'Special Education'. All children referred to the clinic were offered an assessment. All of the available parental and professional feedback was analysed.

METHOD OF RECRUITMENT

During 2003 letters describing the clinic were sent to all community paediatricians and paediatric ophthalmologists in Northern Ireland. They were invited to refer children with neurological disability in whom there was a concern about visual impairment. Particular emphasis was placed on recruiting children for whom the process for 'statement of special educational need' was either imminent or ongoing. All parents and referrers of children who attended the clinic were invited to participate in a follow up questionnaire.

Visual assessment tools were chosen on the basis of the team's particular expertise with certain tests and on reports in the literature that demonstrated reliable methods of assessing visual ability in young children and adults with neurological impairment.[22,23]. The assessment was individualised to meet the needs of the child. For each child a full medical and ocular history and functional visual assessment was obtained. A parent /carer was always present. In order to provide additional information a visual behaviour questionnaire was sent to families prior to attendance at clinic which provided a preliminary baseline of the child's visual ability. This was supplemented by a discussion with the carer during the clinic setting as to the child's current visual behaviour at home and at school where appropriate. Each individual recorded their assessment findings. Following a round table consultation a consensus was reached on results to be included in the report. The clinical report summarised some of this information in 'lay' terminology. Recommendations on size, colour, contrast and type of visual material were presented as part of the report. The report was reviewed by the whole team before dissemination to families and professionals. This method of reporting visual information to families and professionals has been used by other specialist low vision clinics.[24] A list of the visual assessment tests and techniques is provided in Table 1. An analysis of the visual assessment process and results obtained will be reported in a further paper.

This paper focuses on parental and professional satisfaction with the specialist visual assessment clinic visit and report. Satisfaction data was obtained by administration of a brief 5 point Likert scale questionnaire- Strongly Agree to Strongly Disagree. This was based on similar questionnaires in the research literature and adapted by the clinic staff.[25-28] The Likert scale questionnaire was composed mainly of 'closed' statements.[8,11,24,29] There was also free response. Two questions

asked for a rating on the usefulness of the clinic both at the beginning and the end of the questionnaire. Key questions were the accessibility of the clinic, the appropriateness of the clinic environment for children with neurodisability, the helpfulness of clinic staff, the ability to ask questions during the consultation, clarity of the report and if it was useful on a day to day basis. There were two sections for free response one rating the most beneficial and least beneficial aspects of the clinic and one question on the clinic overall. The parental questionnaire was administered by one of the clinic team by telephone. The professional questionnaire was returned by post. Sample questions included: 'I think there was a need for this service', 'the report was meaningful and relevant (it aids my practice)' a further question examined if they had acquired new information about their patient. Copies of the questionnaires are provided in Appendix 1.

RESULTS

All of the available parental and professional responses to the follow up questionnaire were analysed. A total of fifty children were seen at the pilot special visual assessment clinic. Four additional children failed to attend their appointment. The age range was from 0.6-15.9 years with an average of 5.7 years. Twenty nine were female. A total of 34 parental questionnaires were completed by telephone. Forty one health professionals responded to the follow up questionnaire in writing.

MEDICAL CONDITIONS IN THE CLINIC POPULATION

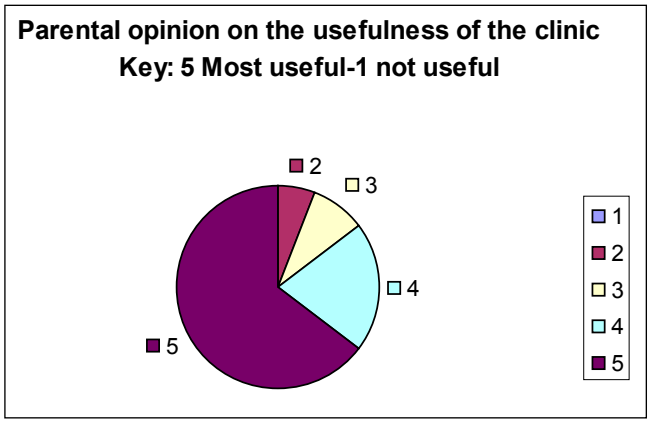
The most prevalent condition in the clinic population of fifty children was cerebral palsy (CP). There were seventeen children with quadriplegic cerebral palsy and five children were described as having hemiplegic cerebral palsy (see Table 2). Severe epilepsy and epileptic encephalopathy were the next most common cause of a neurological disability. Other conditions included congenital brain malformations and retinal disorders.

INFORMATION INCLUDED IN THE CLINICAL REPORTS IN THIS POPULATION

A complete visual assessment including acuity, refraction and visual fields was undertaken in the majority of children (31/50). Four children with mild or moderate impairment did not have visual field testing performed, one child was noted to be poorly co-operative and no reason was given for the other three cases. Formal assessment was not possible in 15 children identified as having either severe or profound visual impairment. Thirty three (66%) children were given advice on visual ability specific to their education needs. Twenty (40%) were affected by a severe or profound visual impairment and required advice about non-visual methods of education. Six (12%) children with moderate impairment received similar advice, two children in this moderate group were below the age of two years and a further two children did not receive advice as the relevant professional was not present at the clinic. Seven (14%) children with mild visual impairment benefited from advice for school, this mainly consisted of recommendations on materials, toys, size of print/objects and distance for working. This was also an opportunity for the clinic professional to recommend if the child would benefit from regular input from a specialist teacher of the visually impaired.

RESULTS OF THE PARENTAL FEEDBACK QUESTIONNAIRE

This questionnaire was administered by telephone following clinic attendance. A total of 34 parents were available to respond to the questionnaire. Satisfaction data was based on a 5 point Likert scale questionnaire- Strongly Agree (5) to Strongly Disagree(1). See Appendix 1. The majority responded that the clinic visit was useful. This was asked at the beginning and end of the questionnaire. Parental response was not significantly different depending on the timing of the question. Twenty nine (85%) graded it as Agree (4) or Strongly agree (5) initially. Thirty give this response at the completion of the questionnaire. Two (5%) parents rated the usefulness as Poor (1 or 2).

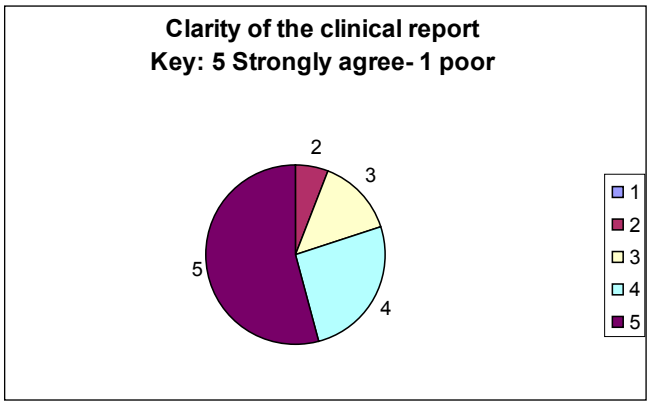


Thirteen (38%) families reported they did not receive any information describing the clinic prior to attendance. Of those who did receive information 17 (50%) rated it as Agree (4) or Strongly agree (5). Thirty one (91%) parents expressed a high degree of contentment with the explanation give by the clinic staff when they arrived for the appointment. Thirty three (97%) families rated the staff as being as helpful as possible. Thirty two (94%) families reported they had the opportunity to ask questions during the clinic visit.

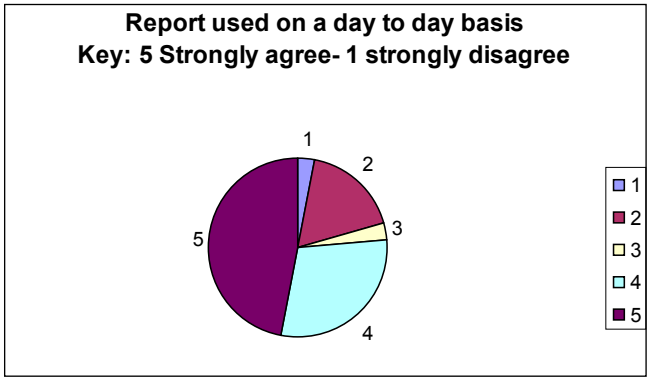
Accessibility was a major problem for 11 families. Twenty four of the 34 respondents described parking access as 3 or less. The main comment made when asked was the lack of disabled access parking.

The clinic environment was rated as three or less by 17 (50%) families. Free text responses in the 'other comments' section of the questionnaire described it as a 'boring environment for non-visual patients' and that the room used was 'small… stuffy….overcrowded'.

As described a standardised clinic report was generated after every clinic attendance. This was sent to parents and the professional who referred the child. Responses were analysed using the Likert scale and also free comment. Thirty one (91%) of 34 parents rated the report as Useful (4) or Very useful (5); one parent stated it was poor. Twenty eight (80%) reported it was written in a way that could be understood, but seven (20%) felt this was not the case. In the free text responses these parents described the report as 'too technical' and the language should be 'plain and simple'.



Parents were asked to respond freely regarding the most beneficial and least beneficial aspects of the report. The responses were coded for analysis. Benefit appeared to be mainly due to the perceived usefulness of written information to be shared with professionals and the use of the report as a meaningful summary of a detailed visual assessment. Overall there were 25 comments around this theme. Five (15%) parents commented on the benefit of specific advice in relation to equipment or educational aids and three found the comments on promoting visual development helpful. Six (18%) described the technical nature of the report as not beneficial. Two (6%) parents felt the report was not detailed enough. The majority (76%) of parents felt the report contained information that was useful on a day to day basis.



Responses about the most beneficial aspects of the clinic generated four themes: Approachable and helpful staff, knowledge about the child's visual status, advice and equipment and no benefit. There were 19 positive comments based around the theme of knowledge and visual assessment and 8 comments on the approachable and helpful staff. Six parents(18%) commented positively about the additional benefit of detailed and advice about visual promotion and the supplying or recommendation of appropriate equipment. When asked to comment on what was of least benefit, the majority of parents reported nothing negative. A small number of parents found the distance and parking problems to be detrimental, others commented on the late timing of appointments and unsatisfactory clinic environment. One parent commented on the technical nature of the assessment and four reported they would have liked more detailed advice following the assessment. One parent felt the assessment was inaccurate.

The final section where parents were asked to comment freely generated seven themes:

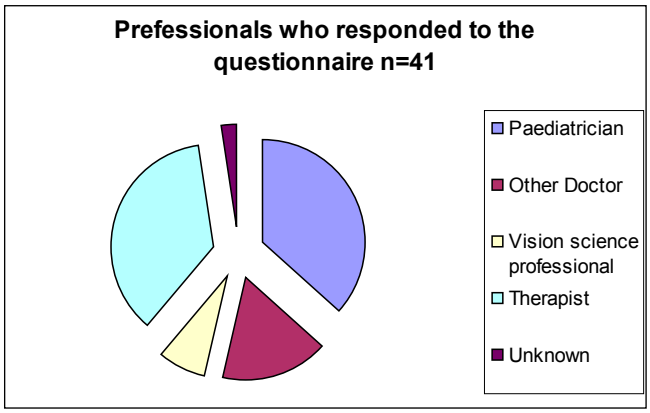
- Staff
- Knowledge and information
- Visual equipment
- Negative responses around travel and appointment timing
- Technical report
- Lack of information regarding follow up arrangements
- Parental distress during and following the appointment

Parents valued the honesty and approachable nature of the clinic staff. The use of informal and non-medical terminology was welcomed. Parents reflected positively on new knowledge acquisition and commented on how this affected their ability to work with their child at home and also communicate meaningfully with health professionals especially about visual equipment which may be beneficial for their child. The clinic population was primarily composed of children with neurological difficulty, the majority of whom had mobility problems. Six (18%) families reported that the late afternoon appointments, distance to the clinic and parking was a negative experience. Overall there were a range of comments about the technical aspects of the clinical report. Five (15%) parents commented on the benefit of specific advice in relation to equipment or educational aids and three found the comments on promoting visual development helpful. Two (6%) parents felt the report was not detailed enough.

Five (15%) parents commented on the lack of clarity regarding a follow up appointment. Four (12%) parents commented on the impact of being told a child had a severe visual impairment. One (3%) parent reported the difficulty of hearing this news from unfamiliar professionals and how it was not an accurate assessment. Another described the stress of the detailed assessment in an overcrowded clinic room she felt this was difficult for her as a parent and 'daunting' for a child.

HEALTH PROFESSIONAL'S RESPONSE TO THE CLINIC QUESTIONNAIRE

There were a total of 41 responses to the written questionnaire that was sent out to professionals with the clinic report. Most professionals listed their name and professional group in their response. Responses were coded in a Likert scale 5: strongly agree, 1: strongly disagree.

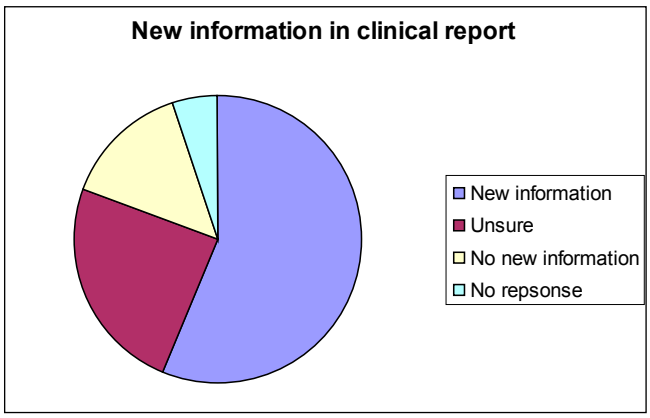


NEED FOR THE SERVICE

The majority 90% (37/41) of professionals were in strong support of the need for this service. Twenty six (63%) were confident it did not duplicate existing services, although eight respondents were unsure.

PROFESSIONAL SATISFACTION WITH THE CLINIC REPORT

Thirty two (78%) professionals felt the reports were meaningful, relevant and aided their practice. Interestingly, 23 (56%) stated the reports contained previously unknown information.



The majority of professionals (62%) agreed that parents would find the report useful. Four (10%) were unsure and two (5%) felt parents may find it unhelpful. There were few free text comments and therefore the development of themes was not possible. One paediatrician commented that the detail in the report was very helpful. Therapists from a range of backgrounds stated they had found it useful for preparing therapy sessions and treatment plans.

DISCUSSION

The structure and feedback from a specialist assessment is particularly important in children with neurological disability. There are implications for the length of the appointment, the information gathered beforehand, professionals present and feedback afterwards. A detailed referral document is helpful in reducing the amount of time spent going over history which is familiar to the family and the local team. Sending out questionnaires and letting the family know the structure of the appointment could be helpful prior to clinic attendance. Inviting a local professional to attend is common practice in many paediatric neurodisability clinics although this is dependent not only on parental consent but also on space.

Table 1

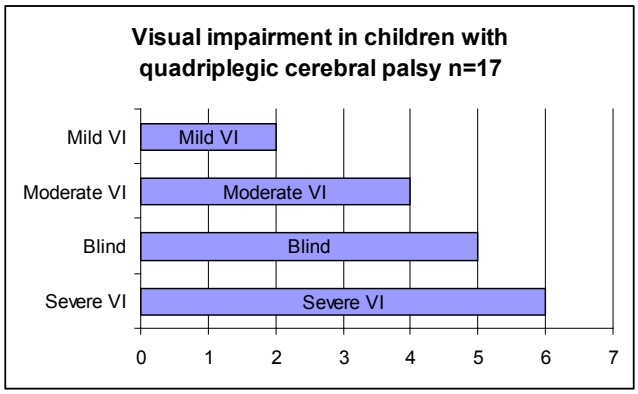
1. Refraction type and assessment technique
   - Retinoscope
   - Full aperture lenses
2. Accommodation
3. Pupillary reflexes
4. Eye contact
5. Nystagmus
6. Ocular posture
7. Pursuit movements
8. Saccadic patterns
9. Stereopsis
10. Colour vision (where appropriate)
11. Acuity Tests:
    - Logmar
    - Snellen
    - Kays
    - Keeler
    - Cardiff cards
    - Sheridan Gardiner
    - LH cards

    Techniques included:
    - Crowded letters
    - Single letters/symbols
    - Preferential looking
12. Electrophysiology - Visual evoked potentials
13. Assessment of strabismus
14. Visual field testing
15. Developmental review

Four parents commented on the distressing impact of being told their child had a severe visual impairment by a new team. This reflects the ongoing difficulties experienced by many families in coming to terms with the diagnosis of a neurological disorder.[8] This may be adversely affected by the number of consultations and specialists seen in order to obtain a coherent diagnosis.[10] Baird et al demonstrated that these expressions of dissatisfaction are often associated with parental depression.[9] However, comments in this study highlighted the value parents place on open and honest consultations that provided detailed knowledge and recommendations on how to work with their child. Research has shown that parental satisfaction is dependent upon the amount of medical language used, interpersonal skills of the professionals and the amount of information exchanged. [11] It would appear that the format of this pilot clinic and the subsequent report was noted to be helpful by the majority of parents. Comments on the testing environment and technical detail in the reports should be considered for future clinic design. Professionals who referred children also appeared to value the summary report which was shared with them. The majority identified that it contained previously unknown information and provided useful advice on how to progress with the child's visual management. Clinicians commented how the clinic supported their local Child Development Team by allowing therapists to devise realistic and appropriate programmes.

TABLE 2

Visual impairment in children with CP



The importance of the history and examination by an appropriately trained medical professional was valued by families and seemed to provide useful contextual information for the interpretation of visual tests. The inclusion of a specialist teacher of the visually impaired allowed the team to consolidate the visual findings in terms of relevance to education and home environment. It also facilitated recommendations on suitable visual materials. The inclusion of these two team members appears to have heightened parental and professional satisfaction in terms of the content of the consultation and the summary report. As previously discussed parents are often supported by a large number of local professionals. Good communication between clinic staff and local teams resulted in accurate and valued assessments. It is likely that the addition of a local team member to the clinic team at the time of consultation may have provided further helpful background information and contributed to putting families at their ease. [10,30]

A specialist clinic for children with neurodisability- what is important to families

- Appropriate facilities
  - Parking
  - Level access
  - Suitable changing and hoisting facilities
  - Appropriate play materials and information
- Experienced professionals
  - Knowledge of community teams and educational system
  - Confident practitioners in the relevant assessment process
  - Links to specialist professionals for further evaluation
  - Skills in providing verbal and written feedback to families and local professionals
  - Invitation to local professionals to attend for joint assessment
- Clear follow up arrangements
- Provision of support after diagnosis
- Advice on how to access appropriate developmental and educational material

LIMITATIONS OF THIS STUDY

The pilot clinic format was devised by a group of professionals who work regularly with children with neurological disability and their families. Their aim was an exploration of the potential need for a specialist service. This resulted in an open and fluid approach to the development of the clinic assessment techniques and report writing over the three year study period. This was responsive to the needs of the clinic population and the feedback from families and professionals, but as a result meant that there was less standardisation of clinical documentation and assessment techniques than would be found in a research clinic setting which usually has a strict protocol. The follow up questionnaires provided useful positive feedback reflecting the support of local teams for such a specialist service. It would have been preferable to use a recognised validated scale.[12] Ideally the questionnaire administered to parents should have been carried out by an independent person. There was no agreed protocol for the time period for administration and this too may have affected the responses as they are dependent on recall of the clinic consultation and the report.[31] Similarly there was a lack of protocol for following up non-respondents in both the parental and professional groups. This resulted in an incomplete data set.[29]

CONCLUSION

The numbers in this study are small. However, the affirmative responses of parents and professionals when asked if the service provided them with new and useful information supports the recommendations of other researchers who have demonstrated that specialist expertise is needed in assessing vision in children with neurodisability.[32;33]

The authors have no conflict of interest.

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Case Report

Neurosurgery in an octogenarian with dementia

Gemma Andrew[1], Estelle Healy[2], Brian Herron[2], Stephen Cooke[3], A. Peter Passmore[1], Stephen Todd[1*]

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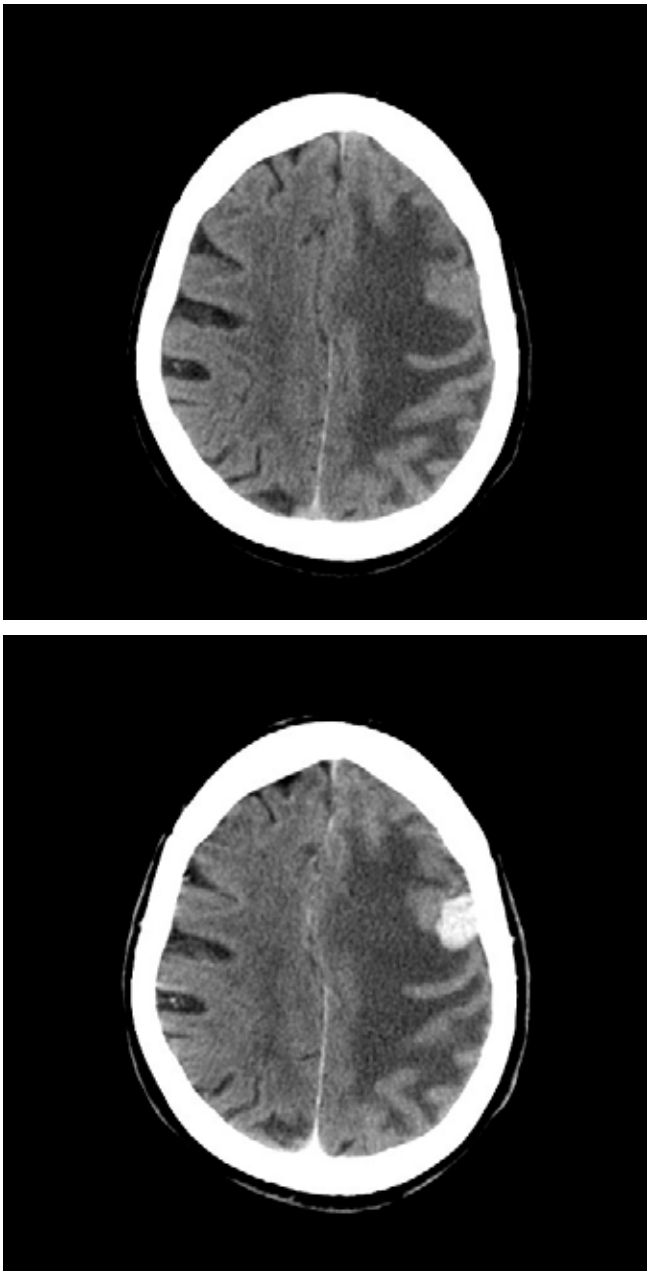

*Fig 1.*CT head. Scans pre (top) and post (bottom) administration of intravenous contrast demonstrate a soft-tissue density lesion measuring 2.2cm, the lateral border of which is confluent with the vault. There is extensive vasogenic oedema with some midline shift to the right side.

ABSTRACT

We report the case of an 83 year old female referred for evaluation of memory impairment. Routine neuroimaging showed unusual findings. Following subsequent clinical deterioration, she proceeded to neurosurgery with an excellent functional outcome. This case highlights that major surgery should be considered in older patients with comorbidities if an indication to operate is present.

CASE REPORT

An 83 year old lady was referred to the Memory Clinic by her general practitioner. Corroborative history from her son was of 1 to 2 years duration of insidious onset and gradual progression of short term memory loss, disorientation in time and place, and behavioural change with apathy and occasional agitation. She remained independent in activities of daily living with supervision from her husband. Past medical history included ischaemic heart disease, type 2 diabetes mellitus and chronic kidney disease. Medications were mirtazapine, glibenclamide, aspirin, bisoprolol, isosorbide mononitrate, ramipril, frusemide, amlodipine and rosuvastatin.

Physical examination was unremarkable, with no focal neurology in particular. On neuropsychological testing, she scored 67/100 on the Addenbrooke's Cognitive Examination (ACE), including 23/30 in the Mini-Mental State Examination (MMSE). Laboratory studies including full blood count, biochemistry panel, thyroid function and serum vitamin B12 and folate levels were unremarkable. A routine CT head scan was arranged (*Figure 1*). This showed a soft tissue density mass lesion measuring 2.2cm, the lateral border of which was confluent with the vault, which showed avid enhancement after intravenous administration of contrast material. There was extensive left hemisphere vasogenic oedema and midline shift. An urgent MRI was arranged (*Figure 2*). This showed a dural based extra-axial mass lesion causing significant mass

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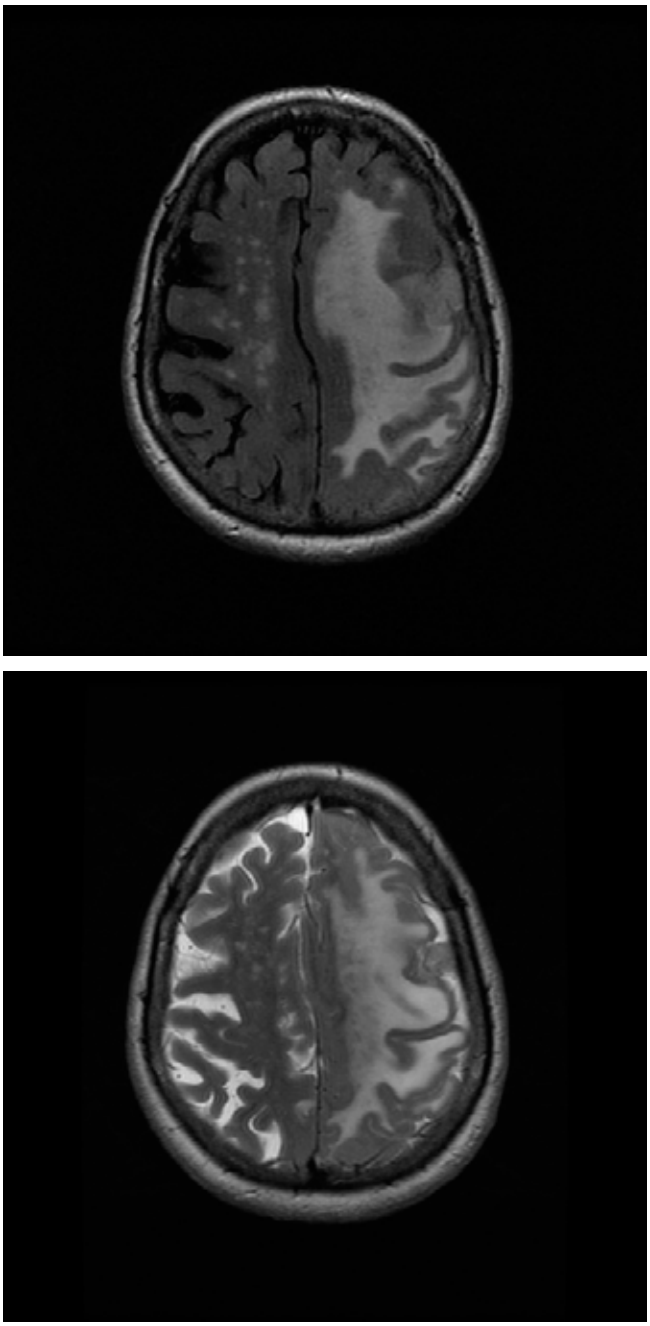

Fig 2. MRI head. These FLAIR images (pre top and post-contrast below) show a dural based mass lesion causing significant mass effect in the left hemisphere. It has a lobulated contour and indents the adjacent cortex. There is extensive vasogenic oedema in the subcortical white matter and there is effacement of the left lateral ventricle. No other lesion was identified.

effect on the left hemisphere. There was extensive vasogenic oedema in the subcortical white matter.

At follow-up four weeks after the initial assessment, her family reported that her cognition and function had declined. Based on the neuroimaging findings, dexamethasone 2mg tid was started and neurosurgical opinion sought. Three weeks later after a generalised seizure which spontaneously resolved after 2-3 minutes she was seen again. Further deterioration was reported. Dexamethasone had been stopped due to oral candidiasis.

After discussion regarding the risks and benefits of surgery, she underwent image guided resection of the left posterior frontal tumour seven weeks later. Considerable adherence to underlying brain was noted but complete tumour removal achieved (Simpson grade 1).[1] Histopathological examination of the operative specimen showed a secretory meningioma WHO grade 1 (*Figure 3*).[2] Post operative course was complicated by brachial vein thrombosis treated with anticoagulation. After a short period of rehabilitation, she was discharged home independent in ADLs. MMSE was 16/30. When last seen twelve weeks later, her condition had significantly improved and MMSE was 25/30.

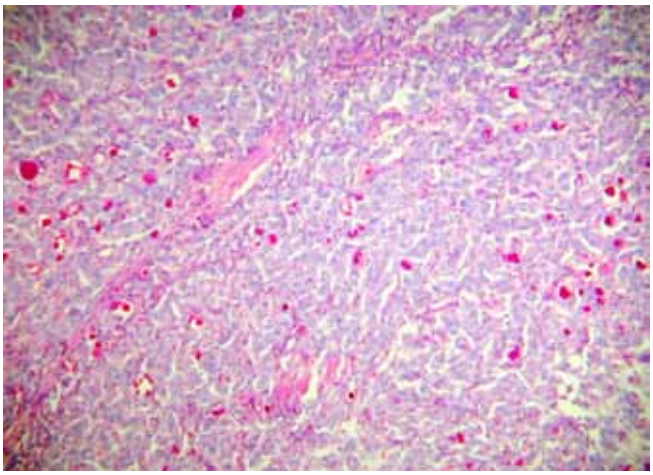

Fig 3. PAS stain of resected tissue showing typical features of secretory meningioma

Several important issues are highlighted by this case. First, neuroimaging is recommended[3] in all cases of suspected dementia to exclude other cerebral pathologies, as in this case. Second, good teamwork and communication between several specialists (geriatrician, neurosurgeon, pathologist, rehabilitation team and general practitioner) is essential to optimise the patient's outcome. Third, meningiomas are graded according to histopathological features as I, II or III with increasing risk of recurrence, morbidity and mortality with increasing grade.[4] This rare subtype, although grade I and therefore unlikely to recur, is associated with significant morbidity because of the unusual association with cerebral oedema. A detailed discussion of the pathological features of secretory meningiomas is beyond the scope of this report. Interested readers are referred to an in-depth review.[4] Finally, an excellent recovery from a major invasive procedure is possible despite presence of comorbidity. One recent prospective analysis found older age (>70 years) was associated with increased risk (OR 3.0, p=0.01) of perioperative mortality from surgical resection for intracranial meningioma.[5] Another single institution report suggests several features of our patient indicate good surgical outcome and short- and long-term survival – tumour size and location, extent of resection, presentation with confusion and seizure, medically controlled comorbidities and performance status.[6]

The authors have no conflict of interest

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Commentary

Giants of the British Isles

Lisa Bradley, Patrick J Morrison

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Most countries and civilizations have stories about giants in their culture. In Greek and Roman times, Giants were an integral part of history. Ovid documents the story of Giants who once piled mountains up to the stars and were destroyed when Zeus hurled his thunderbolts at them. Homer, in his Odyssey, describes many Giants, often the Cyclops, including the cannibal Polyphemus and the Lestrygones. The Cyclops apparently built the great stone walls of Argos, Tiryns and Mycenae. Several European legends attribute construction of Megalithic remains, including Stonehenge, to Giants so clearly they were very useful. Pliny records that primeval man had greater strength and abilities, and men of the time were but degenerate compared with them.

Geoffrey of Monmouth in his 'History of the Kings of Britain' tells of the exploits of Brutus, the first king who landed on British shores at Totnes in Devon and found the land inhabited by men of no normal stature. The Annual Register of Cornwall for 1761 documents that the tin mine at Tregoney-on-Fal had a stone coffin 11 feet 3 inches long containing a skeleton of a man estimated at 10 feet. Clearly Giants migrated as far as the British Isles fairly early in history.

Angus MacAskill (1825-63), the 'Scottish Giant' born on the island of Berneray, in the Western Isles stood 7ft 9in (236cm) tall. At his memorial museum a life size model illustrates his acromegalic features while documentation alludes to 'another giant' in his ancestry.

In Northern Ireland, we know of course that the Giant's Causeway columns of hexagonal and octagonal basalt could only have been handled by a group of engineering-conscious giants who ran a combined operation with the giants of Scotland to facilitate easier access between the two sister countries. Before it collapsed, the causeway stretched as far as the island of Staffa, which is also famous as the home of another Scottish giant, Fingal, whose cave was remembered by Mendelssohn.

Charles Byrne, another 'Irish Giant' was born in Littlebridge, Northern Ireland in 1761. His father was native to the area but his mother was Scottish. Incidentally, he was supposedly related to the Knipe brothers, the tallest identical twins (at 7ft 2in), born in nearby Magherafelt. He grew rapidly and in his late teens featured in street shows in Ireland, and later in London (on occasion with the Knipe brothers). After his death his skeleton was acquired by the surgeon John Hunter and was eventually deposited in the Hunterian Museum in London. In 1909 Harvey Cushing (a Boston neurosurgeon) and Sir Arthur Keith (the museum curator) documented

Fig 1. Antoine and Baptise Hugo with their five siblings.

that he had an enlarged pituitary fossa, concluding that his gigantism was most likely due to a pituitary adenoma[1]. Recent DNA studies have confirmed that mutations within the Aryl Hydrocarbon Receptor Interacting Protein (AIP) gene cause pituitary tumourigenesis, and are now recognised as a cause of familial pituitary adenomas displaying autosomal dominant inheritance and variable expression. Screening for AIP mutations is now recommended for patients with any type of pituitary adenoma occurring in a familial setting;

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allowing subsequent presymptomatic testing of relatives with the hope that early diagnosis should allow prompt treatment intervention to avoid excessive growth[2].

The hereditary aspect to pituitary disease is not new. The first recorded patients with isolated familial acromegaly were the Hugo brothers Antoine and Baptise, in the early 20th century. Their heights were over 2.3 metres and they had five normal siblings although looking at photos, at least one of the sisters is taller than her 'normal' brothers and has an acromegalic jaw and could potentially be an AIP gene carrier (figure 1). The only difference between the terms acromegaly and gigantism is one of timing - gigantism occurring before the fusing of the epiphyseal plates in puberty. Baptise was regularly exhibited in Paris, often for effect with little Adriens, a midget born in 1882 who appeared sometimes with his sister Marguerite.

It is not clear if Finn McCool or the Scottish or Cornish giants were related. Perhaps they were and if excavations ever commence around Staffa and a tooth or bones are recovered, we may get genetic confirmation of some hitherto unknown genetic ancestry of the Giants inhabiting the British Isles.

Acknowledgement. We thank Professor Marta Korbonits for helpful discussions and clinical guidance. The authors have no conflict of interest.

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Grand Rounds

Optimal Management of Peripheral Arterial Disease for the Non-Specialist

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ABSTRACT Peripheral arterial disease (PAD) now affects approximately 20% of adults older than 55 years to an estimated total of 27 million people in the Western World. The aim of this paper is to describe the medical management of PAD for the non-vascular specialist, particularly general practitioners, where PAD has now been included in the Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service).

KEYWORDS Peripheral Arterial Disease, Epidemiology, Investigation, Treatment.

DEFINITION

Peripheral arterial disease (PAD) is defined by the presence of significant narrowing of arteries distal to the arch of the aorta, most often due to atherosclerosis[1, 2]. Clinically, PAD most commonly affects the lower limbs as a consequence of arterial narrowing distal to the aortic bifurcation[1, 2].

CLINICAL PRESENTATION

PAD is initially asymptomatic. Intermittent Claudication (IC) is defined as reproducible lower extremity muscular pain induced by exercise and relieved by short periods of rest. It is the symptomatic expression of the inability of the lower limb vasculature to maintain adequate tissue perfusion and oxygenation during exertional activity[2, 3]. Although an ankle-brachial pressure index (ABPI) less than 0.9 suggests arterial disease, only 10% to 30% of such patients will have classic symptoms of IC[4]. ***The presence of slight abnormalities in peripheral blood flow does not necessarily result in symptomatic PAD.*** **Table 1** describes the differential diagnoses of lower limb exertional discomfort.

Critical limb ischaemia is lower extremity arterial occlusive disease of a magnitude that potentially threatens the viability of the limb. Critical ischaemia (CI) is persistent rest pain for a period greater than two weeks duration requiring regular analgesia, with an ankle systolic pressure of less than 50mmHg or toe pressure of less than 30mmHg, with or without associated tissue ulceration or gangrene[5].

EPIDEMIOLOGY

PAD now affects approximately 20% of adults older than 55 years with an estimated total prevalence of 27 million people in North America and Europe[6]. The peak incidence is 60 new cases per 10,000 persons per year with a prevalence of 8 million people in the United States[7]. In Europe, Hooi *et al* (2001) documented an overall incidence of 1.0 per 1000 people for symptomatic PAD in the Netherlands[8].

The Framingham study, and others, documented an increasing prevalence of intermittent claudication (IC) with age and a two-fold male predominance (1.8% for women and 3.6% for men). However, the Edinburgh Artery Study failed to demonstrate any significant difference in PAD between men and women[9]. The risk of PAD increases two- to three-fold for every 10 year increase in age after 40 years[10]. More recently, IC was reported to be more common in men, whereas asymptomatic PAD and severe ischaemia were more frequent in women[1].

NATURAL HISTORY OF PERIPHERAL ARTERIAL DISEASE

Between 5% and 10% of individuals with asymptomatic PAD develop IC over 5 years and 75% of such patients will experience symptom stabilisation or improvement over their lifetime without intervention[11]. This trend occurs despite arteriographic evidence of disease progression in the majority of patients. Symptoms may then deteriorate in the remaining 25%, most commonly in the first year (7-9%), and subsequently at rates of 2% to 3% per year, resulting in an incidence of CI between 0.25 to 0.45 per 1000 people per year[3]. In the first 5 years following diagnosis, 5% of IC patients will require a therapeutic intervention, while only 2% to 4% will ever require a major amputation[12]. The Edinburgh Artery Study demonstrated that 28.8% of IC patients still had pain after 5 years, 8.2% had undergone a vascular surgical revascularization or amputation and that 1.4% developed leg ulceration[9]. ***Although PAD progression is usually slow and the risk of limb loss is low, approximately 20-25% of symptomatic PAD patients will die from coronary or cerebrovascular events within 5 years***[9, 13]. For this reason, risk factor modification and secondary prevention treatment

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Table 1

Differential diagnoses for lower limb exertional symptomatology.

Condition	Prevalence	Anatomical Distribution	Character of Pain	Effect of Exercise	Effect of Rest	Effect of Position	Additional Factors
Thigh and Buttock Claudication	Rare	Buttock, hip and thigh	Crampy, aching discomfort	Reproducible onset (same distance for each episode)	Quickly relieved	None	Proximal pulses may be reduced combined with normal distal pulses
Calf Claudication	3% - 5% of the adult population	Calf muscles	Crampy, aching discomfort	Reproducible onset	Quickly relieved	None	May have atypical symptoms on exercise
Foot Claudication	Rare	Foot arch	Severe pain on exercise	Reproducible onset	Quickly relieved	None	Numbness can also be associated with pain
Venous Claudication	Rare	Entire lower limb affected. Worse in calf.	Tight, bursting pain	Occurs after walking	Slow to settle	Elevation enhances recovery	Signs of deep venous congestion and oedema present. May have history of iliofemoral thrombosis
Chronic Compartment Syndrome	Rare	Calf muscles	Tight, bursting pain	Occurs after walking	Very slow to settle	Elevation enhances recovery	Tends to affect heavily muscled athletes
Spinal Stenosis	Common	Buttocks and posterior aspects of lower limb. Often bilateral	Pain and weakness	Occurs with exercise and can mimic claudication	Varies but can have a prolonged recovery time	Lumbar spine flexion eases discomfort	Exacerbated by standing and extending spine
Nerve Root Compression	Common	Radiation of pain down lower limb	Sharp	May be induced by sitting, standing or walking	Often present at rest	Positional change can improve symptoms	History of back pain
Bakers Cyst	Rare	Behind knee down calf	Tenderness and associated swelling	Occurs with exercise	Present at rest	None	Usually a constant discomfort
Hip Arthritis	Common	Lateral aspect hip and thigh	Dull to severe ache	Can occur following a period of exercise	Not relieved quickly	Rest and minimal weight bearing helps	Symptoms can vary. Increased in patients with high BMI
Foot or Ankle Arthritis	Common	Ankle and foot arch	Aching pain	Variable onset following exercise	Not quickly relieved	Rest and minimal weight bearing helps	Variable. Can relate to exercise but present at rest

in PAD patients is as important as in patients with coronary and cerebrovascular disease.

MODIFIABLE RISK FACTORS

Atherosclerosis is a multifactorial disease process associated with the interaction of numerous risk factors. The National Health and Nutrition Examination Survey (1999-2000) analysed 2174 participants over the age of 40 and identified a 4.3% prevalence of PAD based on ABPI < 0.90 in either lower limb[14]. Using age and gender adjusted logistic regression analyses, they reported odds ratios for risk factors significantly associated with PAD including current smoking (4.46), black race (2.83), diabetes (2.71), poor kidney function (2.00), hypertension (1.75) and hypercholesterolaemia (1.68).

Smoking: Smokers have a 3 times greater relative risk of developing IC and experience symptoms 10 years earlier than their non-smoking counterparts[3]. The Framingham study also showed that smokers are twice as likely to develop PAD as coronary artery disease[15]. There is also a dose-dependant relationship between smoking and severity of PAD[16].

Diabetes: Diabetes mellitus is strongly linked to early onset vascular disease, leading to premature cardiovascular events and mortality[15]. The Framingham study showed that 20% of IC patients have diabetes and that diabetes increases two- to three-fold the risk of IC. Although most reported studies do not stratify patients according to Type 1 and Type 2 diabetes, patients with both diabetes and IC have a two- to four-fold increased risk of a further cardiovascular event[15]. PAD prevalence increases with the duration of diabetes with 15% of diabetic patients affected by PAD at 10 years following diagnosis, rising to 45% at 20 years[17]. ***Of major concern, Elhadd et al (1999) reported a 25% prevalence of undetected***

TABLE 2

Provisional service descriptions of the Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service) for the treatment of PAD.

Year	Target Goals
1	• Purchase of equipment for ABPI assessment (doppler, sphygmomanometer). • Training of staff to conduct ABPI assessment. • Completion of a symptomatic PAD registry.
2	• Completion of appropriate treatment for all symptomatic PAD patients on registry. • Commencement of PAD assessment registry for at-risk patients over the age of 50 years who smoke.
3	• Completion of appropriate treatment for all at-risk PAD patients on registry.

PAD in Scottish diabetic patients attending hospital clinics[18]. There is a more rapid progression in diabetic patients with an 11 times higher rate of major lower limb amputation compared to non-diabetics and a doubling of the five-year mortality[18]. Diabetic ulcers also heal more slowly and are the main cause of non-traumatic lower limb amputation in developed countries accounting for more hospital bed occupancy than any other diabetic complication[19].

Hypertension: Hypertension contributes to atherosclerosis development, particularly in the coronary and cerebral circulations as well as a two- to three-fold increased risk of developing IC[15].

Hypercholesterolaemia: Elevated serum cholesterol, triglyceride and low density lipoproteins (LDL) with reduced high density lipoprotein levels are all implicated as important factors for the progression of atherosclerosis.

Hyperhomocysteinaemia: Elevated homocysteine level may initiate atherosclerosis by modulating cholesterol biosynthesis, thus inducing other cardiovascular risk factors. It is considered an independently graded risk factor for arteriosclerotic vascular disease[20].

INVESTIGATION OF PERIPHERAL ARTERIAL DISEASE

Risk Factors: All patients should have a risk factor analysis on their first consultation, particularly smoking and blood pressure measurement. Assessment of haemoglobin, urea and electrolytes to determine baseline renal function as well as fasting serum glucose and lipid profiles should also be performed. Liver function testing should be considered at this stage prior to commencing pharmacological therapy, particularly statins.

Vascular Flow Investigation: An assessment of peripheral blood flow ranges from non-invasive ankle-brachial pressure index, arterial duplex, computerised tomography and magnetic resonance imaging to conventional transfemoral angiography.

Ankle-Brachial Pressure Index (ABPI) is derived from the brachial, posterior tibial and dorsalis pedis artery systolic pressures which are measured using cuff occlusion by a sphygmomanometer and Doppler ultrasound (**Figure 1**). A resting ABPI of <0.90 indicates a haemodynamically significant arterial stenosis and is most often used as a haemodynamic definition of PAD. An ABPI <0.5 would suggest moderate to severe claudication while an ABPI <0.3 is suggestive of impending critical ischaemia. An ABPI < 0.90 is also 95% sensitive in detecting arteriogram-positive lesions in symptomatic individuals[2]. Calcification and inability to compress the arteries secondary to diabetes or renal insufficiency may result in a false elevation of ABPI > 1.4 in some cases[2]. In these patients, arterial duplex at multiple sites in the lower limb may identify a haemodynamically significant lesion[2]. Significant disease may also be demonstrated by the characteristics of the actual Doppler waveforms which range from normal triphasic waveforms to atherosclerotic biphasic and monophasic patterns which occur distal to 50% and >70% stenoses respectively.

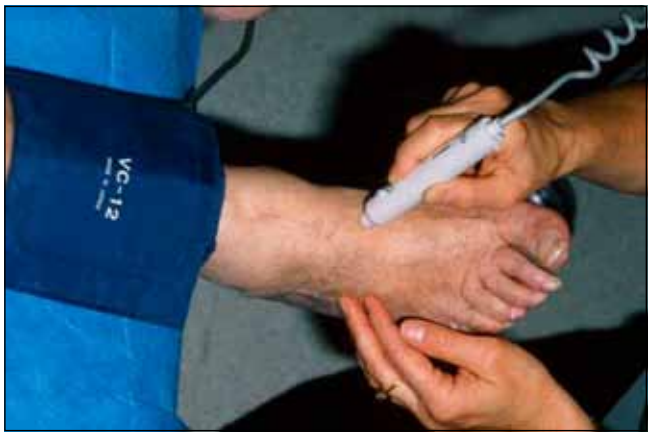

Fig 1. Ankle-brachial index – Doppler assessment of dorsalis pedis which is measured using cuff occlusion by a sphygmomanometer and Doppler ultrasound (Super Dopplex® II Huntleigh Healthcare, UK).

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) II guidelines recommend that ABPI measurements should be performed in all patients between the age of 50-69 with a cardiovascular risk factor, who have exertional leg symptoms, who are over the age of 70 regardless of their risk-factor status and in all patients with a Framingham risk score of 10-20% (Framingham risk score is based on patient gender, age, blood pressure, total cholesterol and HDL levels and presence of smoking and diabetes)[2].

Magnetic resonance angiography (MRA) is a relatively safe modality offering three-dimensional images of the abdomen, pelvis and lower extremities (**Figure 2**). The use of techniques to minimise venous contamination have improved the accuracy compared to invasive angiography[21]. Although gadolinium-based contrast agents administered during MRA scanning may be associated with a lower risk of renal dysfunction when compared to iodinated contrast media, nephrogenic systemic fibrosis has now been reported which can lead to severe disability and even death through the induction of skin, muscle and organ fibrosis in patients with background renal impairment.

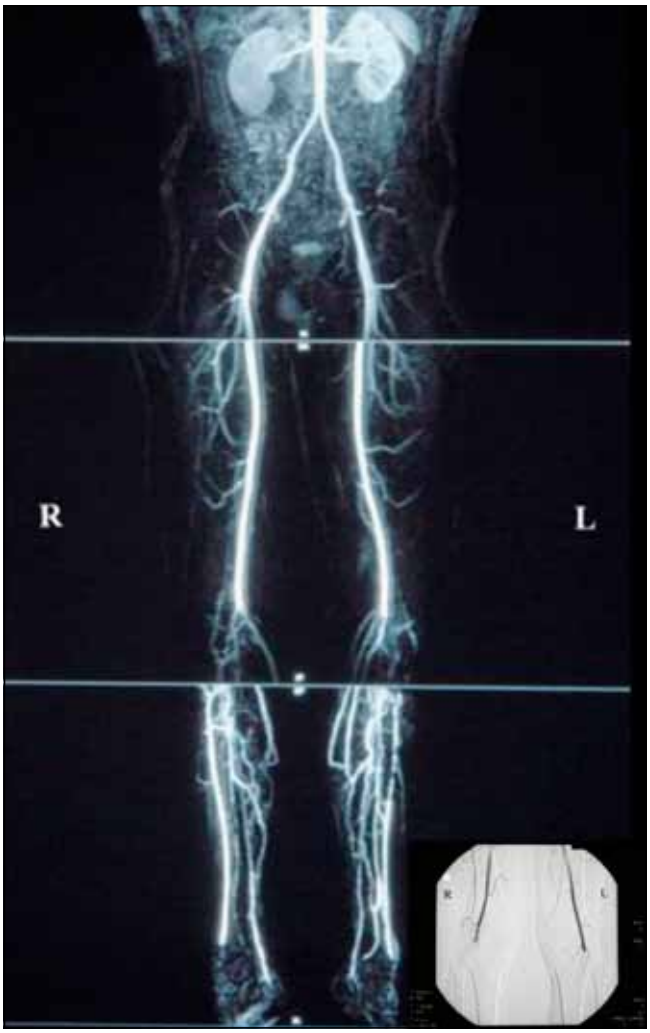

Fig 2. Magnetic Resonance Angiogram (MRA) of the peripheral arterial system extending from the abdominal aorta to the pedal vessels which demonstrated bilateral popliteal artery occlusion with surrounding collateralization (Inset figure is patients pre-operative transfemoral angiogram demonstrating bilateral popliteal artery occlusion).

Multidetector Computerised Tomography Angiography yields rapid high quality imaging (Figure 3)[22]. Major limitations include iodinated contrast and radiation exposure combined with the requirement for careful interpretation during automated digital subtraction due to the presence of arterial wall calcification which has a Hounsfield unit value close to arterially opacified blood.

Transarterial Angiography assessing the infrarenal vasculature remains the "gold standard" arterial imaging test, with concurrent therapeutic intervention potential (Figure 2). However, complications can arise as a consequence of the arterial puncture or from administration of the contrast material[2].

Vascular Function Assessment: includes both a subjective assessment of quality of life combined with quantitative walking distances on a treadmill.

Quality of Life is an important outcome measure for interventions based on global and specific measures[23]. Generic health questionnaires such as the Short Form-36 (SF-36)

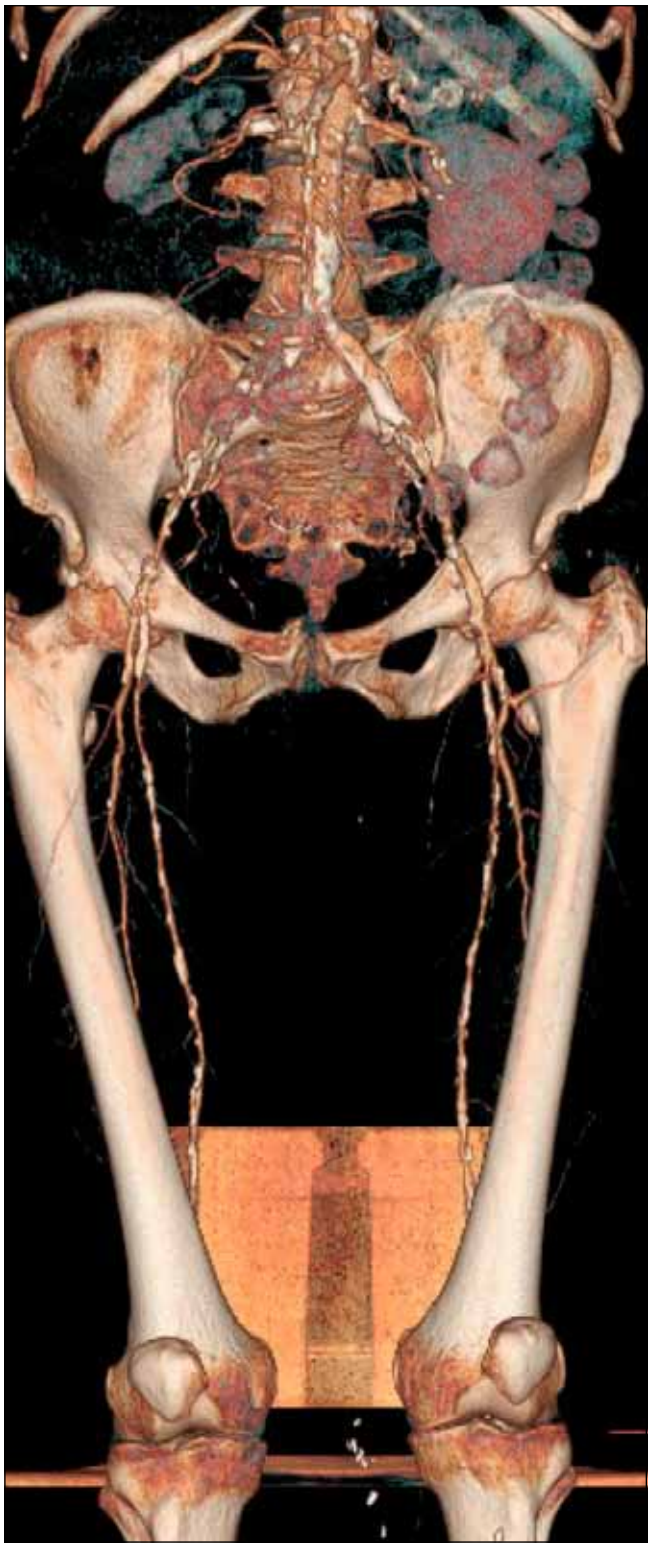

Fig 3. Computerised tomography angiogram of the peripheral arterial system demonstrating proximal disease of both lower limbs extending from the external iliac to the superficial femoral arteries.

evaluate QoL through measurement of physical, social and emotional dimensions of health. However, they are less sensitive in detecting subtle but clinically important treatment differences[24]. Disease-specific QoL instruments for patients with PAD include the Walking Impairment Questionnaire (WIQ) and the VascuQoL Questionnaire[23, 25].

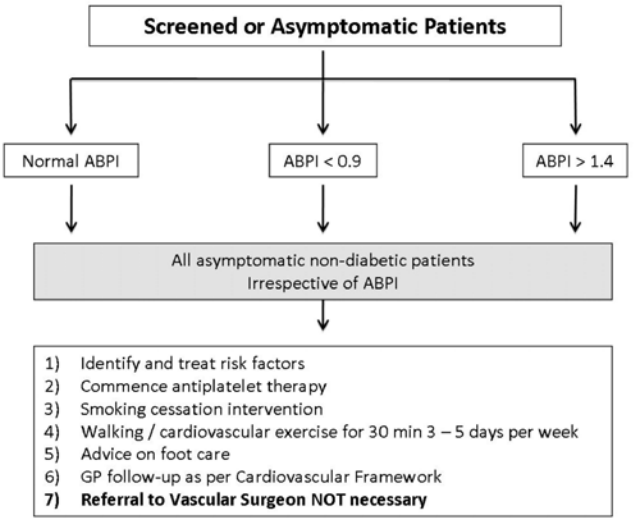

Fig 4. Belfast Health and Social Care Trust Referral Pathway for screened or asymptomatic patients.

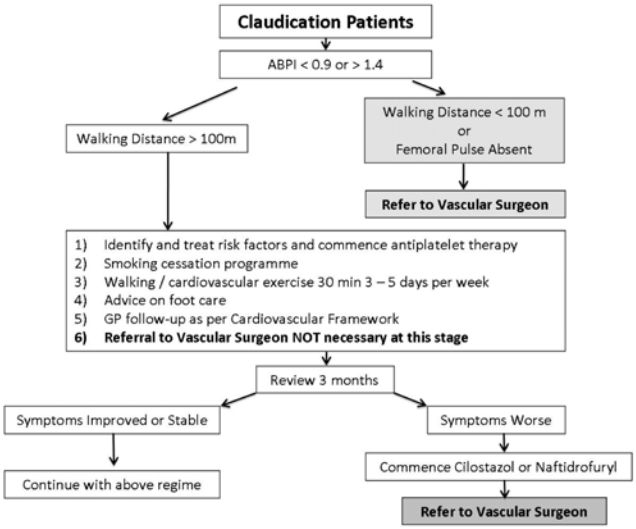

Fig 5. Belfast Health and Social Care Trust Referral Pathway for patients with intermittent claudication.

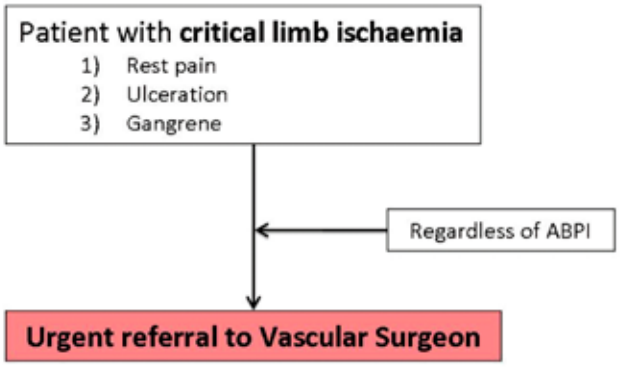

Fig 6. Belfast Health and Social Care Trust Referral Pathway for patients with critical ischaemia.

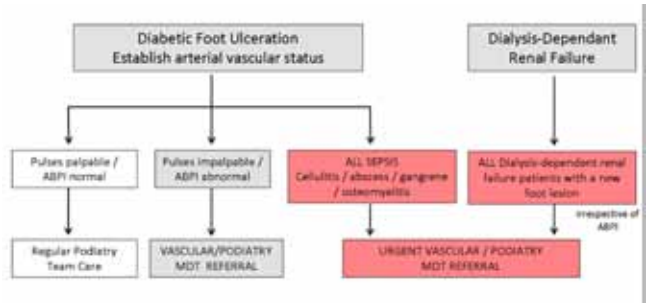

Figure 7. Belfast Health and Social Care Trust Referral Pathway for patients with diabetes and renal failure.

Treadmill Testing provides an objective measure of walking capacity, performed on calibrated treadmill machines at a constant speed of 2mph (3.2 kph) and gradient of 10%[2, 26]. The time of onset of claudication pain is called the initial claudication distance (ICD) or claudication onset time (COT). The maximal walking performance before the patient stops due to pain is called the absolute claudication or maximal walking distance (ACD or MWD)[27]. Claudication patients have reduced walking capacities, with a 50% to 60% reduction in peak treadmill performance, compared to age-matched healthy controls. A therapeutic intervention which results in a greater than 25% increase in both ICD and ACD is considered significant[28].

TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Treatment of PAD aims to improve longer-term cardiovascular outcomes through risk factor modification combined with antiplatelet and lipid lowering primary medical therapy whilst attenuation of lower limb symptomatology is mediated through walking specific pharmacological agents, endovascular or surgical interventions. The Vascular and Endovascular Units from the Belfast Health and Social Care Trust have issued PAD referral pathways to assist non-vascular practitioners in their management of such patients (**Figures 4-7**).

CONSERVATIVE

Dietary therapy has beneficial effects on the occurrence and progression of atherosclerosis[29]. The National Cholesterol Education Program III (NCEP) report recommends a tiered dietary approach to weight reduction, with the further addition of cholesterol lowering agents if required[29].

Smokers should be strongly advised to stop through physician advice, group counselling sessions and nicotine replacement[2]. Smoking cessation reduces the severity of claudication and the risk of developing rest pain[30].

Exercise significantly improves maximum walking time and overall walking ability in stable IC patients. The absolute or peak walking distance can be improved by more than 100% with a greater effect identified in longer-term programmes[31]. Exercise has been reported as more effective than angioplasty or antiplatelet therapy for improving walking time and quality of life, but remains similar to surgical treatment. Exercise also improves gait patterns in non-surgical patients[32]. Exercise programmes deliver better outcomes when supervised by hospital based-departments compared to home based-programmes and if the mean duration is greater than 2

months[31]. Badger *et al* (2007) also commented on the efficacy of a supervised exercise programme, which led to further improvements in walking distance after lower limb arterial bypass surgery.

MEDICAL

PAD medical therapies include systemic cardiovascular or walking specific therapies.

Systemic Cardiovascular Therapies

Antiplatelet Therapy: Antiplatelets delay the rate of PAD progression, reduce the need for intervention and the rate of graft failure following revascularisation procedures[33]. More importantly a meta-analysis of 195 placebo-controlled trials of antiplatelet therapy demonstrated a reduced cardiovascular death risk of approximately 25% in high risk patients including those with symptomatic PAD[33]. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial reported a 8.7% relative risk reduction for MI, stroke or cardiovascular death when clopidogrel (75mg/day) was compared to aspirin (325mg/day) in high-risk patients[34]. Aspirin (75mg) is therefore indicated in all patients with PAD while Clopidogrel (75mg) should be considered for higher risk patients particularly those with severe cardiac disease and diabetes. Other antiplatelet therapies including picotamide, triflusal and ketaserin have not been reported to be superior to aspirin for preventing systematic complications in PAD patients[33].

Lipid Lowering Therapy: Statins are clearly efficacious in cholesterol homeostasis with additional cardiovascular benefits which include a 20% relative risk reduction of stroke, MI, vascular death and revascularisation procedures in PAD patients with increased baseline cholesterol levels[35]. Statins have been reported to reduce the incidence of new onset intermittent claudication whilst improving pain-free walking distances as well as reducing intimal-media thickness in patients with carotid artery stenosis[36, 37]. Current guidelines for lipid control state that symptomatic PAD patients should have their LDL lowered to <2.59 mmol/ with a target for further reduction down to <1.81 mmol/l in patients with concomitant vascular disease elsewhere[2]. In conjunction with dietary modification, statins are the primary pharmacological agent with fibrates and/or niacin reserved for patients with abnormalities in triglyceride and HDL profiles.

Antihypertensives: Control of hypertension in PAD patients reduces cardiovascular co-morbidities over the medium to longer-term period[38]. All PAD patients with hypertension should have blood pressure controlled to <140/90 mmHg or <130/80 mmHg if they also have diabetes or renal insufficiency. Thiazides and angiotensin converting enzyme inhibitors are the initial antihypertensive agents to reduce the risk of cardiovascular disease[2]. Angiotensin-converting enzyme inhibitors, in hypertensive patients with PAD, may also improve walking distances without a change in ABPI measurements[39]. Although ß-blockers do not affect IC distance and are not actually contraindicated in PAD, a cautious approach is advocated for more severely affected PAD patients[40].

WALKING SPECIFIC THERAPIES

Traditional PAD vasodilators such as naftidrofuryl and pentoxifylline have largely been superseded by cilostazol whereas other arterial vasodilators such as α-blockers, papaverine, nylidrin and nifedipine are not clinically efficacious in PAD[41, 42].

Cilostazol: Cilostazol (Pletal® - 100mg twice a day orally) has antiplatelet, antithrombotic, vasodilatory, antimitogenic and cardiogenic properties[43]. A meta-analysis showed a significant increase of 67% vs. 40% in ICD and 50% vs. 21% for ACD for oral cilostazol 100mg and placebo respectively[27]. A further meta-analysis from the Cochrane Peripheral Vascular Diseases Group confirmed cilostazol's efficacy on ICD and ACD in patients with stable, moderate to severe IC[44]. Thompson *et al* (2002) and Regensteiner *et al* (2002) have also reported improvements in quality of life with cilostazol therapy as assessed by the SF-36 and Walking Impairment Questionnaires[25, 27].

Cilostazol is contraindicated in congestive heart failure, haemostatic disorders or active bleeding. Although cilostazol does not alter coagulation parameters, caution is advised with initial clinical monitoring of patients on antiplatelet and warfarin therapy as well as its use in patients with moderate renal or hepatic dysfunction. Cilostazol is associated with a high frequency of side effects, particularly headache, diarrhoea and palpitations due to vasodilatory properties, occurring in up to 32% of patients[27, 45]. However, most of these effects are reported to settle within 6 weeks[45, 46].

Naftidrofuryl: Naftidrofuryl (Praxilene®) has vasodilatory effects, improving tissue oxygenation and muscle metabolism[2]. In a meta-analysis of 888 patients with IC, naftidrofuryl increased pain-free walking distance by 26% compared to placebo[47]. Patients with IC who have a poor quality of life may be considered for treatment with naftidrofuryl[2, 48].

Pentoxifylline: Pentoxifylline (Trental®) produces dose-related haemorrheologic effects, lowers blood viscosity and improves erythrocyte flexibility. Although pentoxifylline is associated with modest increases in walking distance over placebo, the overall clinical efficacy is unclear. It is no longer recommended for use in PAD patients[2, 48].

Inositol and Cinnarizine: Inositol nicotinate causes vasodilation, lysis of fibrin, a mild hypolipidaemic effect and inhibition of oxidative metabolism in hypoxic tissues. Cinnarizine acts via antagonism of vasoconstrictive substances such as noradrenaline, serotonin and angiotensin[49]. Although trials for these agents suggested efficacy by improving walking distances, their overall methodology was poor and have not shown clear evidence of benefit over placebo[48].

Alternative Peripheral Vasodilators and Treatments: Ticlodipine and ginkgo biloba special extract (Egb 761) significantly increase pain-free walking distance[50, 51]. Assessment of angiogenic stimulation of new collateral channels by growth factors, autologous bone marrow cells and transcription factor gene therapy modalities are currently being evaluated[52-54]. Although dietary supplementation with B-vitamins and / or folate has been shown to lower homocysteine levels, high-level evidence for beneficial effects in PAD patients in terms of preventing cardiovascular events is lacking and such therapy is not recommended[55].

THERAPEUTIC INTERVENTION

Revascularisation should be considered in patients with critical limb ischaemia or severely debilitating claudication symptoms that persist despite maximal medical treatment. Although operative arterial bypass appears to have a better long term patency, the risks of surgery are significantly greater when compared to endovascular interventions in terms of mortality, major morbidity and return to the normal activities of daily living.

Endovascular

The technical success of percutaneous transluminal angioplasty (PTA) and/or stenting for proximal lesions in the iliac artery exceeds 90% with reported variations between 80% and 100% depending on the presence of either long or focal stenotic iliac lesions respectively[2]. Five year primary patency rates range between 64% and 75% for all cases with a higher rates of 79% reported for claudicants[2, 56, 57].

Endovascular treatment of infrainguinal disease is also associated with a low morbidity and mortality with a technical and clinical success rate of PTA for femoropopliteal stenoses exceeding 95%[2]. However, longer term outcomes are lower compared to proximal iliac interventions with 5 year patency rates of 55% (range 52-62%) and 42% (range 33-51%) for femoropopliteal stenoses and occlusions respectively[2].

Although PTA improves symptomatology and median ACD at 6-months in patients with mild to moderate claudication, longer term benefits are limited with no significant difference in walking distances or quality of life at 2 or 6 years post-PTA[58]. Independent risk factors for re-stenosis include the disease severity (claudication vs. critical ischaemia), the actual length of the stenosed / occluded segment and the quality of the distal outflow (run-off) vessels.

Surgical

Surgical intervention is indicated for critical limb ischaemia where the primary goal is to relieve pain, encourage ulcer healing, prevent limb loss and improve patient function, quality of life and survival[2]. Surgical intervention may also be considered in intermittent claudication in patients with proximal lesions or deteriorating symptomatology despite best medical therapy and endovascular intervention. Although surgical procedures improve medium to long-term outcome rates compared to endovascular intervention, they carry a higher early post-procedural complication rate[2, 59, 60].

An aortobifemoral arterial bypass is usually recommended for diffuse aortoiliac disease with limb-based patency rates for patients with claudication of 91.0% and 86.8% at 5 and 10 years, respectively, as compared with 87.5% and 81.8% for patients with critical limb ischemia[59]. In higher risk patients with medical co-morbidities, extra-anatomical bypass modalities include femoro-femoral or axillo-femoral arterial conduits. However, these routes have a lower success rate with 5 year patency rates between 51% and 75%[2]. Infrainguinal arterial bypass requires uncompromised inflow at the proximal anastomosis, preferably to a native artery rather than graft. A satisfactory distal run-off vessel is the most important determinant of longer-term patency which ranges between 35% for prosthetic material to 60% for vein grafts over 5 years[2].

IMPLICATIONS FOR NORTHERN IRELAND

General Practitioners in Northern Ireland participate in the Quality and Outcomes Framework which incentivises a number of activities to enhance patient outcomes. The Department of Health is currently drafting a Cardiovascular Service Framework including a care pathway from prevention, promotion, protection of health and wellbeing, to appropriate assessment, diagnosis, treatment and care provision, rehabilitation and end of life care based on evidence from established sources such as the National Institute of Clinical Excellence. The Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service) is now developing standards which will cover risk assessment for those patients who have a high risk of or who have PAD[61].

Provisional service descriptions as described in **Table 2** suggest the initial training of staff members in the assessment of PAD and the development of two disease registers to account for all patients with PAD followed by a second phase to incorporate patients greater than 50 years of age at risk of peripheral and cardiovascular disease particularly those who smoke. Finally, treatment protocols should then be implemented for patients on both registries[61].

CONCLUSION

Peripheral arterial disease (PAD) now affects approximately 20% of adults older than 55 years. However, less than 30% of patients diagnosed with PAD based on the ankle-brachial index will have classic symptoms of IC. Asymptomatic and patients able to walk greater than 100 yards should be initially managed in the community with risk factor modification, peripheral arterial examination combined with the calculation of ankle-brachial indices. All patients should be considered for antiplatelet and lipid lowering therapies. Diabetic patients should also receive foot care advice. Symptomatic patients able to walk further than 100 yards require walking-specific medication such as cilostazol for a period of three months. Tertiary referral should be reserved for refractory symptomatology despite maximal conservative management in the community and short distance claudication (<100 yards). Critical limb ischaemia warrants urgent referral.

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Medical History

William Wilde and the Early Records of Consumption in Ireland

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Summary Absence of documentary or bony evidence before the seventeenth century in Ireland is not conclusive evidence of freedom from tuberculosis. Clear records begin with Bills of Mortality kept in Dublin, the city at the centre of English administration of Ireland, and they show that the basis for an epidemic was firmly established therein before 1700. In the middle of the nineteenth century the cataclysmic Famine opened the floodgates of poverty and urban overcrowding that resulted in an alarming death rate that continued to increase until the early years of the twentieth century.

It is to William Wilde (1815-1876) we owe the nuanced investigation of the earliest numerical records of consumption and related disorders in Ireland.

INTRODUCTION

By the seventeenth century consumption had begun to replace the technical term *phthisis* to describe wasting with cough accompanied by sputum, variable in amount and character from trace to profuse and catarrhal to purulent, and fever. But even though the tubercular nature of the disease was firmly established in the nineteenth century the term consumption – or the euphemism decline - survived well into the twentieth.

Those linguists who have examined the medical manuscripts that have survived from the old Gaelic order are agreed that these are direct, unalloyed translations of Latin classics made between 1400 and 1650. These verbatim versions of *Regimen Sanitatis Salernitium, Lilium Medicinae* of Bernard de Gordon and *Rosa Anglica* by John of Gaddesden were made without addition or marginal comment about the translator's clinical experience, so they are of small value in the present context [1,2]. No evidence of tuberculous disease has been found in the bones that have been recovered in large interments dating from the sixth to ninth [3], seventh to sixteenth [4,5], or tenth and eleventh centuries [6].

BILLS OF MORTALITY

Our earliest numerical knowledge of consumption in Ireland stretches no further back than to the seventeenth century, and depends on Dublin Bills of Mortality, poor relations of their London counterparts.

The weekly, quarterly and annual numbers of deaths in the several parishes of London were kept by the parish clerks and collected into bills of mortality published for general circulation. For a small gratuity these bills, to which in time were attached market notes of a more extended character, were distributed from house to house, and at the bottom of each was printed 'POST THIS FOR THE USE OF YOUR FAMILY', an admonition hardly necessary at the time of an epidemic or outbreak of pestilence.

The numbers and causes of deaths were ascertained by 'searchers' - 'ancient Matrons, sworn to their Office' - who, by looking at the corpse and by other inquiries, determined from which 'Disease, or Casualty, the Corpse died' [7]. In his *Natural and Political Observations mentioned in a following index and made upon the Bills of Mortality*, John Graunt (1620-1674) summarised the London statistics for the years 1604 to 1661. He recognised the diagnostic limitations of the 'searchers', but felt that their reporting was sufficiently reliable for his purpose, and he was not unduly concerned if the 'searchers' ascribed to 'consumption' those corpses which were 'very lean, and worn away' even if the disease was not pulmonary phthisis as would be defined by Sylvius, Willis, Morton or Marten. In an Appendix Graunt included notice of 20 deaths recorded in Dublin between 6-7 July and 2 August 1661: eight were attributed to consumption [7, 8].

Nine years after Graunt's death, *Observations on the Dublin Bills of Mortality* (1683) were published 'By the Observator on the London Bills of Mortality', who, had he been 'the Observator', was in no way coy about his opening remarks: 'The Observations upon the London Bills of Mortality have been a new light to the World, and the like observations upon those of Dublin may serve as Snuffers to make the same candle burn clearer' [9].

The pamphlet compared total burials and births in Dublin and London for the six years 1666, 1668, 1674, 1678, 1679, and 1680. When the second edition came out in 1686 [10] the author came out too: he was William Petty (1623-1687). In reading them it must always be kept in mind that Dublin bills included only the births and deaths of Protestants; the Irish nation as officially defined (and described in all Petty's works) excluded Catholics whose existence was 'unknown' to parish

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Figure 1. William Stokes pouring a libation with William Wilde.

clerks. By their very nature the bills were ephemeral and very few survived into the nineteenth century [11].

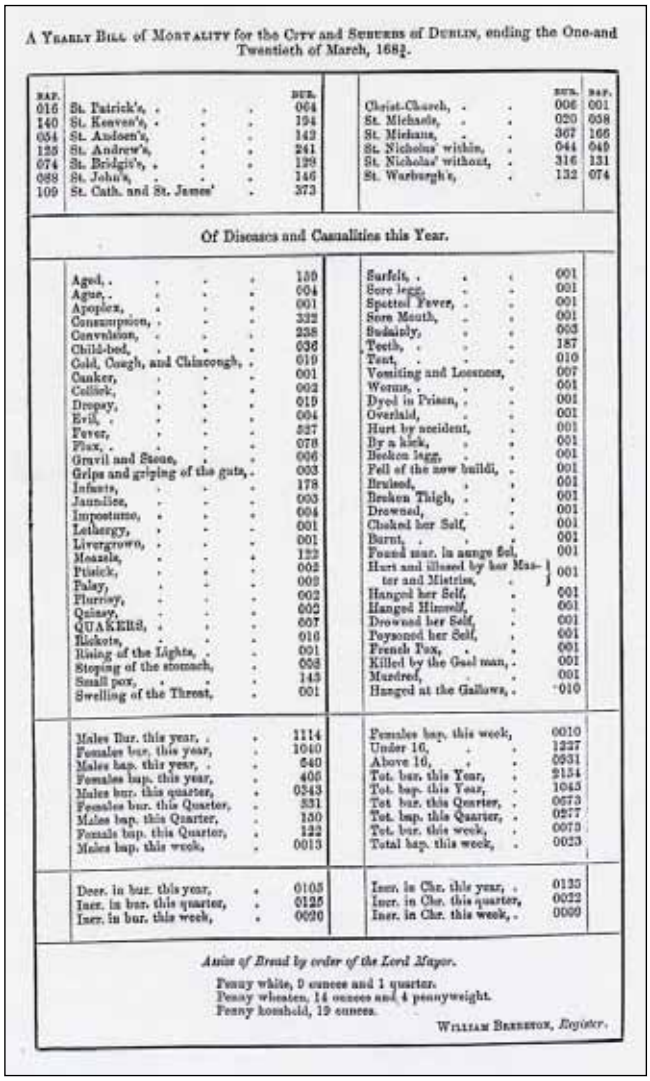
A DUBLIN BILL OF MORTALITY 1683-4

William Robert Wills Wilde (1815-1876) obtained his medical licence in 1837 and eventually became an aurist and oculist with an active interest in archaeology and antiquities (Figure 1). However, it was his literary contributions which 'showed him to have the necessary attributes of statistical interest, experience of Irish folk habits, language, and *mores*, literary ability and professional and historical flair' that brought him to the attention of the Census Commissioners to help in their analysis of the 1841 census [12].

When he came to comment – at great length – on the 1851 census returns, Wilde provided a transcript of the bill for the year ending 31 March 1684, prepared by William Brereton, Registrar, and published in Walker's Magazine (Figure 2). Burials from the ten Protestant parishes were 2,154 in number and in the same year 1045 were baptised, an increase of 135 over the previous year compared to a decrease of 105 in burials. The 'diseases and casualties of the year' were listed alphabetically. Numerically, Consumption, responsible for 322 deaths (15.0 per cent) and Convulsions, for 238, headed the list. The difficulty in assessment is highlighted by noting that 'Ptisick, Palsy, and Plurrisy' each accounted for 2 deaths. 'Convulsions' undoubtedly covered a multitude of infantile diseases; it was in common use up to the middle of the twentieth century. A computing failure occurred in age assortment: 1227 deaths under 16 and 931 above 16 reach 2,158, four too many (p 504) [13].

ANNUAL BILLS 1682 TO 1690

Robert Boyle (1627-1691) encouraged a young Oxford graduate, John Locke (1632-1704) to investigate the possibility that a thorough study of weather conditions might help to solve the nature of epidemic diseases. When Boyle recognised that the task was beyond his failing powers he asked Locke to prepare for the press his manuscript of A General History of the Air. In it Locke included his Oxford register and, with his interest in medical meteorology refreshed, he circulated, with Charles Goodall (d 1712) of the College of Physicians in London, a questionnaire enquiring about Bills of Mortality, Airs, Diseases, etc., in 'Paris, Madrid, Amsterdam, Venice, Hamburgh, Rome, Constantinople, Smyrna, Dublin, Edinburgh, etc., As also in New England, Barbadoes, Jamaica, and other Plantations'. His only replies came from Amsterdam and Dublin [14].



A Yearly Bill of Mortality for the City and Suburbs of Dublin, ending the One-and Twentieth of March, 1683.

BAP.		BUR.
016	St. Patrick's,	064
140	St. Keaven's,	194
054	St. Audoen's,	142
135	St. Andrew's,	241
074	St. Bridgit's,	129
088	St. John's,	146
109	St. Cath. and St. James'	373

BUR.	BAP.
Christ-Church, 006	001
St. Michaels, 020	058
St. Michans, 367	166
St. Nicholas' within, 044	049
St. Nicholas' without, 316	131
St. Warburgh's, 132	074

Of Diseases and Casualties this Year.

Aged,	159	Surfeit,	001
Ague,	004	Sore legg,	001
Apoplex,	001	Spottel Fever,	001
Consumption,	322	Sore Mouth,	001
Convulsion,	238	Sudainly,	003
Child-bed,	036	Teeth,	187
Cold, Cough, and Chincough,	019	Tent,	010
Canker,	001	Vomiting and Loosness,	007
Collick,	002	Worms,	001
Dropsy,	019	Dyed in Prison,	001
Evil,	004	Overlaid,	001
Fever,	327	Hurt by accident,	001
Flux,	078	By a kick,	001
Gravil and Stone,	006	Beaten bagg,	001
Grips and griping of the guts,	003	Fell of the new buildi,	001
Infants,	178	Bruised,	001
Jaundice,	003	Broken Thigh,	001
Impostume,	004	Drowned,	001
Lethargy,	001	Choked her Self,	001
Livergrowe,	122	Burnt,	001
Measels,	002	Found mur. in sange fel,	001
Ptisick,	002	Hurt and illused by her Master and Mistriss,	001
Palsy,	002	Hanged her Self,	001
Flurrisy,	002	Hanged Himself,	001
Quinsy,	007	Drowned her Self,	001
QUAKERS,	016	Poysoned her Self,	001
Rickets,	001	French Pox,	001
Rising of the Lights,	058	Killed by the Gaol man,	001
Stoping of the stomach,	143	Murdred,	001
Small pox,	001	Hanged at the Gallows,	010
Swelling of the Throat,			

Males Bur. this year,	1114	Females bap. this week,	0010
Females bur. this year,	1040	Under 16,	1227
Males bap. this year,	540	Above 16,	0931
Females bap. this year,	405	Tot. bur. this Year,	2154
Males bur. this quarter,	0343	Tot. bap. this Year,	1045
Females bur. this Quarter,	331	Tot bur. this Quarter,	0673
Males bap. this Quarter,	150	Tot. bap. this Quarter,	0277
Female bap. this Quarter,	122	Tot. bur. this week,	0073
Males bap. this week,	0013	Total bap. this week,	0023

Decr. in bur. this year,	0105	Incr. in Chr. this year,	0135
Incr. in bur. this quarter,	0125	Incr. in Chr. this quarter,	0022
Incr. in bur. this week,	0020	Incr. in Chr. this week,	0009

Assize of Bread by order of the Lord Mayor.

Penny white, 9 ounces and 1 quarter.
Penny wheaten, 14 ounces and 4 pennyweight.
Penny houshold, 19 ounces.

William Brereton, *Register.*

Figure 2. A seventeenth century Annual Dublin Bill of Mortality [13].

Charles Willoughby (d 1694), Registrar of the College of Physicians in Dublin, replied to Locke on 17 April 1691 providing him with details of burials for seven years: 1682, 1685, '86, '87, '88, '89 and '90. Of the 15,696 deaths 1,419 (8.7 per cent) were ascribed to consumption, and 1449 (9.1 per cent) to convulsions. He commented:

> 'The two most remarkable of the seat of the distempers that help to swell our bills are Convulsions and

> Consumptions, their middle rate is near that the same in both, butt in the beginning of the 7 years, those that died of consumption were most, the convulsions being fewer increased every year till at length they outnumbered the former. ... I'm apt to believe that Spring and Autumn, being the verticall seasons of the year, doe carry of most of those that dye of consumptions or rather lingering distempers, tho I could nott in the bills make out any thing of certainty to demonstrate it'.[15, 16]

The Hippocratic writer advised a traveller to consider the situation of a city he was about to enter: 'whether it lies to the north, or the south, to the rising and setting sun'. Willoughby 'had heard it observed in Spain that the North side of a River is more unwholesome than the South', and because 'Dublin stands upon a River that runs East and West ... 'tis made a Question whether the North or South Side has the healthiest habitation ...' [15, 16]

William Wilde, who came across a copy of Willoughby's reply in a huckster's shop, discovered that Patrick Dun (1642-1713) sent Locke 'so many Bills of mortality as he had for 1695'. Diseases were still listed alphabetically and consumption (125 of 2,593; 4.8 per cent) and convulsions (137, or 5.3 per cent) were still prominent. In comparison, of 19,433 deaths in London from all causes other than suicide in 1700, 2,819 (*i.e.* 18.5 per cent) were from consumption [17].

THE CENSUS REPORTS.

As a consequence of the Population Act (1800) the First Census of Great Britain was conducted on 10 March 1801 by observers of the poor and by parish priests. By an Act of 1836 the General Register Office was set up in London and a Registrar appointed to organise the 1841 Census. William Farr (1807-1883), after serving his apprenticeship, studied medicine in London and Paris where he was influenced by Pierre Louis (1787-1872) and his 'Numerical Method' designed to undermine the phlebotomists. Farr returned to general practice in London and his indifferent success gave him time to pen an 1837 article on "Vital Statistics" for a *Statistical Account of the British Empire*. Soon after this article came to the notice of the Registrar General, Thomas Henry Lister, Farr was appointed as Compiler of Abstracts in that worthy's office, and he contributed a report on the deaths in the form of a Letter to the First Report of the Registrar General (1839), the first in a long series over forty years. An Appendix to this Letter carried a new system of classifying diseases. 'The recorded causes of death are exceedingly numerous … Some classification of theses causes was necessary … In casting about for a classification it struck me that it should have special reference to the causation and prevention of death …' [18].

At the time of taking a Census, a schedule was distributed to each householder, and he was directed, under penalty, to record name, age, marital status, place of birth, and nature of work of every member of his household. It fell to Wilde to assess the information accrued in the 1841 Census in Ireland, which was part of Great Britain since the Act of Union (1801). By 1843 Wilde had devised his own classification of diseases based on Farr's approach. He distributed the 1,187,374 deaths between 1831 and 1841 by area, cause, age, year and sex, and introduced 'occupation' as a guide to what later became 'social class' [19]. He moved on to specialise in aural and ophthalmic surgery in St. Mark's, the Hospital he founded; its original site was in the converted stables he leased from Wrigley Grimshaw (father of Thomas, *vide infra*) at 11 Molesworth Street, Dublin. But he continued as Assistant Commissioner for the 1851, 1861 and 1871 Irish censuses. 'Not so much in recognition of high professional reputation .. in Europe but for the services rendered to Statistical Science, especially in connection with the Irish census' he was knighted by the Lord Lieutenant, Lord Carlisle, on 1 February 1864 [12].

THE REPORT ON THE CENSUS OF 1851

The report on the 1851 Census was addressed to Henry Wilkie, Acting Secretary, Census Office, Dublin, dated 20 June 1856, and was signed by William Donnelly, Registrar General, Chief Commissioner, and William R Wilde, Assistant Commissioner, but at all times it was common knowledge that it was penned by the Assistant.

PULMONARY CONSUMPTION

Of Consumption he had much to say:

> Consumption - Phthisis: synonyms - Decline, Decay (of youth or manhood), Pulmonary Consumption; Irish - Seirglighe, decay; Seirgean as, shrinking of ones self; Cnaoid, wasting; Etige, pulmonary consumption (West); Creacht na Sgamhain, ulcer of the lung'. (Eiteann is the derivative of Etige in current use).
>
> In the Report of the Census Commissioners for 1841 we read:
>
> Consumption - by far the most fatal affection to which the inhabitants of this country are subject - exceeding the returns of articles of fever by 23,518 deaths during the ten years - is reported to have destroyed 135,590 of the population of those families from whom the returns were received upon the 6th June 1841, being to the deaths of all causes 1 in 8.75; to those of the class of diseases of the respiratory and circulatory organs 1 in 1.31; to the total number of deaths from epidemic, endemic, and contagious diseases, as 100 to 281.17; and to fever alone as 100 to 82.65.
>
> We have now to report as many as 153,098 deaths, from this cause, the sexes being 96.7 males to 100 females; of these, 138,732 were received upon the "A form" or household schedule - viz. 107,383 from the rural area and 31,369 from the civic districts, the latter localities affording in proportion to their population a greater number of deaths from this cause than the former. 2,272 deaths from phthisis were returned from hospitals, and 12,074 from workhouses, being with the exception of those deaths from diseases classed under 'Infirmity, Debility, and Old Age,' the fifth most fatal affection in that class of institutions (pp 447-449) [13].

These were the Famine years when consumption was perhaps more acceptable to a family as the cause of death than starvation - a tacit admission of dire poverty.

Like the rest of the country (though not quite so badly) the population of Ulster suffered, and the population fell. Belfast

escaped, increasing from 75,305 to 100,301. The average annual rural (r) and civic (c) death rates from consumption (calculated on the 1841 population) was highest in the three eastern counties: Down r 2.20, c 3.62; Antrim r 1.66, c 2.57; Belfast c 3.19; Armagh r 1.88, c 2.55. The combined deaths in the towns of Down (Newry, Newtownards, Downpatrick, Banbridge, Donaghdee, especially) made the civic rate in that county higher than that in urban Belfast. The gradient fell westwards: Monaghan r 1.38, c 2.36; Londonderry r 1.38, c 2.24; Tyrone r 1.46, c 2.16; Fermanagh r 1.51, c 2.27; Cavan r 1.22, c 1.90; Cavan r 1.22, c 1.90; and Donegal r 1.22, c 1.99; with the lowest rates rural. Land-locked Cavan fared equally well with coastal Donegal (Figure 3). Taken together, the rural death rate in the nine counties was 1.58 and the civic at 2.83 was not quite twice as high. In the province 14 per cent of the deaths occurred in civic districts, 85 per cent in rural districts and 1 per cent in institutions; in the country as a whole, according to Wilde, 'about 21 per cent of the deaths from consumption occurred in civic districts, 70 per cent in the rural, and 9 per cent in the hospitals and sanitary institutions' (pp 413-478) [13]. Density of population undoubtedly facilitated spread of contagion in the civic districts but nearly three out of every four consumptive deaths occurred, if widely scattered, in the rural areas.

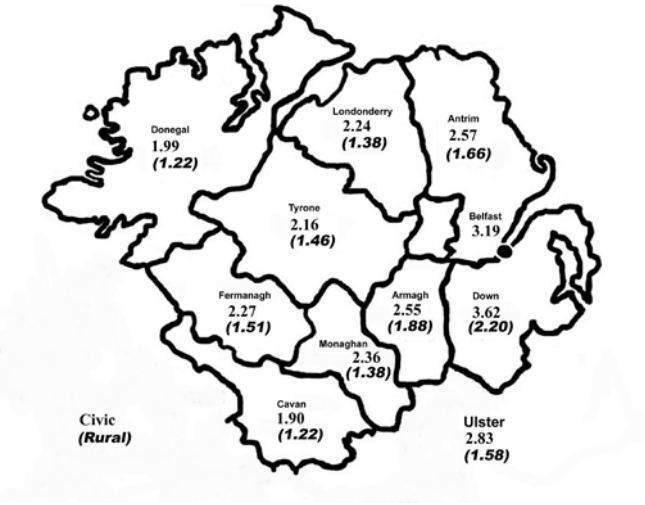


Figure 3. Average annual death rates between 1841 and 1851 from consumption per 1,000 population in civic and *rural* districts of Ulster.

> In the country as a whole yearly deaths from consumption varied widely. During the years from 1842 to 1845, both inclusive, the average annual number of deaths from consumption was 10,919; in 1846 we find the number increased to 15,792; and in the following year, when the general mortality reached an almost unparalleled height in Ireland, the annual average deaths from consumption rose to 21,975; but in 1850 the return for this disease fell to 19,755. In proportion to the total deaths from all causes, those from consumption were 1 in 8.8 (or very nearly that returned for 1841) [13].

This might possibly explain why Wilde did not provide a map of Ireland to display the geographical distribution of average annual death rate from consumption, a feature all the more remarkable since Harty in 1820 had used a map of Ireland to show dates and places of outbreaks of 'contagious fever' in 1816-18 as Frontispiece in *An Historic Sketch of the Causes, Progress, Extent and Mortality of Contagious Fever Epidemics in Ireland* ... 1820 [20]. The dramatic change in population from 8,175,124 to 6,552,285 was another deterrent. (A further 'complication' arises because the decade of observation was six weeks short.) However, using the population in the initial year and the total deaths from consumption in the 32 counties provided in his voluminous Tables (pp 413-478) [13], it is possible to calculate the average annual death rate in each county and so arrive at a useful indication of the geographical distribution of the disease in Ireland in the middle of the nineteenth century. The counties along, or close to, the eastern seaboard displayed the highest rates. Similar rates were shown in the great central plain and the inland counties in the south east (Figure 4).

Such a map might have saved Wilde from indulging his meteorological fixation in relation to diseases of the respiratory organs for he concluded, from the deaths from pulmonary consumption in seaboard counties, that 'the coastline of a county is more salubrious than inland districts [though from] a more minute examination of the inland and seaboard mortalities we find some very remarkable irregularities' (pp 448-9)[13]. It would have shown that the Atlantic breakers had some secret advantage over the gentler tides in the Irish sea, for there was a very clear east-west divide.

The seasons influenced the consumptive death rate 'as might naturally be expected': mortality was lowest in the mild autumn after the warm summer, rose during the cold winter and peaked 'with the harsh, trying weather of spring' (p 447)[13]

After alluding to the necessary assumptions arising from the methods of registration, he remarked

> Taking all these circumstances into consideration, we find that the period of life at which most deaths from consumption were returned was from 15 to 25; a remarkable disproportion of cases occurred between the first and second five-year-period of that age; as from 15 to 20 the sexes are 78.3 male to 100 female, while from 20 to 25 the proportion is reversed - for the numbers are 100 female to 115.5 males; from 25 to 30 the males also predominate; but from 30 to 50 the females again take the lead; and from 55 onwards the deaths of the male sex again predominate'(p. 448) [13].

NON-RESPIRATORY MANIFESTATIONS.

Abdominal, lymphatic and cutaneous manifestations were clearly, if not always precisely, identified, but the concept of bony affection was nebulous.

Amongst Diseases of the Digestive Organs Wilde described Marasmus:

> Marasmus - Tabes mesenterica, Anemia, Tuberculosis mesenterica: synonyms - Atrophy, Emaciation,Wasting away, Decline and Decay (infantile), general Cachectic and Tubercular disease of early life. Infantile Consumption. Fairy Stricken, 'Backgone', Struck, a Blast; in Irish Cnai or Cnaoidh, wasting, with or without disease of the chest; Cuirrethe or Milte, fairy-stricken.

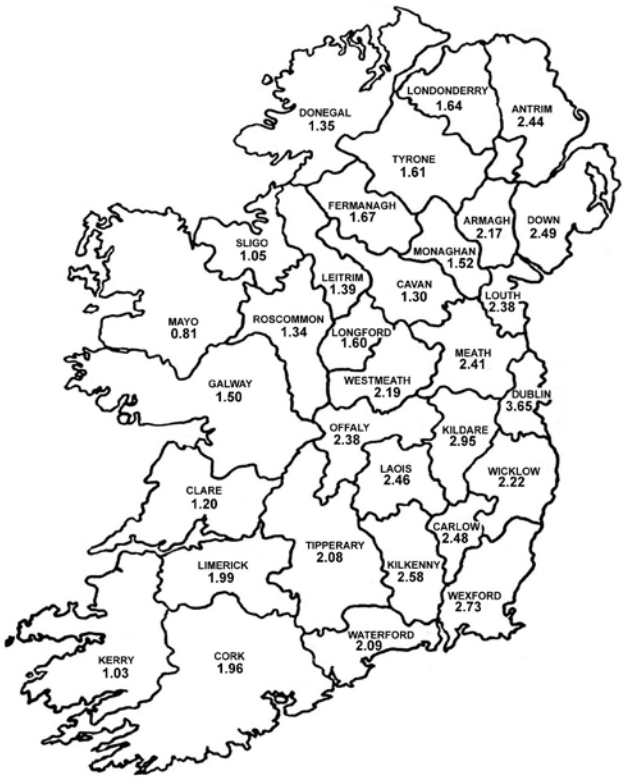


Figure 4. Average annual death rates between 1841 and 1851 from consumption per 1,000 population in the counties of Ireland.

> In the Census Report for 1841 the name Marasmus was adopted as a generic term, under which to class all those various afflictions of infancy and early youth returned on the different Forms as "Consumption (infantile), wasting, decay, decline, emaciation, general debility, and loss of strength." This assignment became necessary from the multitude of deaths returned as consumption and decline under 1 year of age, and from 1 to 10. There can be little doubt that the great majority of cases of infantile deaths returned under the above popular headings were caused by scrofulous tubercular diseases, chiefly of the abdominal cavity, many of *tabes mesenterica*, and very many of *chronic peritonitis*, a disease of frequent and fatal occurrence in young children in this country ... "changelings", ... supposed "fairy stricken" children.
>
> …. In proportion to the deaths from all causes, those registered under the head of marasmus are 1 in 20 ... As might be expected ... the great bulk of these deaths occurred at very early ages; as many as 16,990 were of children under 12 months old; 34,035 from that age to the end of the fourth year; 14,248 at 5 and under 10; and 2,742 during the remaining years of life' (pp 455-6) [13].

Within Diseases of Locomotor Organs were three categories: Diseases of Bones and Joints, Hip Disease, and Spine Disease. The first included necrosis, caries, periostitis, synovitis, 'white swelling' and the Irish term was Teamadh. The 1,836 deaths recorded in the 1851 Census were reported at every age, but chiefly between 10 and 25 years; 58.1 females to 100 males. (One hundred years later 'white swelling' was invariably associated with tuberculous synovitis.) One of the synonyms for Hip diseases was psoas abscess; the Gaelic term was Galar na leise. The 89 deaths recorded in 1841 rose to 390 in 1851; of these 266 were in males and 124 in females; the greatest incidence was between 10 and 25 years. Synonyms for Spine Disease were psoas and lumbar abscess, or Galar droma. The 325 deaths accumulated in 1841 rose to 800 in 1851, the sex ratio being 62.6 female to 100 male. Deaths from spinal disease were returned at all ages, but from 5 to 20 was the period of life which showed the greatest proportionate numbers (p 460) [13].

Osteomyelitis was not mentioned; rickets was included among the diseases of bones and joints with no allusion to dietary deficiency or age.

Scrofula or Struma appeared in the Tegumentary System. Synonyms were:

> The Evil, King's Evil, The Running Evil, Running Sore, Felloon, Bone Evil, Glandular Disease, an Impostume; in Irish Easbaidh bragadh, deficiency in the neck; Fiolun, the treacherous disease; Cneadh Cnaithneach, the wasting ulcer; Cuit bragach, cuts in the neck. How far scrofula, in any of its numerous and protean presentations, influenced either directly or indirectly the 621,710 deaths from sporadic diseases, which are specified in our tables, is a question to which numbers cannot be applied, but to which concurrent testimony of all medical authorities would assign a very large proportion (p 465) [13].

In 1841 3,149 deaths were so assigned; the number was 6,774 in 1851, 69.1 females to 100 males, amounting to 1 in 201 of the general mortality. The seasonal distribution mimicked that of consumption with the highest number of deaths in spring and the lowest in autumn. All ages, though chiefly those under middle life, were affected (p 465) [13].

The City of Dublin

Section VIII provided a Special Sanitary Report upon the City of Dublin; population in 1841 – 232,726, in 1851- 258,396. In this he was greatly facilitatated by Sir Richard Griffith's (1784-1878) *Tenement valuation* (1882) [21]. After describing and defining the localities, including paving, lighting, scavenging and sewage arrangements, Wilde provided three Tables.

> I. Deaths by Ages and Localities,
>
> II Localities with Causes of Death, and
>
> III Deaths by Occupation and Causes of Death.(pp 479-499) [13]

'His intuitive commentary shows that he was aware of statistical principles, of the importance of sampling, of reliable disease classification, and of gradients between occupations and districts (special classes). He followed rational order and, as a modern statistician has noted, understood the necessity of validating his estimates' [12].

As he worked through the Returns he might have remembered and paraphrased Horace (30 BC):

> *Pallida mors aeque pulsat pede pauperum tabernas regumque turres*,

the captain of the men of death strikes with impartial foot the hovels of the poor and the town house of the aristocrats [22]. Wealth could no more prevent than poverty, of itself, could cause consumption. Deaths from all forms of tuberculosis in first and second class streets accounted for 1.56 per cent of the population compared with 3.00 per cent in the crowded districts of the wards in the centre of the city; in the first class shopping streets the rate was 1.43, compared with 3.00 in the second and third class shopping streets; and in the mixed commercial streets taken together the rate was 2.73. (pp 478-521) [13].

While he was composing his Report, the Assistant Commissioner, as noted above, had already come across a copy of Willoughby's reply to Locke and later published a transcript [17]. He decided that Dublin, built upon a river running from west to east might, indeed, answer Willoughby's Hispano-Hippocratic question 'whether the North or South Side has the healthiest habitation'..So far as consumption was concerned, there was no evidence that the north side of the Liffey was more unwholesome than the south side; consumptive mortality was lower in the first- and second-class private streets, on either side, than elsewhere, but regardless of location the rates were similar. Although the percentage of deaths due to consumption (1.48) was lower in the first- and second-class private streets on the south side than the north (where it was 1.68), the percentage for all localities on the south side (2.94) was slightly higher than that for the north (2.78). Salubrity resided in the first- and second-class houses: total deaths per 1,000 were similar on the south (152) and north sides (181), but in the more choice neighbourhoods the rates were 89 per 1,000 on the south side and 109 on the north side (pp 482-499) [13].

DUBLIN AND LONDON

In the middle of the nineteenth century Dublin was the second city in the Three Kingdoms. Henry Ancell (1802-1863) remarked that in 1847 16.1 per cent of all deaths in England were attributed to consumption, 78.4 per cent of them from pulmonary disease [23]. In London in 1851 deaths from all forms of tuberculosis accounted for 17.7 per cent of deaths, pulmonary consumption causing 71.5 per cent of that percentage. And almost three out of every four of the 41.3 per 10,000 Londoners with tuberculosis suffered from the pulmonary form (29.6 per 10,000) [23], rates in excess of, but not very different from, those in Dublin.

REFLECTIONS

When the soil was prepared by the Great Famine of 1847 [24], the seed for an epidemic of inordinate proportions was there in abundance. Abject rural poverty, dismal urban overcrowding, and railroad extension ensured that the tubercle bacillus (identified in 1882) would rule the second half of the nineteenth century in Ireland.

The Census schedules distributed throughout the country were filled in by the head of the household, so Wilde was at the mercy of the memory and veracity of each householder for the medical and mortality information in the returns, not to mention the likelihood that a professional diagnosis had never been made in many instances. Although registration of births and deaths were long-established in Britain, Westminster did not pass a Births and Deaths Registration Act (Ireland) until 1863, and thereafter vital statistics passed into the care of a Registrar General. Even so Wilde, as Commissioner, provided a chapter in the 1871 Census Report [25]. As late as 1887 Thomas Wrigley Grimshaw (1839-1900), who had become Registrar General in 1879, was aware that some deaths were not registered, and that in a considerable number the causes of death were not medically certified – his map, in spite of all the isopleths and isotherms – refuted Wilde's notion of seaboard salubrity [26].

In 60 years the population had fallen from 8,175,124 in 1841 to 4,458,155 in 1901. Slowly 'consumption' was replaced by the dreaded term 'tuberculosis', and no reliable remedy had been found. 'The fact that the epidemic was taking place in a country in which the population was falling overall and which was still primarily rural, did not appear to inhibit the rise in tuberculosis mortality' [25]. The rising incidence in a falling population might suggest that the reduction was selective, i.e. emigration of the fittest, but the label or slur 'tubercular Irish' commonly used in the United States of America suggests otherwise. And although overcrowding in towns and cities helps spread of infection, it was the rural districts that held the greater number of consumptives. Of the 2,238,473 making up the total population of Ulster of in 1841 as many as 2,161,248 were rural dwellers, and of 43,828 who died from consumption between 1841 and 1851, 34,104 were living in rural districts (Tables, pp 413-478) [13]. Almost 8 out of every 10 deaths from consumption occurred in the rural population which comprised 96 per cent of the total. This has to be seen in the light of the 'Framingham factor': for each annual consumptive death 9 patients with active disease and 9 with inactive disease were alive [27].

From graphical examination of the causes of mortality per 100,000 population in London, Stockholm and Hamburg, Grigg estimated that the wave form of tuberculosis epidemics in cities extends over approximately 300 years, reaching its peak in about 50 years, followed by a steady decline; the rural curve rises more slowly to a lower peak, and declines more slowly over a similar time span [28].

Three centuries after the earliest records identified consumption as a major cause of death in the population of Dublin, the Irish epidemic came under control, and by the close of the twentieth century the tuberculosis death rate (mortality) had yielded to morbidity its value as an index. With 13.1 new cases detected in 2002, Dublin still exceeds the national rate of 10.2 per 100,000 population nationally [29]. Episodic clusters of tuberculosis infection serve as a reminder that eternal vigilance in the form of continual surveillance is the price of freedom from the ravages of *Mycobacterium tuberculosis*.

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The authors have no conflict of interest.

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Letters

ACUTE ENCEPHALOPATHY IN CHILDHOOD ASSOCIATED WITH NOVEL INFLUENZA A H1N1 VIRUS INFECTION: CLINICAL AND NEUROIMAGING FINDINGS

S S Tang, A Siddiqui, S Andronikou, M McDougall, N Martinez-Alier, C T Lundy.

Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London.

Editor,

The emergence of the novel H1N1 influenza virus resulted in numerous infected children. There appears to have been an increase in the likelihood of an intensive care admission particularly for pregnant women. We report the first United Kingdom case of acute necrotising encephalitis (ANE) in a child associated with the H1N1 virus.

A healthy 4 year old Caucasian girl presented to hospital with seizures. She had a 48 hour history of low grade fever, vomiting and rhinorrhoea. On admission, she was febrile (38.9°C) and was observed to have a herpetic lesion on her lip. She was fully immunised as per the UK schedule with no infectious contacts and an unremarkable family history. She remained in generalised status epilepticus despite benzodiazepine therapy. She received an intravenous load of phenytoin and was intubated and ventilated. Her initial blood results showed a white cell count of 14.7 x 10^9 (neutrophils 10.9 x 10^9, lymphocytes 3.2 x 10^9), C reactive protein of 31mg/L, glucose 8.2mmol/L, normal renal, liver function and coagulation. She was given intravenous aciclovir, ceftriaxone and oral oseltamivir. A lumbar puncture demonstrated a cerebrospinal fluid (CSF) opening pressure of 38cm water. CSF was acellular with protein 0.53g/L (normal range 0.10-0.38g/L) and glucose 3.6mmol/L.

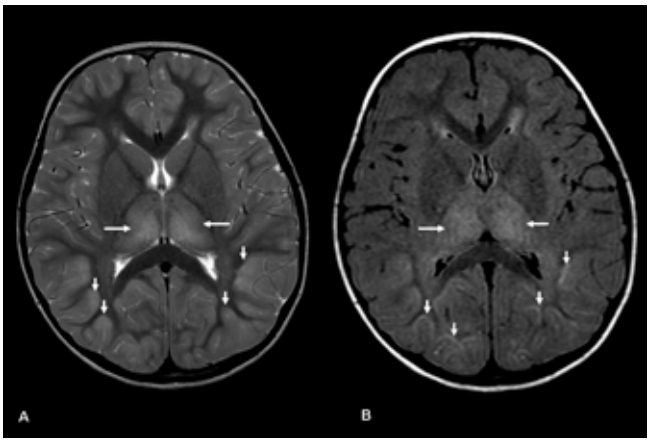

Figure 1. Axial T2-weighted and FLAIR images at the level of the basal ganglia show T2 hyperintensity and swelling of the thalami (long arrows) and cortical/subcortical high signal within the parieto-occipital regions bilaterally (short arrows).

She had an unenhanced Computerised Tomography (CT) brain examination, which was unremarkable except for mild cerebral swelling and some subtle low density change in the thalami. A Magnetic Resonance Imaging (MRI) examination was recommended to clarify further.

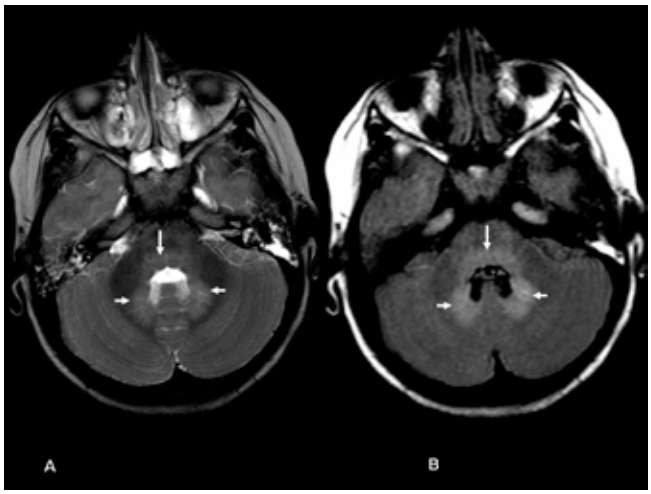

Figure 2. Axial T2-weighted and FLAIR images at the level of the pons show T2 hyperintensity within the pontine tegmentum (long arrows) and dentate nuclei bilaterally (short arrows).

She had no further seizures and was extubated the next morning. She remained encephalopathic with lower limb hypertonia, hyperreflexia and upgoing plantars and required reintubation. MRI brain scan on day 3 revealed symmetrical high signal changes on T2 weighted and Fluid Attenuation and Inversion Recovery (FLAIR) images involving the dentate nuclei, dorsal pons, midbrain and thalami with subcortical white matter high signal predominantly in the parietal and occipital regions (Figures 1 and 2). No abnormal contrast enhancement was observed. On diffusion weighted imaging (DWI), only minor patchy diffusion restriction was noted in the cerebral white matter, but the thalami, brain stem or cerebellum did not show any evidence of diffusion restriction. T2-weighted gradient echo images did not show any evidence of haemorrhage. Electroencephalogram was encephalopathic with no epileptiform activity.

Throat swab and broncho-alveolar lavage returned positive for H1N1 by RNA PCR. CSF was negative for H1N1 by PCR. All other plasma and CSF serology were negative. Scrapings of her lip lesion were positive for Herpes Simplex Virus Type 1. Serial platelet count, liver function and coagulation remained within normal limits.

The clinical and imaging findings were compatible with acute necrotizing encephalopathy (ANE). She was treated with intravenous immunoglobulin on day 4 (2g/kg over 2 days) and intravenous zanamivir on day 5 (20mg/kg for 5 days). This was made available on a compassionate basis from GlaxoSmithKline. She made a rapid recovery and neurological examination at day 8 was completely normal.

DISCUSSION

ANE was first described in 1995 by Mizuguchi et al in Japan[1]. ANE is an acute onset encephalopathy which often presents with characteristic neuroimaging features of multiple, symmetrical deep grey-matter lesions involving the thalami, cerebral white matter, internal capsule, putamen, upper brainstem tegmentum cerebellum and medulla[2].

ANE has been associated most commonly with influenza A and B viruses[2]. To the authors' knowledge, this is the first childhood case in the United Kingdom of ANE in association with novel H1N1 virus.

There are few reports of neurological complications of H1N1 in children. In 2009, Evans et al in Texas reported 4 children with influenza like illness, seizures and altered mental state. They had H1N1 positive nasopharyngeal aspirates although no evidence of infection within the CSF. Electroencephalograms in 3 patients were abnormal. Neuroimaging in all 4 showed non-specific changes and no suggestion of ANE. All 4 patients recovered with no neurological sequelae at discharge[3]. More recently, there have been a few published cases of ANE during the current H1N1 pandemic, with imaging findings similar to our case, both from Europe/Eurasia[4,5] and North America[6,7]. The rapid neurological deterioration with a minimal respiratory prodrome and seizures described in these reports was comparable to the case we present. These case reports also describe a similar pattern of involvement of the thalami, dorsal brain stem and cerebellum, with variable involvement of the cerebral white matter, except for the case described by Haktanir[5] where there was bithalamic and perirolandic cortical involvement. This case report had limited clinical information but appears to have presented in a similar way to the others. MRI findings in the case report describing fatality by Martin et al[6], showed extensive white matter change and cerebral swelling, presumably leading to raised intracranial pressure and herniation, findings that were much less extensive in our patient. Ornitti et al[4] describe diffusion restriction with haemorrhage in the thalami and diffusion restriction in the cerebellum and white matter, which presumably explains the residual damage noted on follow up and the protracted neurological recovery. Although we do not have radiological follow up in our case, the absence of restricted diffusion or haemorrhage within the thalami, brain stem or cerebellum on the day 3 MRI, together with the prompt clinical recovery, would probably indicate less severe residual damage in these areas, if any.

ANE has not been universally associated with a good outcome. In a Japanese review of 89 children with ANE, 53 (59.6%) had proven influenza virus. Thirty-three (37.1%) died and 17(19.1%) had neurological sequelae[8]. Elevated interleukin six has been associated with adverse neurological outcome in the Japanese literature on ANE, it was elevated at 441pg/ml in this case however it is of uncertain significance as other interleukins were also elevated. One possible explanation is sample transit time.

Unlike other reported cases, this child did not have CSF pleocytosis, abnormal liver function or coagulopathy. However, she did have a raised CSF protein which is typical. It has been suggested that children with normal CSF protein and liver function tend to recover well. Normal CSF protein seems to have the strongest correlation to a good outcome[9]. Correlation of MRI findings and clinical outcomes has resulted in the development of a radiological scoring system which may be helpful.[10] The possibility of familial encephalitis was considered in this case but there was no relevant family history.

There is no specific therapy for ANE. Corticosteroids, dexamethasone, intravenous methylprednisolone, intravenous immunoglobulin and plasmapharesis have been used in different centres with variable long term outcomes[9]. In this case, intravenous immunoglobulin was given for its potentially beneficial non-specific immunemodulatory effects. This decision was aided further by the reluctance to use steroids in the presence of Herpes Simplex type 1 virus positive skin lesion. Other similar cases published recently have demonstrated ongoing neurological deficits.[4,5]

Intravenous zanamivir is an unlicensed treatment with currently unknown efficacy and has not been described in other published case reports of ANE associated with H1N1 in children. In this case, given the clinical and neuroimaging findings supporting a diagnosis of ANE and its potential severity, intravenous zanamivir was given after 4 days of oral oseltamivir. The patient did not have any adverse effects and demonstrated a full neurological recovery. This virus may re-emerge in the coming months.[11] For the vast majority of children it appears to have been a mild even asymptomatic infection, however monitoring is required to assess the prevalence of neurological sequelae of this particular strain of influenza.

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Ulster Med J 2011;**80(1):**51-52

Abstracts

Autumn Meeting Ulster Society of Gastroenterology Thursday 18th November 2010

Hilton Hotel, Templepatrick

PROGRAMME

Approved for 3 external CPD credits (RCP)

13:30 – 14:00	Registration & Tea / Coffee
14:00 – 14:05	Welcome
14:05 – 14:45	Free paper presentation (4 papers)
14:45 – 15:00	NICAN Regional Colonoscopy Audit Results C Rodgers
15:00 – 15:15	Can't scope, won't scope ! SD Johnston
15:15 – 15:30	Coffee/ exhibition stand
15:30 – 16:00	Nonalcoholic Steatohepatitis **Dr N McDougall** Consultant Hepatologist Royal Victoria Hospital
16:00 – 17:00	IBD and its Complications **Dr Stuart Bloom** Consultant Gastroenterologist University College London Hospitals
17:00 – 18:00	Business meeting
18:00	Meeting close & USG Dinner

ORAL PRESENTATIONS

Prize Winning Presentation: Investigation for Biomarkers of Barrett's Oesophagus

Jawad Ahmad, Ken Arthur, Andrew Kennedy, Helen Mulholland, Perry Maxwell, Liam Murray, Brian Johnston, Damian McManus

Introduction: The incidence of oesophageal adenocarcinoma (OAC) has increased dramatically over recent years and Barrett's oesophagus (BO) is the most established risk factor for its development. Endoscopic surveillance of BO has been widely advocated but hinges on assessment of repeated endoscopic biopsies, which is problematic. The use of biomarkers presents an opportunity to reduce sampling bias and improve our ability to risk-stratify these patients.

We evaluated three novel biomarkers namely P504S, CD133 and Twist, in the setting of BO, low grade dysplasia (LGD) and OAC.

Materials and Methods: After ethical approval, the biomarkers were immunostained on an automated Ventana immunostainer. The archived biopsy materials were assessed for biomarkers expression by two independent observers using a QScore method. 25 cases each of BO, LGD and OAC were included along-with 25 cases of oesophagectomy for OAC. Any inter-observer score discrepancy of ≥ 2 was settled at a case meeting.

Results: P504S did not express in BO. Its expression was significant in cases of LGD (56%), OAC (40%) and resections (60%). CD133 also did not express in BO or LGD. It was up-regulated in cases of OAC (24%) and resections (68%). Twist expression was weak in BO and LGD. However, It was significantly over-expressed in cases of OAC (56%).

Discussion: This cross sectional study has shown increased expression of P504S, CD133 and Twist in the metaplasia-dysplasia-adenocarcinoma sequence and has suggested their possible role as potential biomarkers of Barrett's progression. Further longitudinal and prospective studies are required to validate these results.

Laparoscopic repair of para-oesophageal hernias

R Lambon, R Kennedy, G Irwin, Z Bell, A Kennedy

Department of Upper Gastrointestinal Surgery, Belfast Trust, Royal Victoria Hospital, Grosvenor Road, BT12 6BA

Background: Para-oesophageal hernias (POH) are rare but potentially lethal disorders of the oesophageal hiatus. Laparoscopic repair is a recently introduced minimally invasive surgical innovation. We aimed to assess the efficacy and safety of this approach at our institution.

Methods: A prospective cohort study was performed. Patients who underwent laparoscopic POH repair were included. Data regarding operative time, conversion to open rate, repair method, operative and post-operative complication rate, symptomatic assessment and hernia recurrence rate was collected.

Results Over the 4 years study period, 26 patients had surgery. The mean age was 63.1 years (37-82) and 60.9% were female. Most patients had co-morbidities with American Society of Anaesthesiology (ASA) grade I (3), II (14), III (9). The most common presenting complaint was with recurrent chest pain (39.1%). Emergency presentation with gastric volvulus and acute abdominal pain occurred in 4 patients (17.4%). Conversion to open was necessary in 1 patient, who had 2 previous repairs at another institution. Mean operating time was 165 minutes (64-240) and repair of hiatus achieved with biological mesh in 13 (56.5%). Mean postoperative stay was 3.7 days (1-8 days, median 3). At mean follow-up of 24.3 months, complications encountered were mortality 1 (due to pulmonary embolism), pneumonia 1, acute recurrence requiring re-operation 1, dysphagia requiring gastroscopic dilation 3, mediastinal collection treated with percutaneous drainage 1.

Conclusion: Laparoscopic repair of para-oesophageal hernias is safe and efficacious.

IBD Patient Service Satisfaction Survey – 2010. Northern Ireland.

Gerard Rafferty, Mary Kane. Peri Gillespie, Graham Turner.

Introduction: Public and client involvement is essential in trying to improve the quality of a service. There had previously been no regional IBD patient satisfaction survey performed in Northern Ireland.

Methods: A patient satisfaction survey was designed with NACC input. 410 questionnaires were posted to NACC members. Categories included: information given to patients at any stage during illness, IBD nurse specialists, out-patient care, care during flare-up of IBD and overall rating of IBD service currently provided.

Results: 42.2% questionnaires were returned. 36.8% male.

38.5% patients were given written information about IBD. 50.0% total patients were given information about the medications they were prescribed. 37.9% total patients were given explanation about how illness was likely to affect them in future. 24.2% total patients felt they received sufficient information about illness and treatment available. 5.2% have access to IBD nurse specialist and 88.8% felt it would be beneficial to have access to IBD nurse specialist. 69.5% patients have regular OP appointments with 40.2% have 6 monthly or more frequent appointments.

44.8% patients felt that they have access to a satisfactory contact with IBD service during a flare-up. 77.4% were satisfied with in-patient care. 50.6% satisfied with out-patient care.

Conclusion: IBD service can be improved and need more patient and client involvement. Immediate fixes include: better information to patients, advice regarding joining NACC, written info sheets including medicine and spend more time discussing future. In the long-term we need better management of chronic disease (including community care) and increase IBD specialist nurse numbers.

If it walks like Crohn's and talks like Crohn's, it must be……..

Hall PSJ [1], Allen PB [1], Patterson J [2], Manikure G [1], Diong K [1], Varghese A [1]

Departments of Gastroenterology [1] and Colorectal Surgery [2], Causeway Hospital.

A 30 year old male presented with a six month history of nausea, vomiting and diarrhoea. He experienced almost daily episodes of vomiting with abdominal pain, and had lost over 25 kilograms of weight during this time. He had intermittent diarrhoea, occasionally with bloody stools, and a migratory abdominal colic often localising to the right side. He was lethargic, had anorexia, and complained of profuse sweating. He had been provisionally diagnosed with Crohn's disease 6 months previously and treated with budesonide and mesalazine. This provided minor relief from his diarrhoea, but had no effect on abdominal pain or weight loss. There was nil other past medical history of note. He had no allergies and did not drink alcohol or smoke. On examination he had no rashes, lymphadenopathy, anaemia or jaundice. He had mild tenderness in his right lower flank. There were no abdominal masses palpable and no ascites. Bowel sounds were present. Investigations including C-reactive protein, white cell count, coeliac antibodies, fasting gut hormones and faecal elastase were all normal. Colonoscopy and ileoscopy was normal macro- and microscopically. Small bowel series and labeled white cell scan were both unremarkable. A computerised tomography (CT) scan of the abdomen demonstrated the presence of mild right sided lymphadenopathy which raised the possibility of small bowel pathology. Laparoscopy of entire small bowel and colon was normal and an appendicectomy was performed. But was there something that had been missed?

Book Reviews

'CLINICAL ONCOLOGY – BASIC PRINCIPLES AND PRACTICE', 4TH EDITION,

Anthony J. Neal, Peter J. Hoskin. Hodder Arnold. April 2009. Paperback 402 pp. £24.99. ISBN 987-0-34097-293-9

The authors' motivation for writing a scientific text book is often around the academic rigour of setting out the science of their specialist area for the benefit of novices entering their scientific specialty. The motivation of the publisher is more complex since selling copies is a pre-requisite to a successful book. Therefore the preface of such books often envisages a wide readership of interested professionals in associated fields of interest. This book carries the subtitle 'Basic Principles and Practice' and in its preface the authors suggest that it will be of interest and relevance to undergraduates in medicine, junior doctors and to nurses and other health professionals with an interest in oncology.

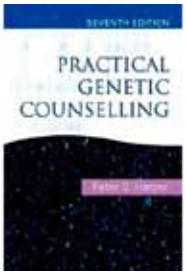
It is undoubtedly attractive to read although the page is intensively used with tight margins and a dearth of restful open spaces. The layout is clear, but with a slightly idiosyncratic use of pink text for headings within the text and on the top margin of each page. The illustrations are truly fascinating with high quality images of a striking range of clinical and radiological cases and signs. The text is interspersed with self assessment questions and with clinical vignettes which add variety to the learning experience. One minor quibble is that many of the subject areas would benefit from more liberal use of tables and diagrams to illustrate and clarify points in the text.

The first six chapters cover the general principles of a range of oncology disciplines. This is followed by fifteen disease specific chapters and a chapter each on Oncological Emergencies and Palliative Care to complete the volume. The range of subject matter is well chosen and the depth of coverage is uniform, which is a benefit of having only authors. The text is quite authoritative and both authors are senior academics in UK clinical Oncology.

The book is well-written and this is an approachable primer for individuals wishing to study the subject or a particular disease site in more detail. As such it would be of interest to oncology trainees as a basic text for their early training but would not be sufficient for the more advanced trainees or Sub-Specialist Consultants. As discussed above, the preface also suggests that this text book would be of interest to Undergraduates, nurses with a specialist interest and Physicians and Surgeons in other specialities wishing to have a grounding in the oncological principles. This text book would be very suitable for gaining a basic knowledge of the specialty and should be on the library shelf for these groups. However, it may lack the detail required by a Consultant in a linked speciality. For example, I do not think that a Respiratory Physician with a interest in lung cancer would be satisfied with the level of information provided about chemotherapy in lung cancer ,but would find this text book useful in setting out the basic principles, supplemented by published expert reviews and peer-reviewed articles.

In summary, I would recommend this book as the authoritative primer in clinical oncology which sets out the scientific basis and rationale for clinical practice in the United Kingdom and it would provide Clinical Oncology trainees with a sound basis for future studies.

PRACTICAL GENETIC COUNSELLING (SEVENTH EDITION)



Peter S Harper. Hodder Arnold. August 2010. Paperback, 407pp. £39.99. ISBN: 978-0-340-99069-8.

When I started my training in clinical genetics in the 1980's, Professor (now Sir) Peter Harper was one of the leading influences. His textbook, at that stage in its second edition, was 'The' guide to genetic counselling, and I remember purchasing the third edition in 1988, hot off the press. This edition has not changed in the tried and tested format of three sections – Part 1 provides and excellent overview of 'general aspects of genetic counselling' , Part 2 gives details of 'specific organ systems', and Part 3 details the 'wider picture', and also includes an excellent appendix and glossary of terms. Although I am now supposed to be an 'expert', I occasionally refer to the 6th edition in my bookshelf to check some facts and approaches, and suspect I will do the same with this book if my colleagues haven't pinched it off my bookshelf to do the same. This text is not geared for genetic specialists however, and the generalist, GP or specialist nurse will all find this book the equivalent of the experienced hand on their shoulder, helping guide their consultation smoothly through the usual can of worms that hereditary conditions usually have.

The book's strength is in the title. It deals with genetic counselling – the approach that health specialists should take when dealing with families with hereditary disorders. The first part of the book should prove extremely useful in setting the context of counselling for those in medicine, nursing and other health specialties where genetic information is increasingly creeping into their practice, and who are unsure about the approach they should take. The experience of Harper's lifetime skills in counselling comes through the pages clearly. General practitioners who think they have the scientific facts at their fingertips, might find a copy in their practice library a useful tool in helping tailor their (and their trainees) approach to dealing with the complex web of interactions that initiating genetic referrals on families usually reveals, and help shorten the gap between theoretical knowledge and practice at the coal face of the consulting room.

The sections on individual systems has particularly helpful chapters on neurological disorders, hearing loss, skin and eye, and reflects Harper's personal interest in Myotonic dystrophy and Huntington disease, and his invaluable experience from years of counselling in genetic clinics comes through.

Harper mentions in the preface that this will be the last edition in this format due to his retirement. Where will the book

go next? I think for the next edition the audience probably needs to be defined. Increasingly generalists and specialists are looking online so a web version might encourage the new web-savvy breed of trainees in all disciplines to take a look. There are weaknesses in the 7th edition in areas outside Harper's personal interests. The chapter on cancer genetics doesn't contain much helpful information and needs considerable revision. – Counsellors looking to find what the BRCA1 gene does will find it limited and recent advances in other cancer genes aren't mentioned – and when the majority of referrals to our own service are cancer, and an increasing number are cardiac genetics, then new co-authors need to be brought in to help the book to survive in the era of instant knowledge.

Overall this book continues to be an excellent and invaluable source of guidance for those starting out on their task of dealing with hereditary disorders, which now involve so many areas of disease.

Patrick J Morrison

THE CHECKLIST MANIFESTO

Atul Gawande, Profile Books Ltd, London 2010, 209 pp, £12.99. ISBN 978 184668 313 8,

What should a cholecystectomy and a Van Halen concert have in common? The answer according to Atul Gawande is a checklist to help get things right. In the 'Checklist Manifesto', Gawande argues that the volume and complexity of the knowledge required for the safe practice of medicine now far exceeds our ability to properly deliver it. He believes that doctors can learn from other industries such as aviation and construction where checklists have made possible some of the most difficult tasks. He has worked with the WHO to introduce this concept into the world of surgery and has produced a ninety second checklist which reduced deaths and complications by more than one third in eight hospitals around the world-at virtually no cost and for almost any kind of operation.

Van Halen's insistence on having a bowl of M &M's, with the brown ones removed, was not in fact the unreasonable request of an egocentric pop band. This request was carefully submerged in a 90 page document that they provided for venue organisers to ensure the safety of their concerts. If the brown M &M's were still present they knew that the document had not been carefully read and that further safety checks were required which often revealed preventable hazards.

Will Gawande's idea catch on? Keep an eye on the colour of M&M's the surgeons are eating.....

James Clarke

Ulster Med J 2011;**80(1):**55-55

So you want to be a **Surgeon?**

Accepted 20 December 2010

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There have been enormous changes in surgical training: increasing specialisation; the technical advances of surgery and the ubiquity of advanced laparoscopic and other procedures. There are now several well-recognised surgical sub-specialties such as Breast, Endocrine, Upper Gastrointestinal (including Hepatobiliary), Lower Gastrointestinal, Vascular and Transplant surgery.

The essential criterion the would-be surgeon must possess, is, I believe, a genuine interest: it is very hard work and it can be a long road. Usually, it is interesting and mostly very rewarding but occasionally can be disappointing. During the F2 year, the budding surgeon will apply for Core Training for which there are about 90 places in Northern Ireland. The two Core Training years (CT1 and CT2), entail rotating through various specialities. During this time the trainee should complete an audit project and acquire the MRCS exam. They also will attend various courses such as the ATLS, and CRISP.

The Intercollegiate Membership of the Royal College of Surgeons (MRCS) has two parts. Part A is usually taken in CT1 year and part B in the CT2 year. Part A has two sections: Section 1 is applied basic science based on the single based answer format. Section 2 of part A is on the principles of surgery, examined using an extended matching question format.

Part B is in an OSCE format, testing anatomy, surgical pathology, surgical skills, patient safety, communication skills, applied surgical science, critical care, clinical skills, examination and history-taking.

There is (except for Scotland) uncoupling between Core and Specialist Training. The Core Trainee must apply to become a Specialist Registrar. This is a significant hurdle as there are only 15 trainees per year in all specialities. (At times in general surgery there may be only 1 or 2 trainees appointed to ST3 level). Most trainees will therefore complete a third year of core training. There are a number of ward and operating theatre-based competency assessments, such as peer assessments, mini PAT, clinical acumen, mini CEX, case-based discussions, observation of procedural skills, DOPS, procedure based assessment, log book experience, education supervisor reports and a Deanery interview. It is now increasingly recognised that not all trainee surgeons' progress at the same rate and training should now be 'competency based.' The trainee must demonstrate proficiency with different procedures before being allowed to progress.

The higher training years (ST3 – ST8) are based on a very well developed curriculum. Typically there are between 6 and 8 years of higher training. The early years involve general rotations. During the last few years of training the trainee will gradually (in the current environment) focus on a specialty.

The last major hurdle is the Intercollegiate FRCS examination. Typically, in year ST6, the trainee will take section 1 of the examination. This is a two part written paper: the first, a single best answer paper; and the second, an extended matching question paper. From January 2011, candidates will be permitted only three attempts. The current examination format for section one examines basic anatomy, physiology, pharmacology and statistics in addition to all the clinical aspects of the major sub-specialties within general surgery.

Section two, the clinical aspect of the examination, comprises a critical care viva as well as academic, general and speciality vivas and an emergency surgery viva. There then follows a one hour clinical examination, 30 minutes of which is spent in the generality of surgery and 30 minutes in the candidate's own specialty.

In addition to this rigorous examination system, a number of research-active trainees will take three years 'out of practice' to complete a PhD. More often, trainees will attain an education qualification, part-time and module based.

Ultimately, you become a consultant surgeon – what is your week? Typically, it will comprise 2 or 3 operating sessions; 2 outpatient sessions; 1 endoscopy or special interest clinic; 1.5 sessions for direct clinical care (ward rounds etc.), and 0.5 for indirect care. There will be a session for being on-call, generally, 1 in 5 or 1 in 6, and further provision for teaching, training, and self learning. For all surgeons, interprofessional team working is here to stay. Virtually all cancer patients, for example, are now reviewed before and after surgery by a multi-disciplinary team including the surgeon, oncologist, pathologist, radiologist, and specialised nurses.

A smaller number of surgeons will work for the University in an academic role. Traditionally half their time will be spent working clinically and half will be spent on academic matters. Education and research are valued equally, so some surgeons may major in education and some in research.

So you want to become a surgeon? Rewarding and satisfying? Yes. Teamworking? Yes. Future mentoring as a young surgeon? Probably yes. Will your work and career change over the next 30 years? Definitely yes. So you still want to be a surgeon – and this is your passion – **GO FOR IT!**

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By joining the Ulster Medical Society you will enable us to widen its influence and sphere of usefulness still further. The only requirement is that you should be a registered medical practitioner. A membership application form is appended below. Please return the completed form along with the direct debit form overleaf to the Honorary Secretary at the address above. The annual subscription is claimable against income tax.

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Cover legend: Antoine and Baptise Hugo with their five siblings.