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Editorial

The Johnston – Kennedy Era. A Quarter of a Century of Change

The paper by McConville and Crookes[1] in this issue of the Journal highlights the contribution of many Ulster surgeons to gastric surgery. The era of Professor George Johnston and Mr Terence Kennedy produced some of the most dramatic changes in surgery of benign upper GI disease.

I was a medical student, House Officer, Senior House Officer and then Senior Registrar to these giants of Ulster surgery – these questioning surgeons participated in some of the most important trials of that time in gastric surgery, and assessed scientifically (and independently) the benefits of a logical progression in surgical vagotomy from truncal to selective (with the various drainage procedures) to the highly selective procedure. I would like to take you on a thirty year journey of reflection.

THE SURGEONS

I first met Mr (as he was then) George Johnston and Mr Terence Kennedy in the old Wards 15 and 16 in the Royal Victoria Hospital (now demolished)[2] when I was a student. They had strikingly different personalities - Mr Kennedy was more than a little daunting but both were constantly stimulating and renowned teachers. The teaching ward rounds revealed surgical cases in the true sense of the word 'general', ranging from open cholecystectomy to various vagotomies (both de novo and re-do), fundoplications, colectomies, trauma, breast cancer and much more. In terms of trauma, it was the height of 'The Troubles', a curious euphemism for the times. Trauma of every description was present in the ward, but most common were gunshot wounds of the abdomen accompanied, not infrequently, by a police and army guard outside the ward.

Other cases involved jaundiced patients, some having undergone hepatico-jejunostomy for bile duct problems. There was the frequent presence of patients with oesophageal varices with their dramatic haematemeses. The Registrars of the day were held in high esteem and always seemed to be "around". I cannot recall many rotas and certainly no European Directives on working hours! I next met Mr Kennedy when he examined me in Finals. I had a nervous moment or two until we got past the first few minor cases.

Subsequently, I returned as House Officer, Senior House Officer and Senior Registrar and I enjoyed all of these times enormously. At that time, Sister Cherry ran the ward with firmness (and fairness) and the mid-morning cup of tea with the Registrars was a golden opportunity to hear the stories about Consultants of yesteryear and in particular their previous chiefs. Perhaps we have lost something with the new shift systems and less time available for getting to know junior staff, particularly the House Officers.

I recall Mr Kennedy (I still cannot call him by his first name!) permitting me as a Senior Registrar, to do four consecutive highly selective vagotomies on one of his lists. 'The Troubles' were ongoing and, each night, there were several gunshot wounds, usually managed by the Senior Registrars. During this era, Senior Registrars worked a virtual one-in-one rota and gained an enormous amount of experience. Many from this era are now retiring or have already retired!!

In the 1970s and 1980s, honours fell upon these two surgeons, ranging from the Hunterian Professorship (Mr Johnston), to Presidency of the Association of Surgeons (Mr Kennedy). Both men undertook lectures across the world, travelled extensively and became very well known in the surgical fraternity. They each had differing personalities,[1] but worked closely together. Despite frequent leg-pulling and the occasional good humoured "come, come George!" from Mr Kennedy, I never heard a cross word.

Despite their already formidable reputations in portal hypertension, complex biliary surgery, ulcer surgery and revisional gastric surgery, they were innovative and would tackle new procedures. In particular, I recall them working together to do one of the first restorative 'pouch' procedures in Northern Ireland. One compares that new procedure then with the pre-requisite nowadays of intensive courses and prolonged mentoring!

From my student days in Ward 15 and 16, some thirty years ago, my clear recollection is that the students were not a nuisance. Both consultants personally taught junior and final year students, unless either one was on leave. The variety of cases was enormous, encompassing all of general surgery. Being a final year student in the Unit meant being in the ward at night time. Indeed, junior students on their clerkship were also expected to attend the ward at night time to see the incoming emergency cases. At their worst, these cases involved several gunshot wounds per night, in addition to the usual general surgery cases, such as bowel obstruction and the quite common perforated ulcer (usually one per night in this era before Cimetidine).

With the passage of thirty years, there have been many changes. The wide variety of surgery done by one team is gone; units and surgeons are now super-specialised. "General surgery has gone" goes the lament, although there is an

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increasing realism that we still need general and take-in surgeons and the 'wheel' may yet turn full circle.

The European Working Time Directive has brought in shift work, and decreased hours on-call are now the norm, with the corollary of the demise of the 'Senior' Senior (highly experienced) Registrar, who could handle most general surgery, when appointed as a young Consultant.

While the Consultants then also did seem to lament administration, I doubt that there was the volume of paperwork which is part of daily work in 2007. Malpractice work was present in the 1970s, but the volume in the 21st century is clearly enormously increased.

There seemed to be less talk of budgets then. In fact, I remember the notion that one must spend the budget before 31st March each year. GMC inquiries were virtually unheard of. The words "plagiarism in examinations" were never mentioned. A Patient Complaints Officer seemed not to exist.

So was it all better in1970s surgery? (like the warm summer holidays of childhood that one remembers nostalgically through the mists of time?) As Senior Registrars, there was no doubt we gained enormous experience and, in hindsight, (perhaps through the mists of time), it seemed enjoyable, despite the hours on-call. We had continuity of care and continuity of patient experience. However, the training programme was long and there was an excess of junior surgeons whose average age to be appointed a Consultant was late thirties.

And finally, perhaps the biggest change of all is that the Province is now a quiet and better place, as 'The Troubles' are fading.

Furthermore, many lessons have been learned from the 1970s, such as titanium plates in neurosurgery following gunshot wounds to the head, vascular trauma repairs using stents to maintain blood flow and the fact that we now work in multidisciplinary teams. These are but some of the lessons. There are many more.

In conclusion, a generation of surgeons, myself included, consider it a privilege to have been taught by two giants of Ulster surgery, one a home-grown star, Professor George Johnston, and one an adopted Ulsterman, Mr (I still cannot call him Terence!) Kennedy. Both were world-renowned surgeons but I think both would agree with John Hood[3] in his oration who quoted from Sir Isaac Newton: "If I have seen further, it is because I stand on the shoulders of those giants who have gone before."

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Roy Spence, Assistant Editor

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Commentary

Are We Failing Those With 'The Falling Sickness'? Time to modernise the approach to epilepsy care.

Stephen J Hunt, James I Morrow, John J Craig.

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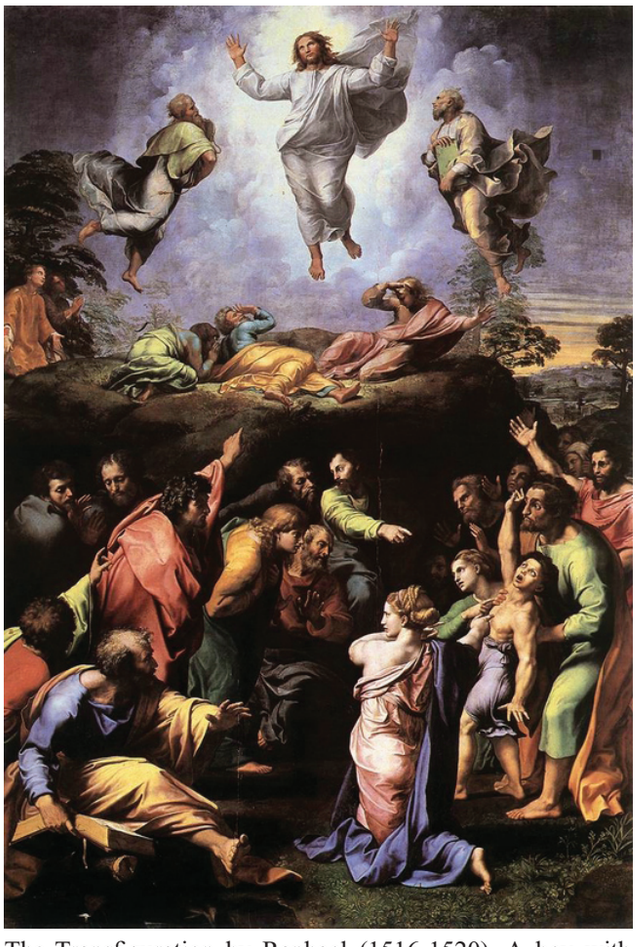
The epilepsies are a common, heterogeneous group of disorders linked by a tendency to recurrent seizures in affected individuals and which have no respect for age, gender, race or social status. A seizure is defined as an intermittent, stereotyped, disturbance of consciousness, behaviour, emotion, motor function, or sensation that on clinical grounds is believed to result from cortical neuronal discharge. Descriptions of seizures can be traced as far back as civilisation itself. In antiquity, seizures were felt to occur as a consequence of supernatural forces. Since the late twentieth century there has been an explosion in the understanding, investigation and management of seizure disorders. Perhaps as a cultural hangover from millennia of myths and the potentially dramatic clinical manifestations of seizures, 'civilised' society remains alarmingly adept at stigmatising the person with epilepsy.

THE FALLING SICKNESS AND SACRED DISEASE

Currently the earliest known detailed description of various seizure types are contained within the stone tablets of the Sakikku (meaning 'All Diseases'), a Babylonian text compiled circa 1000 BC that is held in the British Museum, London. A Sumerian term referring to descriptions of seizures has been translated as 'The Falling Sickness'. The Babylonians thought that each seizure type was thought to represent possession by a particular demon or departed spirit and hence treatment focussed on spiritually based methods.[1] Hippocrates (circa 400 BC) has been credited with authorship of a text 'On the Sacred Disease' which concludes that seizures are purely a physical ailment and a manifestation of an abnormality within the brain rather than some sacred, in other words supernatural, influence.[2] Despite his insightful conclusion this opposing theory failed to rival the notion of supernaturalism in the thinking of others who came after. Galen's (129-200 AD) descriptions of epilepsy were more restrictive than much that preceded him but such was his influence on so many aspects of medicine his theories dominated well into the Renaissance. He concluded there were three forms of epilepsy "In all forms it is the brain which is diseased; either the sickness originates in the brain itself,... or it rises in sympathy into the brain from the cardiac orifice of the stomach... Seldom, however, it can have its origin in any part of the body... and then rises to the head in a way which the patient can feel...".[3] Greek Galenists employed dietary manipulation, pharmacological and surgical intervention depending on the type of epilepsy present.

THE MIDDLE AGES

Raphael's (1483-1520) painting the "Transfiguration of Christ" illustrates passages in the Gospels in which Jesus Christ casts out a devil from a boy with epilepsy. There are several similar references to epilepsy in the Bible, in large part forming the Christian Middle Age view of epilepsy as a demonic disease or result of witchcraft. Galen's restrictive influence on what



The Transfiguration by Raphael (1516-1520). A boy with epilepsy is depicted in the foreground. Reproduced with permission of the Vatican Museums.

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phenomenologically could be considered *epileptic* waned and other manifestations (partial and complex partial events) were recognised as being epileptic in origin. Unfortunately, better recognition of epilepsy did not necessarily translate into better understanding its true origins. Seizures are documented as one of many possible characteristics of witches in the classical text on witch-hunting, *Malleus Maleficarum*, something that led either directly or indirectly to the deaths of thousands of women, many of whom had epilepsy, during the approximately 200 year lifespan of the inquisition.

Toward the late nineteenth century the work of John Hughlings Jackson, a London neurologist, helped further the understanding of many aspects of neurology, not least epilepsy. His recognition that a seizure is merely a reflection of underlying neuronal dysfunction, rather than a stand alone entity in itself was a great leap forward. Jackson's ideas have been refined into what we accept as the principles of modern day epileptology. This enlightenment led Jackson and his contemporaries to found the Chalfont centre for epilepsy near London, an agricultural colony where those with epilepsy could live and work in a compassionate atmosphere free from the negative prevailing social attitudes. Today, the Chalfont Centre continues to look after residents with refractory epilepsy but it now also acts as a national referral centre for investigation and management allied to a world class research portfolio.

In recent years Government advisors have published key documents providing guidance on management of epilepsy (NICE, SIGN).[4,5] The National Sentinel Clinical Audit of Epilepsy-related Death, published in 2002, reported on sudden unexpected death in epilepsy (SUDEP) which is thought to account for 500 deaths per annum in the UK.[6] The factors leading to the excess of sudden death remain a matter of speculation but it is accepted that poor seizure control is implicated.

CLASSIFICATION AND MANAGEMENT

Although imperfect the International League Against Epilepsy (ILAE) classification system has been adopted worldwide and acts as a framework for the organisation and differentiation of seizure types and epilepsy syndromes.[7,8] The terms 'grand mal' and 'petit mal' though part of the vernacular are quoted all too often in medical communication and have no place in the modern lexicon of epilepsy. Our patients deserve an accurate (as possible) diagnosis which in turn helps direct appropriate management and point to prognosis. Pharmacological therapy that may greatly benefit one epilepsy syndrome may lead to a dramatic worsening of another. Furthermore, mindful that 'not all that shakes is epilepsy' it is imperative that patients and their doctors have ready access to expert services to ensure individuals are not inappropriately labelled as having epilepsy. The last decade has seen the proliferation of specialised epilepsy clinics throughout the UK. Such clinics have been demonstrated, through providing ready access to epilepsy specialists, specialist epilepsy nurses and others working within a multidisciplinary framework, to improve epilepsy diagnosis and management.[9]

INVESTIGATION

Modern neuroimaging modalities with their impressive spatial resolution have been integral in improving our ability to identify the aetiology of localization-related epilepsies in particular. We can now easily visualise hippocampal sclerosis in some patients with medically refractory seizures, offering a significant (carefully selected) proportion of them a cure with epilepsy surgery, and even in some cases anti-epileptic drug withdrawal. The rapid expansion in knowledge of disorders of cortical development, the second most frequent cause of intractable focal epilepsy, has also only been possible through advances in neuroimaging,. The combination of structural and functional imaging (fMRI, PETCT) further promises additional insights into ictal and interictal cerebral functioning.

In contrast to all forms of imaging interictal electroencephalography (EEG) is a well established technology and remains a useful adjunct in the investigation of epilepsies. However, requests along the lines of "EEG please, rule out epilepsy" both overvalues EEG and misrepresents its place in clinical practice. Combining continuous long term EEG with real time video capture has become a vital resource for the investigation of episodic attacks, when the diagnosis is not clear, for the classification of seizures and as part of a pre-surgical evaluation. Continuous EEG monitoring for the management of status epilepticus in an ICU setting can also be useful.

The last fifteen years has seen a proliferation in the number of anti-epileptic drugs available. Some confer definite advantages over the older, established therapies but are more costly. To date little in the way of head to head comparison between these newer agents and the established therapies has been published. The NHS R&D health technology appraisal programme has reviewed the available evidence on the longerterm clinical outcomes and cost-effectiveness of standard and new antiepileptic drugs.[4] Choice of therapy should be based on a number of variables including gender, age, seizure types or syndromes, co-existent medications and patient choice. Monotherapy should be the aim where possible with carefully designed schedules for medication changeover periods.

GENDER ISSUES

The last decade has seen a focus on gender issues in epilepsy and local neurologists in tandem with allied specialists have been contributing to the evidence based management of epilepsy during pregnancy, gaining international recognition for the ongoing work of the UK Epilepsy and Pregnancy Register[10]. We now have for the first time accurate data on the teratogenic risk of the most commonly used drugs. As a result of our greater understanding of the complexity of managing women with epilepsy during pregnancy joint specialist epilepsy / obstetric clinics are being set up, with one recently having been established at the Royal Group of Hospitals in Belfast.

FUTURE GOALS

Given an incidence of approximately 50 cases per 100,000 persons per annum and a prevalence of 5-10 cases per 1000 for epilepsy, it can be (conservatively) estimated that for Northern Ireland the number of consultants required to service epilepsy lies in the range 4 to 13. ILAE guidelines contend that all patients with epilepsy should be managed by someone who has an interest in epilepsy. In contrast, at present, there

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is a stark mismatch between that which is required and that which is available in Northern Ireland.

Traditionally general physicians have provided a great amount of the care of patients with epilepsy and other neurological conditions, and not only in the acute situation. However, since the introduction of Calman type training, very few trainees in general medicine have been able to work in neurology units, above the senior house officer level. This might be viewed as somewhat of an organisational faux pas given that one in six of all acute medical admissions is for a neurological problem with one in three of these being seizure related.[11] Given this shift in the organisation of post-graduate medical training it is therefore essential that neurologists become more involved in the management of all patients with neurological symptoms and conditions.

In order to translate advances in epileptology into improved standards of care locally a broad ranging package of measures including improved education and capital investment is required. The current positioning and time given to the teaching of neuroscience at the local medical school does not reflect the prominence of neurological disorders in practice. Numbers experiencing postgraduate training in neurology must undergo dramatic expansion as should the number of career neurologists. We must improve links to primary care, accessibility to specialist opinion and investigations. We need only look sideways at the achievements of our diabetology colleagues to realise that such change is not simply a pipedream but truly achievable given adequate planning, resources and political will. Not to modernise is to fail our patients.

Conflict of interest: The authors have received funding grants from the pharmaceutical industry for an antiepileptic drug population register.

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Assistant editor Rex Wilson retires

After twenty years as Assistant Editor, Rex Wilson has corrected his last paper for the Ulster Medical Journal. He first published a paper in the journal in 1946 when he was a 'penicillin officer' at the Royal Victoria Hospital, and went on to have a career in General Practice. We wish him many more years of 'retirement' following his recent 90th birthday. Rex has an excellent grasp of grammar and rarely missed a spelling or syntax error. His skills will be missed in this era of writers more used to text messaging. He was recently presented with a book 'Meetings with Remarkable Trees' (by Thomas Pakenham) as an appropriate reminder of all the papers that he has handled, and a certificate from the Ulster Medical Society and the journal, by the current editor Prof. Patrick Morrison and former Editor Prof. David Hadden.

Patrick Morrison

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Commentary

Proximate determinants of fertility and reproductive health

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The dramatic decline in mortality rates during the nineteenth century put the countries of the world into an imbalanced stage of demographic transition. Developed societies adopted fertility control methods and achieved a balance in their annual rate of population growth, whilst developing countries and traditional societies are still confronted with the following serious hazards:

1. Poor health of women particularly reproductive health and related problems
2. High infant mortality rate and still birth rate
3. High Maternal Mortality Rate (MMR)
4. Low social respect of women as it is becoming hard for them to fulfil the responsibilities of child bearing and peak expected compatible performance in the office or field.

The International Conference on Population Development (ICPD) held at Cairo in 1994 took due cognizance of these issues and made it mandatory for all the participating countries of the World to reduce the prevailing high levels of their indicators by 2015. Subsequently these indicators also became part of the Millennium Development Goals formulated by 199 countries of the World in New York at the onset of the new millennium.

Massive attempts have been made all over the world to reconstruct public opinion by promoting ICPD and Millennium Development Goals to achieve Women dignity, health and reproductive rights. These attempts have achieved some (but not striking) permanent success. The main reason is that traditional societies whether living in developed or under developed countries, are more in tune to their religious values and their religious leaders inhibit strongly in hidden words against the use of contraceptive methods. Even in developed societies, the birth rate has recently increased. Figures from the Statistics and Research Agency[1] reveal that the number of children born to Northern Ireland mothers rose markedly between 2003-2004. In 2004 there were 22,318 births to Northern Ireland mothers, showing an increase of 3.1% on the 2003 figure. This is largest annual percentage increase since 1979. The stillbirth rate remains at 5 / 1000 but infant deaths reached 5.3 / 1000 because 6.7% of the mothers were in their teenage years.

The population in Northern Ireland has increased by five percent over the last decade, according to the census figures in 2002[2]. The figures also show that on 29th April 2001, there were more women than men living in Northern Ireland with 863,818 females to 821,449 males. Table I shows the expected population by the end of 2004[2].

With the advent of the latest theory of population, the issue seems easier. Kingsley Davis and Judith Blake were the first sociologists to recognise that socio-economic behaviour interacts with biological aspects of human reproduction. John Bongaarts and Robert C Potter[3] developed inhibiting factors of fertility and the mathematical relationship of fertility with the following four proximate determinants of fertility:

1) age of marriage
2) post-partum infundity (breast feeding)
3) contraception
4) abortion

Direct abortion in most of the societies is forbidden but it is allowed to either save the life of mother suffering from cancer or a likelihood of the child being born with significant handicap. There is a need to provide safe abortion services, where they are available; however, the first three measures entail direct relativism for making a significant dent on fertility and thereby reducing the high levels of maternal mortality. Implementation of a combined social and health agenda will help reduce maternal mortality rates. Breast feeding and use of contraception will be acceptable to the traditional / religious group who are still reluctant to use contraception. (In some orthodox Muslim societies contraception is prohibited but breast feeding is encouraged for 2 years; more education would clarify the actual reason for encouragement of breast feeding in Islam which apart from other reasons is contraception indeed!).

With a significant increase in MMR, it is time that doctors and sociologists work together to educate people about the grim outcomes of a high rate of population growth and ill-health of women throughout the world.

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Table 1 – Expected population in Northern Ireland – 2004

Age group summaries	Numbers			Percentages		
	Persons	Males	Females	***Persons***	*Males*	*Females*
All ages	**1,710,322**	**836,491**	**873,831**	***100.0***	***100.0***	***100.0***
All aged under 16	**383,344**	196,741	186,603	***22.4***	*23.5*	*21.4*
All aged under 18	**437,484**	224,514	212,970	***25.6***	*26.8*	*24.4*
All aged 16 & over	**1,326,978**	639,750	687,228	***77.6***	*76.5*	*78.6*
All aged 18 & over	**1,272,838**	611,977	660,861	***74.4***	*73.2*	*75.6*
All aged 16-29	330,107	167,124	162,983	***19.3***	*20.0*	*18.7*
All aged 30-44	**377,519**	185,126	192,393	***22.1***	*22.1*	*22.0*
All aged 45-59F / 64M	**344,105**	190,146	153,959	***20.1***	*22.7*	*17.6*
All aged 60F / 65M & over	**275,247**	97,354	177,893	***16.1***	*11.6*	*20.4*
All aged 16 to 59F / 64M	**1,051,731**	542,396	509,335	***61.5***	*64.8*	*58.3*
All aged 75 & over	**105,951**	38,880	67,071	***6.2***	*4.6*	*7.7*

The authors have no conflict of interest.

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Review

Chronic Myeloid Leukaemia in The 21st Century

Rachel Frazer, Alexandra E Irvine, Mary Frances McMullin.

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INTRODUCTION

What is Chronic Myeloid Leukaemia?

Chronic Myeloid Leukaemia (CML) is a clonal, myeloproliferative disease that develops when a single, pluripotential, haemopoetic stem cell acquires the Philadelphia chromosome. CML was the first haematological malignancy to be associated with a specific genetic lesion. First recognised in 1845, CML exhibits a consistent chromosomal abnormality in leukaemic cells, identified in 1960 by Nowell and Hungerford, termed the Philadelphia (Ph) chromosome[1]. The cytogenetic hallmark of CML was identified in 1973 as the reciprocal translocation t(9;22)(q34:11). Furthermore, in 1984, the *ABL* (Abelson) proto-oncogene was identified as being involved in this translocation. Breakthroughs in cancer biology have led to extensive characterisation of CML and it is now heralded as a 'model' of cancer[2].

The haemopoietic cell lines are transformed by the chimeric oncogene *BCR-ABL*. CML is an unusual malignancy in that a single oncogene product is central to its pathology[1]. CML is capable of expansion in both the myeloid or lymphoid lineages, and may involve myeloid, monocytic, erythroid, megakaryocytic, B-lymphoid and occasionally T-lymphocytic lineages, although expansion is predominantly in the granulocyte compartment of the myeloid lineages in the bone marrow[3].

Epidemiology of CML

The incidence of CML is approximately 1-2 per 100,000 population per year. Consistent with this, there are 10-12 new cases of CML in Northern Ireland each year. The median age of presentation is 45 to 55 years, accounting for 20% of leukaemia affecting adults. As with all leukaemias, males are affected more than females in CML, with a 2:1 ratio. CML is more common with Caucasian ethnicity[3].

Natural History and Clinical Course

The clinical course of the disease may be divided into three main sections[4], (Table I). Signs and symptoms at presentation may include fatigue, weight loss, abdominal fullness, bleeding, purpura, splenomegaly, leukocytosis, anaemia, and thrombocytosis[3]. In approximately 50% of cases it is an incidental finding.

The Ph chromosome is present in 95% of patients with classic CML. The impetus for Ph chromosome formation and the time span required for overt disease progression are unknown. It is proposed that CML, similar to many other neoplasms, may be the result of a multistep pathogenetic process. There is very little evidence to support any additional acquired molecular aberrations prior to t(9;22) translocation[6]. It is generally accepted that the Ph+ clone is susceptible to the acquisition of additional molecular changes that may underlie disease progression. The Ph chromosome is generally the only cytogenetic abnormality present in the chronic phase of disease. Approximately 85% of patients are diagnosed in chronic phase, and this stage of disease responds to therapy[4]. As the disease progresses through the accelerated phase and into the blast crisis, additional cytogenetic abnormalities become evident (see Table I)[7].

MOLECULAR PATHOLOGY

Classic CML is characterised by a reciprocal translocation between chromosomes 9 and 22. This results in juxtaposition of 3' sequences from the Abl-proto-oncogene on chromosome 9, with the 5' sequences of the truncated Bcr (breakpoint cluster region) on chromosome 22. Fusion mRNA molecules of different lengths, are produced and subsequently transcribed into chimeric protein products, with varying molecular weights, the most common being p210 $^{BCR\text{-}ABL}$ (Fig 1)[3].

The SH1 domain of ABL encodes a non-receptor tyrosine kinase. Protein kinases are enzymes that transfer phosphate groups from ATP to substrate proteins, thereby governing cellular processes such as growth and differentiation. Tight regulation of tyrosine kinase activity is essential, and if not maintained, deregulated kinase activity can lead to transformation and malignancy[1].

The portion of *ABL* responsible for governing regulation of the SH1 domain is lost during the reciprocal translocation. The addition of the *BCR* sequence constitutively activates the tyrosine kinase activity of the SH1 domain.

Its activity usurps the normal physiological functions of the ABL enzyme, as it interacts with a number of effector proteins[7]. Thus, the SH1 domain of *BCR-ABL* is the most crucial for oncogenic transformation.

Cellular Signalling

BCR-ABL has several substrates and impacts on key

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signalling pathways resulting in the CML phenotype[6]. The net result is deregulated cellular proliferation and development of growth factor independence, decreased adherence of the leukaemic cells to the bone marrow stroma, and a reduced apoptotic response to mutagenic stimuli (Figs 1 and 2)[1].

CONVENTIONAL CYTOGENETICS

Cytogenetics is the genetic analysis of cells and assesses the structural integrity of chromosomes. The Ph chromosome, discovered in 1960, was identified as the smaller of the two chromosomes derived from a reciprocal translocation involving chromosomes 9 and 22. This translocation can be found in more than 95% of CML patients at diagnosis. CML was the first disease in which the cytogenetic abnormality was defined on a molecular basis and such work pioneered the combination of molecular cloning and hybridization techniques to produce fluorescence in situ hybridization (FISH)[8,9]. FISH uses specific fluorescently tagged DNA probes to map the chromosomal location of genes and identify other genetic anomalies. This technique can be applied in all stages of the cell cycle (interphase cytogenetics). This assay is based on the ability of single stranded DNA to hybridize to complementary DNA. FISH can be performed with substrates such as blood, bone marrow, body fluids, tissue touch preparation and paraffin embedded fixed tissue[9].

FISH assays are relevant particularly at diagnosis and in relapse, when a large pool of affected cells are present. This is due to the inherent low levels of sensitivity with FISH; at best, sensitivities are within the range of 1 malignant cell in every 100 normal cells. Bone marrow and peripheral blood samples are used to diagnose CML by the presence of Ph chromosome. It is unacceptable to use FISH to detect minimal residual disease following therapy[8,9].

Polymerase chain reaction (PCR) analysis is used at CML diagnosis. PCR is used to detect the m-RNA that encodes for the chimeric BCR-ABL protein in bone marrow and peripheral blood samples. As PCR is more sensitive than FISH it can be used at diagnosis and in monitoring response to treatment[9,10].

MOLECULAR DIAGNOSTICS

Molecular techniques are used in the diagnosis and monitoring response to therapy. Response to treatment may be defined as occurring at haematologic, cytogenetic, or molecular levels[11,12]. This is illustrated in Figure 3.

Minimal Residual Disease

On current therapeutic regimens a complete cytogenetic response can be achieved for the majority of patients (Fig 3), but a small proportion of these will relapse. Relapse arises from a persistent malignant cellular population present at a low level, below the level of detection by standard techniques. This reservoir of neoplastic cells detected only by sensitive molecular methods is referred to as minimal residual disease (MRD)[12]. Methods for detecting MRD, should ideally have sensitivity within the 10^5 to 10^6 range, be applicable for almost all patients with the disease, provide information on the target, be inexpensive, rapid, readily standardized and

Table I Clinical course of untreated CML[3,5].

		Advanced Phase	
Parameters	**Chronic Phase**	**Accelerated Phase**	**Blast Crisis**
Median disease duration	3-5 years	6-9 months	3-6 months
White blood cell count	>50x10^9/L	-	-
Percentage blast cells	1-15%	>15%	>30%
Haemoglobin	normal / slightly low	Low	very low
Platelets	normal / high / low	high/ low	Low
Bone marrow	Myeloid Hyperplasia ---------->		
Cytogenetics	Ph+	Ph+	Ph+
		Secondary Genetic Changes additional Ph, isochrome 17q, trisomy 8 *loss of:* myc and p53	
Symptoms	fatigue bleeding, purpura abdominal fullness weight loss	unexplained fever Splenomegaly Hepatomegaly bone pain	severe anaemia, bleeding increased infections CNS disease lymphadenopathy

Disease Progression

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disease specific. Additionally, to utilise results effectively good interlaboratory reproducibility and standardisation of reporting is essential. Measuring patient response to imatinib may be achieved by conventional quantitative real-time PCR (RQ-PCR) or nested PCR. Analysis with RQ-PCR detects up to 1 in 10^4-10^5 cells and nested PCR 1 malignant cell in 10^6 normal cells[9,10]. MRD may be designated as values below 10^9 to 10^{10}. Clinical observation and experience implies a positive correlation between the improving levels of molecular response and better progression-free disease survival[12].

RQ-PCR is used to monitor for MRD in patients that have achieved a complete cytogenetic response. This procedure is more amenable to interlaboratory standardisation, and has been introduced as it facilitates rapid and sensitive detection of the fusion gene transcript showing comparable results when simultaneous analysis has been performed on blood and bone marrow specimens, allowing follow up of imatinib treated CML patients[9,13,14].

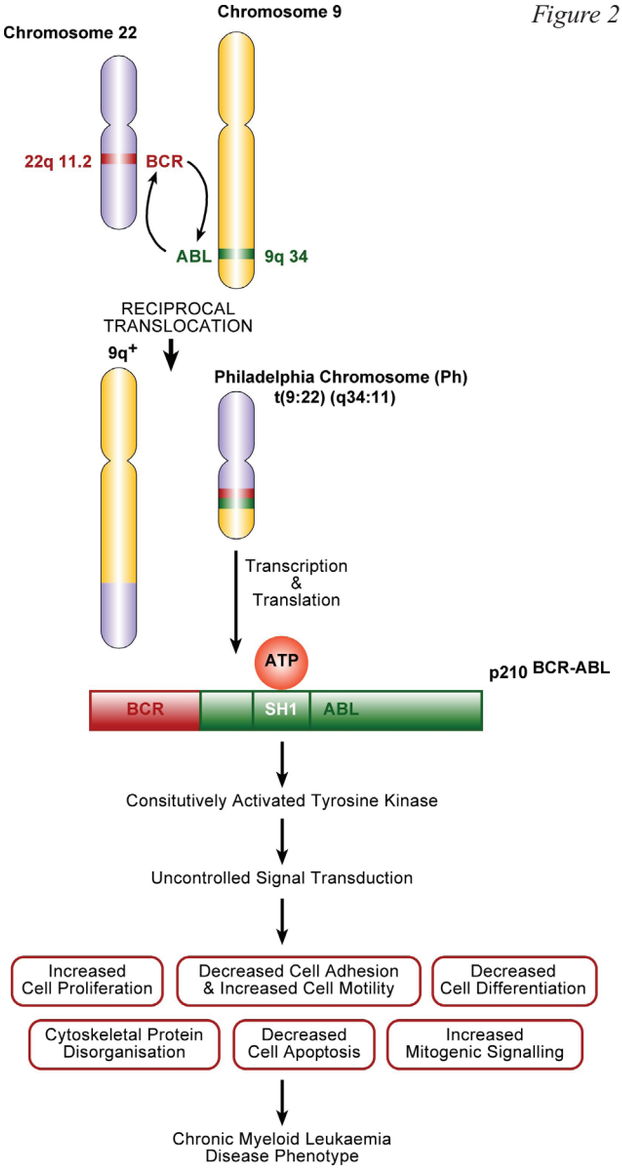

Figure 1 Molecular events leading to the expression of CML disease phenotype.

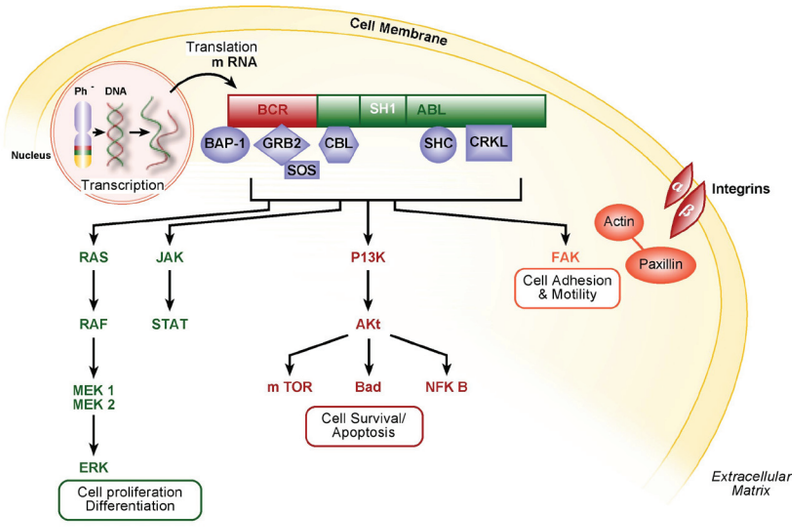

Figure 2 BCR-ABL signalling pathways.

European laboratories from 10 countries have collaborated to establish a standardized protocol for TaqMan-based RQ-PCR, in an effort to analyze the prominent leukaemia-associated fusion genes (including *BCR-ABL*) within the Europe Against Cancer (EAC) program. The EAC protocol has the potential to provide the basis for an international reference of MRD using RQ-PCR analysis of fusion gene transcripts[15]. The Department of Haematology at Queens University, Belfast, have been completing analysis of CML patient samples using these set protocols.

DISEASE MANAGEMENT

Allogenic Stem Cell Transplants

Allogenic stem cell transplant (allo-SCT) has been used since the 1970s in the treatment of CML[1] and is the only curative therapy for CML, however, it bears a significant mortality risk. Age, disease status, disease duration, recipient-donor gender combinations, degree of histocompatability between donor and recipient and the source of the transplant product have all been identified as significantly influencing long-term survival. Evidence in the pre imatinib era suggests that bone marrow transplant is best performed in the early phase of chronic CML[1,16]. Using blood or bone marrow derived stem cells from an HLA-identical sibling performed in the chronic phase of the disease offers a 60-80% probability of leukaemia-free survival at 5 years. If performed in the accelerated phase, disease survival decreases by half[17].

Conventionally, conditioning treatments are necessary prior to allo-SCT. This involves 'myeloablative' doses of chemoradiotherapy, aiming to facilitate engraftment of healthy donor stem cells via permanent elimination of malignant haematopoiesis. This is a rather arduous regimen

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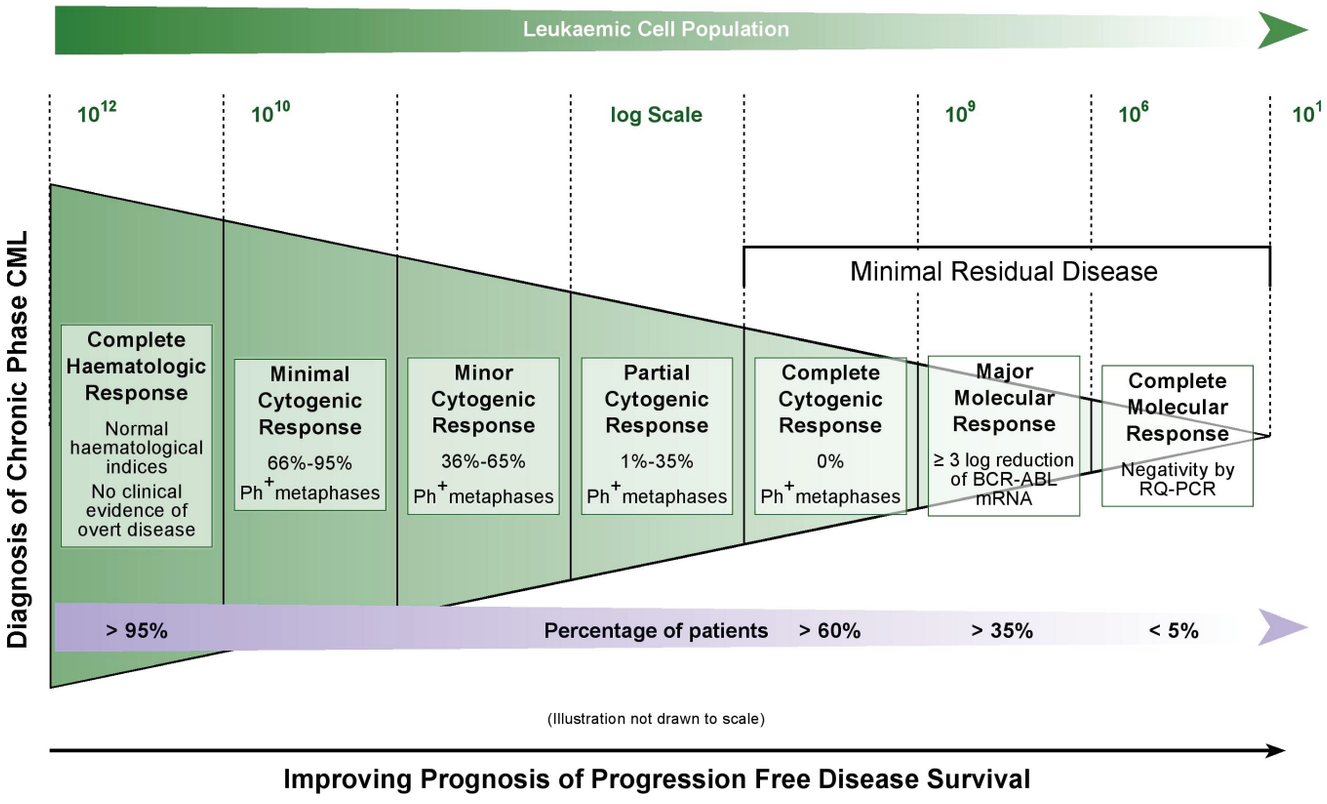

Figure 3 Defining response to treatment and minimal residual disease, for patients diagnosed with chronic phase CML, treated with imatinib.

associated with toxicity and mortality. It is therefore preferably administered to those aged less than 65 years without other co-morbid conditions. Success is generally attributed to an immunologically mediated graft-versus-leukaemia effect[7].

Bone marrow transplants have seen recent developments in research. Reduced intensity conditioning treatments (RICT) or non-myeloablative transplants have been proposed. This endeavours to produce graft-versus-leukaemia effects without exposing the patient to the potential toxicity of conditioning treatments. Here, reconstitution of the immune system and associated anti-leukaemia effect of the donor graft, compete against the growth of the malignancy. Preliminary data suggests that this approach may confer benefit, particularly in chronic phase CML[16].

Interferon Alpha

Interferon alpha (INFα), is a glycoprotein, of biological origin. It displays antiviral and antiproliferative properties. INFα was the first effective therapy for CML. The drug entered clinical trials in the early 1980s, and remained the treatment of choice for CML patients, until a shift in therapeutic strategy after the arrival of imatinib[18]. In CML INFα prolongs survival in patients, especially of those who are cytogenetic responders. It is able to induce a cytogenetic response in 35 to 55% of patients, with a longer survival achievable in combination with chemotherapy. With this therapy the level of disease decreased with time, but CML was rarely completely eliminated[16].

Imatinib Mesylate

The BCR-ABL protein is an ideal drug target for CML treatment. Unique to leukaemic cells, the BCR-ABL protein is expressed at high levels and its tyrosine kinase activity of the SH1 domain is essential for its ability to induce CML[7]. The SH1 domain responsible for oncogenic transformation is an extremely attractive target in combating CML.

The most successful synthetic ATP inhibitor designed was imatinib mesylate (STI 571, Gleevec (Glivec), Novartis, Switzerland), approved by the Food and Drug Administration in May 2001 in the United States, later licensed for use in the UK by the European Medicines Evaluation Agency (EMEA) in November 2001 for the treatment of CML[6,19]. The introduction of this drug has dramatically changed the management of CML[20]. It is currently considered as the 'gold standard' in treating CML, approved for the first line treatment of adult patients with Ph^+ CML at all disease stages[21,22].

Imatinib functions as a mimic of ATP, in the ATP binding pocket in the BCR-ABL SH1 domain (Fig 4). A further characteristic of imatinib is its striking degree of specificity for the ATP binding pocket, as its effect on other cellular tyrosine kinases is negligible[19,23].

In the treatment of chronic phase CML, imatinib produces a superior and sustainable response compared to INFα . The IRIS study (International Randomised Study of Interferon and STI571), a Phase III clinical trial, compared the use of imatinib and conventional drugs used in the treatment of patients with newly diagnosed CML. Conventional drugs included recombinant INFα, and low dose cytarabine having demonstrated superior rates of cytogenetic response and

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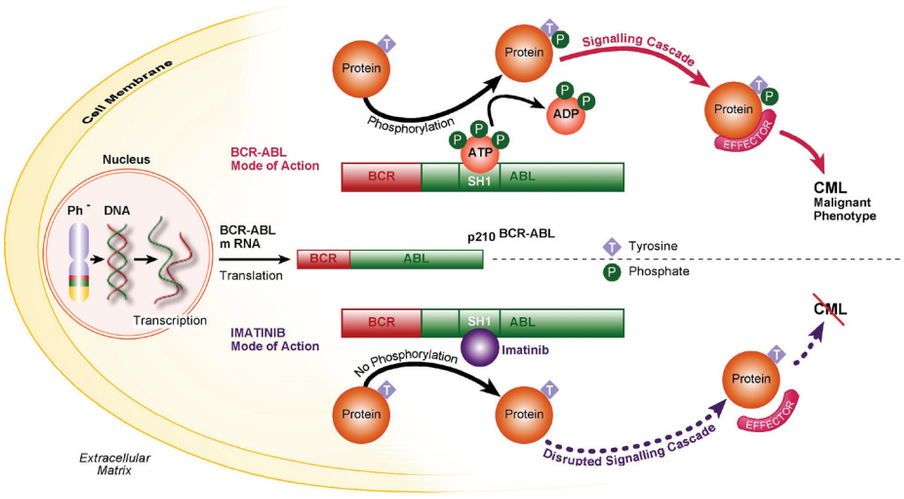

Fig 4 Comparing the mode of action of BCR-ABL and imatinib in CML pathogenesis.

survival than interferon monotherapy. The results of this trial concluded that the haematologic and cytogenetic responses in terms of tolerability and likelihood of progression to accelerated or blast phase CML, provided superior results with imatinib[24-26].

Imatinib has produced a sustained cytogenetic response in the majority of patients and it is clinically well tolerated. The advantages of imatinib therapy have lead to the revision of allo-SCT protocol, even in patients who may be good allo-SCT candidates. Clinicians are currently recommending that *all* newly diagnosed patients are treated with imatinib. Only upon failure to respond satisfactorily on imatinib will allo-SCT be considered in suitable candidates.

Imatinib Resistance

Despite its remarkable efficacy in treating CML, secondary resistance is emerging in a minority of patients. This involves the emergence of a resistant leukaemic clone after regular drug administration[27-29].

Primary or intrinsic resistance differs, and is relatively less common in its incidence. It may be defined by a lack of haematologic or cytogenetic response, treatment having had negligible effects since initiation. It is uncommon in chronic phase CML, as is secondary resistance. In accelerated phase of CML primary resistance is relatively common, whilst in accelerated or indeed blast phase it is the rule, as is acquired resistance[29-31].

Acquired resistance to imatinib therapy is caused most commonly by mutations in the BCR-ABL kinase domain, thus preventing imatinib binding sucessfully. A frequent mutation in this domain, conferring a particularly poor prognosis, is in the ATP phosphate binding loop (P-loop). This is a highly conserved domain involved in ATP binding[32]. Further mechanisms of secondary resistance involve over expression of *BCR-ABL*; acquired additional mutations, clonal evolution, that is the addition of novel chromosomal aberrations, and pharmacological mechanisms, resulting in a reduction in the quantity of available unbound imatinib, resulting in suboptimal levels of imatinib for effect[27,31].

Monitoring treatment response

The advent of imatinib therapy has added significantly to the cohort of patients in whom a complete cytogenetic response is achieved. It would therefore be logical to utilize molecular assays in monitoring treatment response. Indeed, molecular monitoring has become routine in CML management[33]. The aim of monitoring therapy is to identify sub-optimal responders to imatinib therapy and to consider alternative approaches to management in an effort to prolong progression-free disease survival[16].

Studies using RQ-PCR have shown that an early reduction of *BCR-ABL* gene transcript levels can predict a subsequent cytogenetic response in CML[26,34]. Once patients achieve MRD status (Fig 3), it is important to continue monitoring closely. The determination of the trend in the quantitative numbers of residual *BCR-ABL* positive cells is considered to provide important therapeutic information in the follow up of CML patients, providing key prognostic information allowing treatment optimization[15].

Branford, *et al.*[35], concluded from their research that a more than two fold rise in *BCR-ABL* levels by RQ-PCR identified 97% of patients with BCR-ABL domain kinase mutations. Therefore, monitoring levels of *BCR-ABL* could potentially serve as an early indicator or predictor of relapse and precipitant for reassessment of therapeutic management, identifying patients for whom imatinib may not be the best form of long term treatment[1,2].

Additionally, it has been documented that a few CML patients are beginning to exhibit clonal karyotypic abnormalities in Ph-negative cells whilst completing imatinib therapy. Emergence of such events strongly elude that there is a requirement for intermittent bone marrow cytogenetic analysis[9,36].

This prompts the question of how patients with CML should be monitored. Principle laboratory tests used in monitoring CML drug therapy are peripheral blood counts, cytogenetic analysis, RQ-PCR, and assessment of ABL kinase domain mutations. It is accepted that early treatment of disease relapse should translate into a greater response rate[2,9,37,38]. Use of such an approach will require multicentre standardisation of RQ-PCR and mutation analysis[2]. Provisional recommendations in this area have been made. These include proposals for implementing internationally standardised methodologies for measuring and recording *BCR-ABL* transcript levels in patients currently undergoing treatment using RQ-PCR; and reporting and detecting BCR-ABL kinase domain mutations[36].

Molecular mutations can be used to monitor treatment

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response and disease progression. To date haemopoietic stem cell transplantation is the only proven cure[16]. Of the third of CML patients in whom this therapy is both feasible and appropriate, a majority achieve the status of molecular remission. The remainder of patients may have residual but stable levels of *BCR-ABL* transcripts. If we are comparing non transplant therapy with allotransplant, the endpoint for each must also be directly comparable, thus molecular remissions must be the goal. This further emphasises the necessity for standardisation of methodology and reporting in monitoring CML treatment response[33].

Allo-immunity may be a factor in preventing disease relapse in allo-SCT. Imatinib confers no such benefit in its subjects treated to MRD or molecular response, and so cannot guarantee that it can maintain patients in this state indefinitely. However with the excellent response of newly diagnosed patients to imatinib, there has been a reluctance to consider allo-SCT treatment[7]. It is therefore essential that emerging resistance is recognised early, permitting timely consideration of transplant options if appropriate, before overt progression of CML[30,35,38,39]. It would therefore be prudent to set conservative targets for therapeutic achievements to facilitate prompt reassessment of suboptimal therapy. A modest strategy has been proposed, suggesting; complete haematologic response at 3 months, minor cytogenetic response at 6 months, major cytogenetic response at 12 months, and a complete cytogenetic response at 18 months[11]. Failure to meet these criteria would warrant a subsequent re-assessment of disease management.

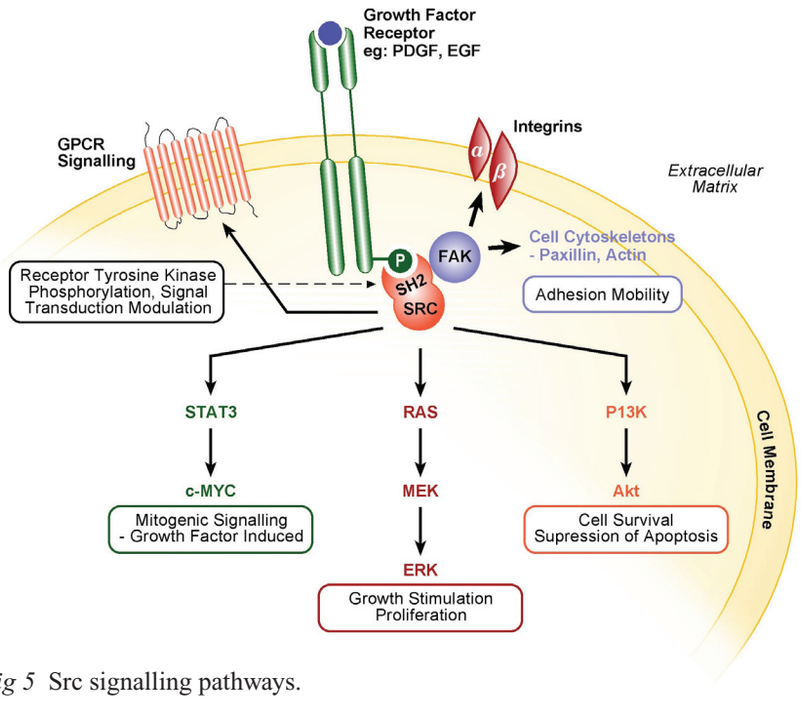

Fig 5 Src signalling pathways.

The Src protein has three functioning molecular domains. SH2 (SRC homology 2) and SH3 are involved in protein-protein interactions. The third, SH1 is a kinase catalytic domain. Src can transfer from inactive to active state through control of its phosphorylation state, or via protein-protein interactions. FAK (focal adhesion kinase) and PDGF (platelet derived growth factor) are capable of rendering Src active by binding to its SH2 domain[50].

GPCR: G-protein coupled receptorsEGF: epidermal growth factor

Strategies to Overcome Imatinib Resistance

Imatinib resistance has been postulated to develop more rapidly and uniformly than other examples of cytotoxic drugs because of its high specificity for its target[20]. Several strategies have been proposed to overcome imatinib resistance.

Firstly, early treatment with imatinib upon diagnosis is considered crucial. Patients who are treated with imatinib within four years of initial diagnosis of CML, have a better prognosis and a significantly lower incidence of mutations than those treated outside the four year time frame. In addition to prompt administration of imatinib an adequate dose is necessary. The lowest approved dose is 400mg daily in chronic phase CML, in advanced stage 600mg daily[14]. A second strategy is imatinib dose escalation[31,40].

Thirdly, combination therapy may be considered. Despite the excellent results achievable with imatinib, only 5-10% of such patients achieve a molecular remission, that is, undetected *BCR-ABL* transcripts. There is therefore a rationale for combining therapies effective against CML to try and improve the efficacy of therapy. Conceivably, resistance to imatinib may be caused by more than one mechanism in each cell[41,42].

By targeting CML cells with combination therapies cross resistance would presumably be prevented and therapeutic performance improved as disease would be tackled by a number of different means.

The two best non transplant therapies approved for use in CML are INFα and imatinib. It would be reasonable to combine both agents to assess if response rates could be improved. One such study that considered the merits of combining imatinib with pegylated interferon was the PISCES trial (PEGIntron and Imatinib Combination Evaluation Study). In this Phase I/II study preliminary results showed that this dual therapy had improved activity over imatinib alone and was clinically well tolerated. Unfortunately, myelosupression was common. Further data would be necessary to confirm these findings, requiring a large, prospective, randomised study[7].

The SPIRIT trial (STI571 Prospective International Randomised Trial) is currently underway. This Phase III study will compare the administration of imatinib at escalated doses of 400 mg/day, 800mg/day and imatinib at 400mg/day with interferon and low dose cytarabine, involving patients who have chronic phase CML, having been diagnosed within a three month time span[7].

Second generation ABL kinase inhibitors

Imatinib has had unprecedented success in the treatment of CML. Despite its capability to achieve clinical remission, disease has progressed in a small minority. Progression made

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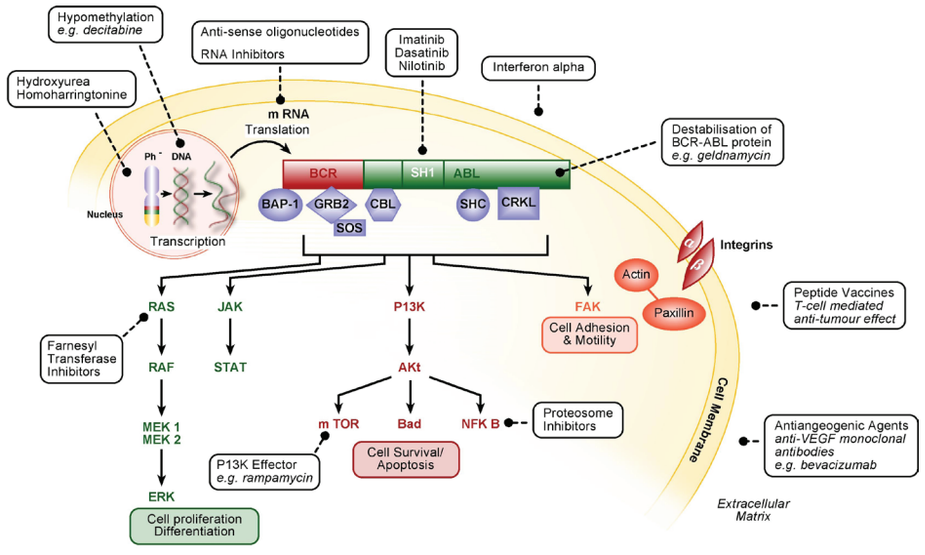

Figure 6 Targets for CML therapy.

in IRIS is very slow and it is no longer a randomised control study. Few patients remain on the control arm of the study; IRIS follow-up may now be considered a long term imatinib follow-up study. Relapsing patients require alternative therapies, and with time the net number of such patients will increase. Whilst imatinib has proven efficacious, alternatives are now required in some patients. Figure 3 demonstrates a minority of patients will achieve a molecular response with imatinib. The remaining majority of patients still have an existing pool of approximately 10^6-10^7 leukaemic cells, from which relapse is a possibility, even in controlled disease[43,44].

Imatinib is now the keystone of disease management, and a model upon which future drug development is based, largely due to the contribution that structural biology has made in understanding imatinib resistance. This has aided the design of new kinase-inhibitors[43], leading to two alternative types of compound.

Nilotinib (AMN107)

Strategy one involved the modification of imatinib structure. Nilotinib (developed by Novartis) is similar to its cousin imatinib as they both bind to an inactive conformation of the ABL kinase domain and function as an ATP inhibitor. There are a number of ways in which they differ. Nilotinib is capable of binding more tightly to BCR-ABL protein to enhance drug efficacy and sensitivity. Most BCR-ABL mutants are 20-fold more sensitive to nilotinib[43-45]. The exception to this rule is the mutant T315I[46,47].Furthermore, with its superior topographical fit to the ABL protein, nilotinib proves to be more potent than imatinib.

A Phase I clinical trial with nilotinib demonstrated rates of complete haematologic response in imatinib resistant patients to be 92% in chronic phase, 75% in accelerated phase, 39% in blast phase. Cytogenetic responses were 35%, 55% and 27%, respectively[48]. Phase II studies are ongoing. With success in refractory CML recognised, further study should be focussed to evaluate if nilotinib has therapeutic potential at all stages of disease[49].

Dasatinib (BMS-354825)

Strategy two involved preparing a compound with a completely different chemical structure to imatinib. This was based upon a drug originally synthesised as a primary Src family inhibitor. Dasatinib (developed by Bristol-Myers Squibb) was observed to inhibit wild type BCR-ABL and most resistant imatinib mutations[43].

Src is a non-receptor tyrosine kinase that has a plethora of roles in cell signalling including cellular adhesion, motility and growth. Many substrates that Src is capable of phosphorylating with its kinase domain form part of intracellular signalling cascades (Fig 5)[50,51]. The deregulated activity of Src has already been recognised in neoplastic cells, such as colon and breast cancer. Due to such properties and activity, Src has been considered as a target in drug development, alongside other protein kinases[50].

Dasatinib is therefore a dual Src/*ABL* kinase inhibitor. It differs from imatinib in a number of ways. Unlike imatinib, dasatinib is capable of binding to both the inactive and active forms of *BCR-ABL*. Thus, dasatinib can bind to a more structurally conserved area between *ABL* and Src kinase than is present in the inactive conformation[52]. It is also more flexible in binding to differing conformations of *BCR-ABL* and is able to recognise multiple states of *BCR-ABL*. This confers enhanced binding affinity due largely to dasatinib's less rigid conformational demands on the kinase structure[53]. Although dasatinib is the most potent *ABL* kinase inhibitor to date, it is not the most specific, its target profile expanding to include other Src family members[54].

Phase I clinical trials have demonstrated that, similar to its colleague nilotinib, dasatinib too is incapable of overcoming T315I mutations. Dasatinib demonstrated complete cytogenetic responses in chronic phase, accelerated and blast phase CML of 92%, 45%, 35%; with major cytogenetic response of 45%, 27% and 35%, respectively. Clinical activity was also noted in patients who received poor or no cytogenetic benefit from imatinib. This may have implications for patients who have received a suboptimal response from imatinib although not displaying frank resistance[55,56].

NOVEL THERAPIES

Hommoharringtonine

Hommoharringtonine (HHT) is a novel plant alkaloid derived from a Chinese evergreen tree. An anticancer agent, it has recognised activity in acute myeloid leukaemia (AML), having been incorporated into the treatment regimen for AML and CML[57,58]. HHT is thought to conduct its anti-leukaemia effect through the inhibition of protein synthesis. HHT displays pronounced activity upon CML, in the past it has been used as salvage therapy in patients who became refractory to

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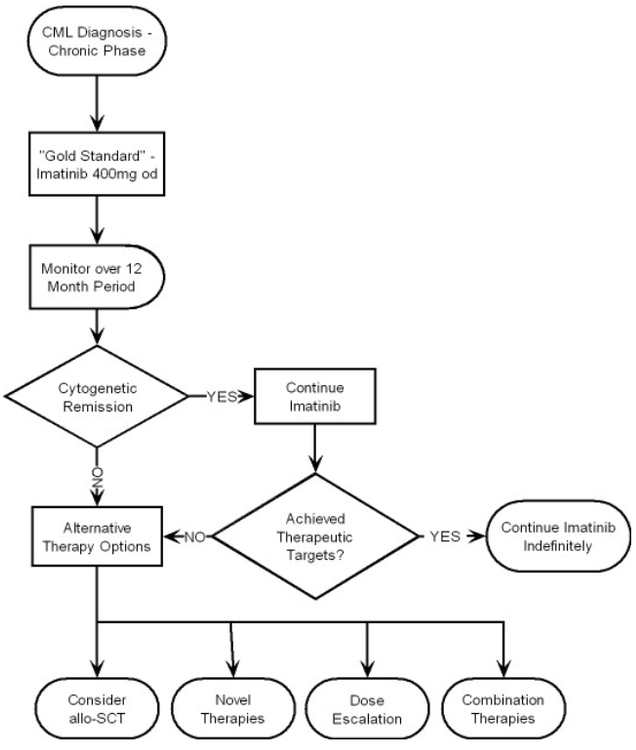

Figure 7 CML therapeutic algorithm.

INFα[59]. Studies have investigated the consequences of HHT in combination with INFα or low dose cytarabine. When in dual therapy or in triple combination therapy, complete haematologic and complete cytogenetic responses equivalent to or superior to HHT single therapy have been shown, suggesting improved survival rates compared to HHT alone[58-60]. Shortly after such studies imatinib was introduced. *In vitro* HHT functions synergistically with imatinib, to decrease BCR-ABL protein expression. Research has shown imatinib and HHT to display synergistic cytotoxicity throughout different stages of disease progression. In chronic phase the duo demonstrated properties of dose dependant apoptosis and growth inhibition[7,16]. Additional examination of the potential therapeutic effects of HHT as a single therapy or as dual regimen with imatinib is warranted.

Arsenic Trioxide

Arsenic trioxide (As_2O_3), an older therapy for CML, has been re-investigated. With the evolution of safer forms of arsenicals and efficacy of As_2O_3 in acute promyelocytic leukaemia recently identified, interest of its potential use in CML was rekindled[59]. It is not certain how As_2O_3 exerts its anti-CML effects. Its ability to promote apoptosis has been suggested[61]. Studies have shown dose dependant growth inhibition and a pro-apoptotic effect when CML cells were treated with clinically tolerable levels of As_2O_3. A significant decline in BCR-ABL protein levels was also noted, and did not coincide with reduction in any other cellular proteins, suggesting specificity of this treatment. CML cell lines studies with As_2O_3 and imatinib have described a synergistic relationship between the two drugs, providing growth reduction and induction of apoptosis[59,62].

Other Novel therapies

Proteasome inhibition has been a further area of interest in CML therapy. The ubiquitin-proteasome pathway is responsible for the degradation of cellular proteins. Proteasome have a dual role of maintenance (disposal of damaged proteins) and regulation (degradation of proteins involved in cell cycle regulation and neoplastic growth) within the cell. Due particularly to its latter property, proteasome inhibitors are being investigated as a new cancer therapy[59]. The inactivation of NF-κB is pertinent to its action. Although the mechanism has not been established by which decreased expression of BCR-ABL protein is mediated when CML cells are treated with proteasome inhibitors; caspase activation and apoptosis were recognised. The proteasome inhibitor PS-341 has shown significant effect upon growth inhibition and apoptosis of several cell lines. These have included both imatinib resistant and sensitive *BCR-ABL* positive cell lines[7]. Again, clinical studies in imatinib resistant patients are ongoing in this field[59].

Further examples of a therapeutic target in CML are farnesyl transferase inhibitors. They predominantly mediate post translational modification to activate Ras G-protein. The Ras pathway is a well characterised downstream signalling cascade attributed to the tyrosine kinase activity of BCR-ABL. Thus, inhibiting Ras via farnesyl transferase inhibitors would potentially prevent expression of CML phenotype[7]. Presently, three such compounds present themselves as anti-leukaemic candidates. The most studied is SCH6636. When combined with imatinib SCH6636 is capable of suppressing the growth of CML progenitor cells in vitro, including imatinib resistant cells, with the possibility that it is capable of sensitizing imatinib resistant cells to imatinib-induced apoptosis[59].

Other novel agents have been illustrated on Fig 6. They include antiangiogenic agents; peptide vaccines; TNF (tumour necrosis factor) related induction of apoptosis; DNA hypomethylation; antisense oligonucleotides and RNA inhibitors; P13K effectors; destabilisation of BCR-ABL protein[7,59]. Many of the agents listed are in preclinical development.

CONCLUSION

Imatinib is the first line agent for treatment of CML. We have examined the aims of imatinib therapy in terms of monitoring and defining disease response to treatment. Fig 7 is a suggested therapeutic algorithm for management of CML upon consideration and appraisal of the current literature. It is not however an ideal, as CML management strategies must be directed by an objective approach due to disease heterogeneity, where various subpopulations of patients may differ in their response to therapeutic regimens.

Imatinib saw the dawn of a new era for CML management. Its success demonstrated the power and efficacy of genomic medicine and set precedents for future therapy. However, emergence of resistance remains a problem. Novel therapies appear at an impressive pace, promising to strengthen the therapeutic regimen for CML. The management of CML in the 21st century is exciting and challenging, as it seems that cure of CML is a possibility, but still just out of reach.

Conflict of interest: none declared

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Paper

Percutaneous Coronary Intervention in the Elderly

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ABSTRACT

Objective: To determine the clinical risks and procedural outcomes for elderly patients undergoing percutaneous coronary intervention (PCI).

Method: A retrospective case-load analysis was performed of all patients over the age of 80 years, undergoing PCI, over a two-year period, in a tertiary referral hospital. Patient demographics, procedural details and in-hospital complications were obtained by reviewing patient notes. Twelve-month outcomes were obtained from telephone follow-up to the general practitioners and all surviving patients.

Results: There were 55 procedures. Procedural risk was high, with a median TIMI risk score of four (IQR 3-6) and a median additive EuroSCORE of nine (IQR 8-10). There was a 95% angiographic success rate. There were no in-hospital complications. Median Canadian Cardiovascular Society angina class fell from four (IQR 3-4) to one (IQR 0-1). At one year there were twelve deaths (10 cardiovascular), eight of these occurred in patients who had incomplete revascularisation.

Conclusion: PCI can be performed in an elderly, high-risk population with a low in-hospital mortality and marked symptomatic benefit. However, there is a significant 1-year mortality, particularly in patients who are only suitable for partial revascularisation.

INTRODUCTION

The benefit of coronary revascularisation in the elderly has not been clearly demonstrated. Most randomised trials, showing a benefit from coronary revascularization, have recruited patients under the age of 75.[1] However, it has been clearly demonstrated that procedure-related complications increase with age for both coronary artery bypass grafting (CABG)[2-4] and percutaneous coronary intervention (PCI).[5,6] Furthermore, co-morbid factors have a greater contribution to late outcomes in an elderly population. Consequently a retrospective case-load analysis of patients over the age of 80 years, undergoing PCI in our institution, was performed to assess procedural risks and clinical outcomes.

METHODS

A hospital database search revealed all patients over the age of 80 years, who had undergone PCI in our institution over a two-year period, from January 2003 to December 2004. All charts were reviewed for demographic and procedural data.

Procedures were classified using the British Cardiovascular Intervention Society categories of stable angina, primary angioplasty and unstable coronary syndromes (including unstable angina, non-ST elevation myocardial infarction and post-ST elevation myocardial infarction). Patient and procedural risk was calculated for each case using the TIMI risk score[7] and the EuroSCORE.[8,9]

Where patients had been discussed with a cardiac surgeon the outcome of that surgical referral was recorded. The coronary anatomy, left ventricular function and the completeness of the revascularisation procedure was documented.

Follow-up was by telephone to all general practitioners to establish the incidence of the major adverse cardiovascular events – death, myocardial infarction, coronary revascularisation and stroke. All surviving patients were also contacted by telephone to confirm the incidence of adverse events and establish angina symptom status. Angina status was recorded using the Canadian Cardiovascular Society classification. Data was available for hospital discharge and complete to 1 year.

RESULTS

A total of 55 angioplasty procedures were performed in 53 patients. There were 25 males (47%) with a median age of 81 (range 80-91) years, 11 patients (21%) were diabetic (Table I).

The clinical presentation was stable angina in 22 patients (40%), an acute coronary syndrome in 32 patients (58%) and acute myocardial infarction in one patient (2%). The median TIMI risk score was 4 (IQR 3-6) the median additive EuroSCORE was 9 (IQR 8-10), and the median logistic EuroSCORE (which is more predictive of surgical mortality

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Table I. Patient demographics including - risk factors, past medical history, clinical presentation, renal function, angiographic findings and calculated risk scores.

Characteristic	No. of patients
Age (years)	81 (81-82)
Male	25 (47)
Diabetic	11 (21)
History	
Prior PCI	10 (19)
Prior CABG	8 (15)
Clinical Presentation	
Stable Angina	22 (40)
Acute Coronary Syndrome	32 (58)
Primary Angioplasty	1 (2)
Glomerular Filtration Rate (ml/min)	41 (31-53)
LVEF	
>50%	30 (55)
40-49%	13 (24)
30-39%	9 (16)
<30%	3 (5)
Angiographic findings of diseased vessels	
1	15 (27)
2	15 (27)
>=3	25 (45)
LMS	3 (5)
TIMI Risk Score	4 (3-6)
EuroSCORE	
Additive	9 (8-10)
Logistic	12 (8-21)

Data are expressed as number (%) or median (inter-quartile range)

PCI; Percutaneous Coronary Intervention. CABG; Coronary Artery Bypass Graft.

LVEF; Left Ventricular Ejection Fraction. LMS; Left Main Stem.

TIMI; Thrombolysis in Myocardial Infarction.

in high-risk patients)[9] was 12 (IQR 8-21). Renal function, calculated by the Cockroft-Gault formula,[10] was significantly impaired with a median glomerular filtration rate (GFR) of 41mls/min (IQR 31-53). Only 7 of the 53 patients had a GFR ≥60mls/min.

Twenty-five patients (45%) had triple vessel disease and 15 patients (27%) each had single or double vessel disease. Eleven patients (21%) had moderate or severely impaired left ventricular function. Eleven patients (21%) were referred for CABG and seven were deemed unsuitable for surgical revascularisation. Four patients were accepted for surgery but underwent PCI because of patient preference (two patients) or because of clinical instability (two patients). During the same two-year period only 19 patients over the age of 80 underwent isolated CABG in our institution.

Table II. Procedural characteristics including vessels treated, equipment used and angiographic success.

Characteristic	No (%)
No of Vessels Treated	
1	42 (76)
2	13 (24)
Incomplete revascularisation	35 (64)
Vessel Treated	
LAD	23 (34)
LCx	22 (33)
Intermediate	2 (3)
RCA	13 (19)
SVG	4 (6)
IMA	1 (2)
Bifurcation branch	2 (3)
Stents	
Median Number per case	2 (1-3)
Stent Diameter (mm)	3.0 (2.75-3.5)
Stent Length (mm)	25 (18-36)
Drug Eluting stent	39 (41)
2b3a Inhibitor use	26 (47)
Intra-aortic balloon pump	1 (2)
Angiographic Success	52 (95)

Data are expressed as number (%) or median (inter-quartile range)

LAD; Left Anterior Descending. LCx; Left Circumflex.

RCA; Right Coronary Artery. SVG; Saphenous Vein Graft.

IMA; Internal Mammary Artery.

The majority of patients had single vessel PCI (42, 76%), but 13 patients had multi-vessel PCI (24%). In the 55 procedures 96 coronary stents were deployed (41% were drug-eluting) and the median total stent length per patient was 25 (IQR 18-36)mm. The angiographic success rate in treated vessels was 95%. Thirty-five patients (64%) underwent ischaemia-driven target vessel (i.e. incomplete) revascularisation; the remainder had complete revascularisation (Table II).

No acute complications occurred as a result of the procedures and all patients survived to hospital discharge (Table III). Total follow-up was 943 patient months. There were 12 deaths (10 cardiovascular) in the first year, giving a 78% 1-year survival. Of the 10 deaths 8 had presented with an acute coronary syndrome and 8 had undergone partial revascularisation. No patient experienced a stroke but there was one non-fatal MI and there were three target vessel revascularisations. The median Canadian Cardiovascular Society angina class fell from 4 (IQR 3-4) pre-procedure to 1 (IQR 0-1) in surviving patients (p=0.003).

DISCUSSION

The early randomised trials demonstrating a clinical benefit

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Table III. In hospital and 12 month outcomes

Complication	No (%)
In Hospital	
Death	0
Q Wave Myocardial Infarction	0
Urgent Target Vessel Revascularisation	0
CVA	0
12 Month	
Death	12 (22)
Non-fatal Myocardial Infarction	1 (2)
Target vessel revascularisation	3 (5)
CVA	0

CVA; Cerebrovascular Accident.

from coronary revascularisation specifically excluded elderly patients.[1] However, it has been well documented that elderly patients undergoing CABG have increased peri-operative morbidity and mortality rates.[2-4] Similarly, elderly patients undergoing PCI have increased procedural complications and death.[5,6] There have been two recent publications looking specifically at clinical outcomes in the elderly population undergoing coronary revascularisation. In the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database, the outcomes of 983 patients over the age of 80 years, who had undergone coronary angiography were reviewed.[11] Of these 983 patients, 289 underwent PCI, 133 received CABG and 561 were treated medically. They were compared with patients aged 70-79 and those aged less than 70. The database demonstrated that, for all age groups, there was a relative risk reduction in mortality for revascularisation compared with medical therapy. Furthermore, this benefit was greatest in the over 80s. However, the authors recognised that this was a non-randomised trial and open to the obvious bias that surgeons and interventional cardiologists are more likely to operate on a healthy elderly patient than one with multiple co-morbidities. In the Trial of Invasive versus Medical therapy in the Elderly (TIME) trial, 282 patients aged >75 years were randomised to maximal medical therapy or coronary angiography and revascularisation where feasible.[12] After 1 year there was no difference with regard to symptoms, quality of life, and the risk of death or non-fatal myocardial infarction between the two groups. However, by the end of the year some 46% of the medical management patients had undergone coronary revascularisation.

Our study involved a very high-risk population. The median age was 81 years, 60% had an acute myocardial infarction or acute coronary syndrome, 50% had left main stem of three-vessel coronary disease and 21% had moderate or severely impaired left ventricular function. The TIMI risk score is a strong independent predictor of outcomes in patients with unstable coronary syndromes.[7] The median TIMI risk score in our population was 4. In one large study, a TIMI risk score of 4 predicted a 20% risk of death, myocardial infarction or urgent coronary revascularisation within 14 days of presentation.[7] The EuroSCORE is used by surgeons to predict mortality for patients undergoing cardiac surgery.[8] The logistic EuroSCORE is a better reflection of predicted mortality in a high risk population.[9] In this study population the median additive EuroSCORE was 9 and the median logistic EuroSCORE was 12. For comparison, the median additive EuroSCORE for a sample of patients accepted for cardiac surgery in 2002 in a neighbouring hospital was 3 and for those turned down by the cardiac surgeons was 5.[13] Eleven of our patients were discussed with the cardiac surgeons and seven were declined surgery on the basis of operative risk. In this study the median GFR of 41ml/min was also a strong indicator of increased clinical risk. In a recent study of patients undergoing CABG, a GFR <60ml/min was shown to be a strong independent risk factor for 30 day mortality.[14] In addition to these markers of a high risk population, the complexity of our procedures is reflected in the interventional equipment required. In particular the median stent length per patient was 25 (IQR 18-36) mm, indicating very extensive disease.

Despite this very high-risk population, there were no in-hospital deaths or clinically significant complications. This contrasts with a large US database of octogenarians undergoing PCI, where the rates of in-hospital mortality, Q wave myocardial infarction and CVA were 3.8%, 1.9% and 0.6% respectively.[6] In our study population there was also a substantial improvement in symptom status, with the median Canadian Cardiovascular Society angina class falling from 4 (IQR 3-4) to 1 (IQR 0-1). However, in our study there was a significant 1-year major adverse cardiac event rate. There were 12 deaths and 10 of these were cardiovascular. Of the 10 deaths 8 had undergone partial revascularisation. The 1 year mortality rate of 23% and combined death or non-fatal myocardial infarction rate of 25% were both greater than those seen in the TIME study where rates were 11% and 17% respectively.[12] However, patients in the TIME study had stable ischaemic heart disease, only being randomised to invasive or conservative strategies if they had survived 6 months after enrolment.

CONCLUSIONS

Percutaneous coronary intervention can be performed in an elderly high-risk population. It is associated with a high angiographic success rate, a low in-hospital mortality and substantial symptomatic benefit. However, there is a significant 1-year mortality, particularly in patients who are only suitable for partial revascularisation, and they should have aggressive secondary preventative therapy.

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The authors have no conflict of interest

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Correction:

We apologise for the printer's error in some editions of the September edition of journal in the Interview by Claire Lundy on page 231. The final word 'skills' was omitted and the final sentence should have read:

'I would recommend being a portfolio GP: it allows choice and variety in your working life and delivers opportunities to develop new skills'.

This was corrected on the website version in early September and the corrected article can be accessed free of charge at www.ums.ac.uk

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Correction:

We apologise for the printer's error in some editions of the September edition of journal in the Interview by Claire Lundy on page 231. The final word 'skills' was omitted and the final sentence should have read:

'I would recommend being a portfolio GP: it allows choice and variety in your working life and delivers opportunities to develop new skills'.

This was corrected on the website version in early September and the corrected article can be accessed free of charge at www.ums.ac.uk

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Paper

The use of contrast-enhanced ultrasound in the characterisation of focal liver lesions

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ABSTRACT

Purpose: To determine the potential application of contrast-enhanced ultrasound in the characterisation of focal liver lesions encountered in radiological practice at a district general hospital.

Materials & Methods: Retrospective analysis of 68 sequential patients undergoing contrast-enhanced ultrasound (CEUS) of liver. All patients were referred for CEUS following identification of 1 or more focal liver lesions on conventional ultrasound or CT imaging. After baseline US examination (Acuson), a bolus of 1.0-2.4 ml of SonoVue (Bracco, UK) was administered intravenously. CEUS images were obtained during arterial, portal venous and delayed phases. Patients were followed up for a mean period of 6 months. The CEUS diagnosis was compared to that indicated by other imaging modalities, histopathology, and clinical follow up.

Results: CEUS correctly identified malignant liver lesions in 19 patients, with the final diagnosis confirmed by histopathology in 5 cases and clinico-radiological follow up in 14 cases. 47 patients were correctly identified with benign liver lesions on CEUS imaging, with all these cases confirmed on clinico-radiological follow up. In the detection of malignancy, the sensitivity was 95.0% and the specificity was 97.9%

Conclusions: In our experience to date, contrast-enhanced ultrasound imaging is highly accurate in characterising malignant and benign focal liver lesions. It therefore has significant potential for utilisation in most general radiology departments.

INTRODUCTION

The effective non-invasive detection and characterisation of focal liver lesions (FLL) can significantly alter patient management[1,4]. Early detection of primary or secondary liver malignancies increases the possibility of curative surgical resection or successful percutaneous ablation. It is becoming increasingly evident that contrast-enhanced ultrasonography (CEUS) using non-destructive low-acoustic-power ultrasound scanning with second generation contrast agents, such as perfluorocarbon or sulphur hexafluoride-filled microbubbles, allows improved characterisation of solid focal liver lesions[5]. CEUS has high sensitivity in the detection and characterisation of hyper- and hypovascular liver malignancies with an accuracy comparable, and in some cases superior to, helical CT[1]. CEUS may also enable definitive diagnosis of haemangiomas and focal nodular hyperplasia (FNH)[3].

The aim of this study was to determine the potential application of contrast-enhanced ultrasound in the characterisation of focal liver lesions encountered in radiological practice at a district general hospital.

METHODS

This study retrospectively reviewed the radiological yield and clinical outcome of 68 sequential patients who underwent CEUS of the liver in Antrim Hospital, a district general hospital in Northern Ireland. The patients were found to have one or more FLLs on conventional ultrasound or contrast-enhanced spiral CT before being referred for CEUS. Information was collated by review of ultrasound examinations, case-notes, and CT and/or MRI investigations. After baseline ultrasound (Acuson, Mountain View, USA), continuous ultrasound images were obtained with the "Coherent Contrast Imaging" setting after the administration of a bolus intravenous injection of 1-2.4 ml of SonoVue (Bracco, UK), followed by a 5 ml saline flush. Images were obtained during arterial (15 – 25 seconds following injection), portal venous (45 – 90 seconds), and "late" (180 seconds onward) phases.

Patients were followed up for a mean period of 6.3 months, using case-notes and further Ultrasound, CT and/or MRI scans as evidence of disease progression or diagnosis confirmation. Comparison was made between the working diagnosis as indicated by clinical follow-up and further imaging, and the original CEUS diagnosis.

RESULTS

Of the 68 patients, 41 were female and 27 male. Ages ranged between 17 and 83 years, with a mean age of 56.5 years. CEUS

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Key Words: Ultrasound, Liver, Contrast

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correctly identified malignant liver lesions in 19 patients, with the final diagnosis confirmed by histopathology in 5 cases and clinico-radiological follow up in 14 cases. One patient with a metastatic liver deposit confirmed on clinico-radiological follow up was incorrectly diagnosed by CEUS as a benign lesion (haemangioma). 47 patients were correctly identified with benign liver lesions on CEUS imaging, with all these cases confirmed on clinico-radiological follow up. One patient with a haemangioma confirmed on clinico-radiological follow up was incorrectly diagnosed as having a metastasis on CEUS. The different diagnoses encountered are listed in tables I (benign) and II (malignant). In the 68 cases where focal liver lesions were characterised, CEUS demonstrated a sensitivity of 95.0% and a specificity of 97.9% in the detection of malignancy. The positive predictive value was 95.0%, and the negative predictive value was 97.9%.

There were 16 cases of metastases, most of which appeared as hypoechoic nodules in contrast to the enhanced background of normal liver parenchyma (fig 1). One case of metastasis demonstrated diffuse enhancement in the arterial phase, suggesting that it was hypervascular, and showed subsequent rapid wash-out of contrast, the lesion becoming hypoechoic to the surrounding liver in the late phase (fig 2). CEUS identified one patient as having metastatic disease, when CT and biopsy confirmed the diagnosis was hepatocellular carcinoma with metastatic liver disease. In the one case of metastasis misdiagnosed as haemangioma, there was a hypoechoic mass which appeared to gradually fill-in during the late phase.

Of the two hepatocellular carcinomas, one demonstrated peripheral enhancement during the arterial phase, followed by isoechoic enhancement with the liver during the portal venous phase, and finally became hypoechoic in the late phase. The other demonstrated isoechoic enhancement with the remainder of the liver in the arterial and portal venous phases, and became hypoechoic during the late phase. The lymphomatous deposit, demonstrated in one patient in whom there was a previous history of lymphoma, remained hypoechoic throughout all phases of CEUS. In the final patient with malignancy, a histologically-proven cholangiocarcinoma was erroneously reported as a metastatic deposit, demonstrating hypoechogenicity throughout all phases of CEUS.

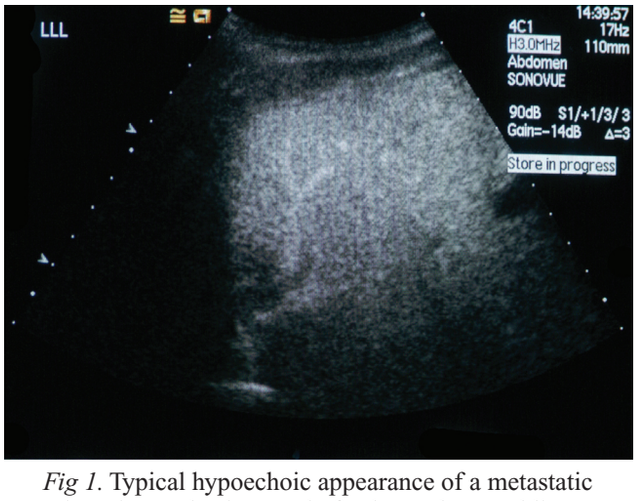

Fig 1. Typical hypoechoic appearance of a metastatic deposit on a background of enhanced normal liver parenchyma.

Table I. Benign focal liver lesions

Diagnosis	Number of patients
Haemangioma	27
Focal fatty sparing	13
Focal fatty infiltration	2
Simple cyst	4
Regenerating nodule	1
Focal nodular hyperplasia	1
	Total = 48

Table II. Malignant focal liver lesions

Diagnosis	Number of patients
Metastasis	16
Hepatocellular carcinoma	2
Cholangiocarcinoma	1
Lymphoma deposit	1
	Total=20

Of the 27 haemangiomas detected, 19 (70%) demonstrated typical appearances of hyperechoic focal lesions on conventional B mode ultrasound (fig 3a), showed rapid peripheral filling-in during the arterial phase of contrast enhancement (figure 3b), and subsequently became isoechoic with the surrounding liver in the portal venous and late phases (figure 3c). A further haemangioma was initially hypoechoic, but demonstrated rapid peripheral filling-in to become isoechoic with the surrounding liver in later phases of the examination. Seven haemangiomas demonstrated atypical behaviour, and were reported as being likely atypical haemangiomas but further follow up was recommended to confirm or exclude metastases. Of these, six haemangiomas demonstrated persistent hypoechoic areas with circumferential filling-in. The other atypical haemangioma demonstrated slow filling-in of peripheral enhancement, and was shown to be unchanged on ultrasound six months later.

Another of the haemangiomas demonstrated peripheral enhancement in the arterial phase with rapid wash-out of contrast in the portal venous and late phases, and was therefore thought to be a metastasis. However, MRI and clinical follow up confirmed this lesion to be a haemangioma.

Focal fatty sparing was shown in 13 patients to be a hypoechoic, well-defined area on B mode which became isoechoic with the surrounding liver during all phases of CEUS. Focal fatty infiltration was shown in two patients to be a hyperechoic lesion on B mode which became isoechoic with the surrounding liver during all phases of CEUS. There were four cases of simple hepatic cysts. A focal regenerating nodule was seen to be a well-defined hyperechoic lesion on B mode, and was obscured when CEUS was performed. The diagnosis was confirmed with repeated ultrasonography and CT. The one case of focal nodular hyperplasia demonstrated early central

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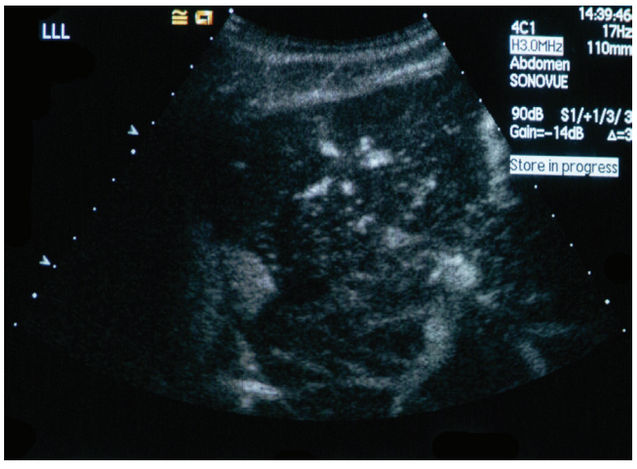

Fig 2a. Diffuse enhancement of the lesion during the arterial phase.

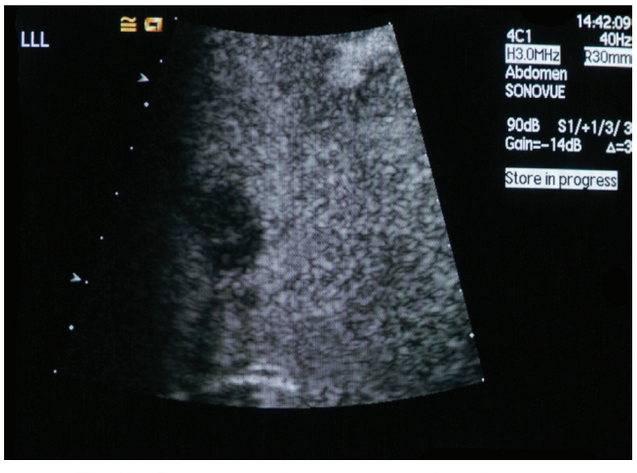

Fig 2b. Contrast wash-out occurred in the same lesion in the late phase.

spoke wheel-shaped contrast enhancement, followed by diffuse homogenous enhancement in the arterial phase.

DISCUSSION

Accurate characterisation of focal liver lesions is essential for the utilisation of new treatment strategies in the management of focal liver malignancies.

Ultrasound is a widely used modality for imaging liver pathology. It is relatively inexpensive, does not expose the patient to ionising radiation, and is widely available. However there are limitations to conventional grey scale B mode ultrasound in the detection of focal liver lesions, especially when the lesions are small (<2cm), in the setting of cirrhosis, or in patients undergoing chemotherapy[2]. Colour and power Doppler has increased sensitivity for focal lesion detection compared to conventional B mode, but sensitivity is still inferior to contrast-enhanced spiral CT and MRI[1].

Ultrasound examination with intravenous contrast agents allows dynamic assessment of focal liver lesions, improving the diagnostic performance of conventional sonography[5]. Perfluorocarbon or sulphur hexafluoride-filled microbubble contrast agents, such as SonoVue, can be used with non-destructive low acoustic power ultrasound scanning. In this

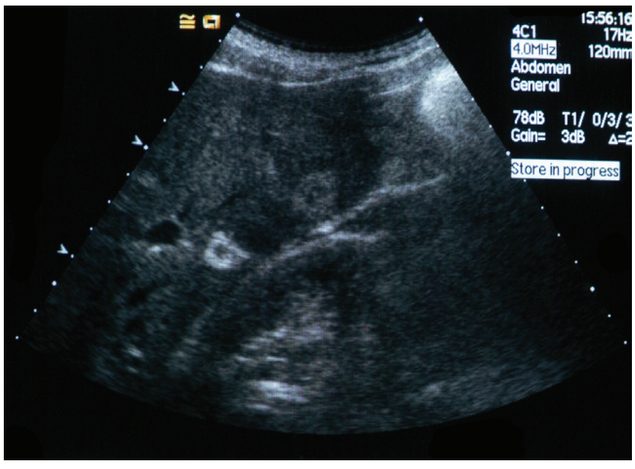

Fig 3a. Typical hyperechoic appearance of a haemangioma on conventional B mode Ultrasound.

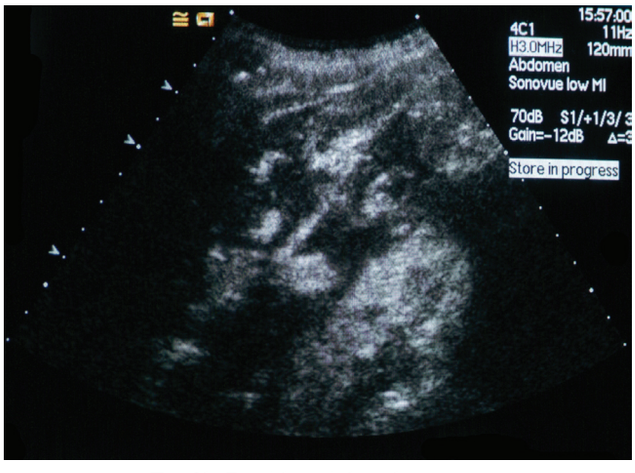

Fig 3b. Rapid peripheral contrast enhancement in the arterial phase.

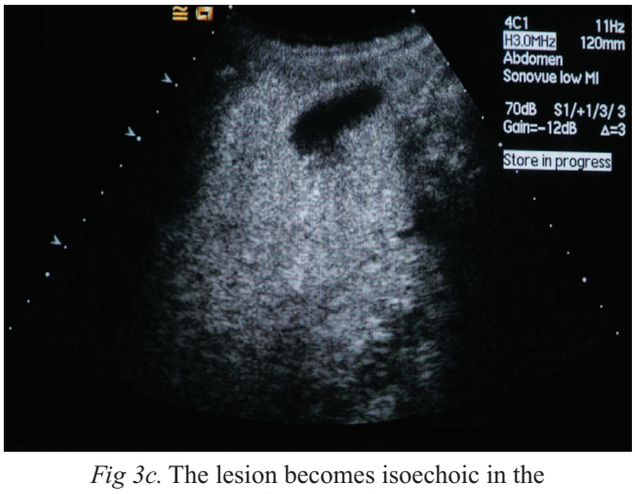

Fig 3c. The lesion becomes isoechoic in the portal venous phase.

way, real-time assessment of contrast enhancement in focal liver lesions is possible. CEUS therefore has the potential to provide firm diagnostic information without the need for other imaging modalities such as CT or MRI. In district general hospitals where imaging resources may be limited, CEUS can be incorporated into radiological practice with a relatively small

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increase in equipment and operator expenditure.

The results of this study indicate that CEUS in our practice has high sensitivity and specificity in determining if focal liver lesions are malignant. Most of the lesions exhibited definite enhancement patterns on dynamic scanning. As demonstrated in previous studies, the principal difference between benign and malignant liver lesions is their appearance during the late phase of contrast enhancement[1,5]. Malignant lesions are usually hypoechoic compared to normal liver parenchyma in this phase, whereas benign lesions are usually hyperechoic or isoechoic. In this study, nearly all of the metastases remained hypoechoic throughout all phases, although one case showed arterial enhancement with rapid wash-out. The two hepatocellular carcinomas showed variable enhancement characteristics in arterial and portal venous phases, but were also markedly hypoechoic relative to normal liver parenchyma in the late phase. The hepatic lymphoma and cholangiocarcinoma encountered in our study were correctly identified as malignant, although the enhancement characteristics were indistinguishable from hepatic metastases.

The majority of haemangiomas in our series demonstrated the usual pattern of peripheral enhancement in the arterial phase, followed by central filling-in on the delayed images (fig 3). A few haemangiomas exhibited slightly atypical enhancement patterns, but were correctly identified as benign. CEUS enabled the accurate characterisation of focal fatty sparing and focal fatty infiltration as the cause of liver lesions in several patients. Focal nodular hyperplasia was identified in only one patient in our series, with the classic features of early central spoke wheel-shaped enhancement and isoechoic appearance on late phase imaging.

CONCLUSION

Contrast-enhanced non-destructive ultrasonography using a low mechanical index is the sonographic modality of choice for the detection of liver malignancy[1]. In our experience, contrast-enhanced ultrasound imaging is highly accurate in characterising malignant and benign focal liver lesions. The equipment and expertise required for this investigation can be incorporated into most general radiology departments. Contrast-enhanced ultrasonography therefore has significant potential for utilisation in district general hospitals as well as specialist centres.

Conflict of Interest – none declared.

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Ulster Med J 2007; **76 (1)** 26-30

Presidential Address

Medicine Then and Now.

Presidential Address to the Ulster Medical Society, 12th October 2006

Gary E McVeigh

The themes presented in this Presidential address are introduced through masterpieces of medicine in art from the very earliest depictions to the modern day. The representations of medicine in art provide a commentary on the place of medicine in society and how it was viewed by society. Some artists used their work both to highlight important health issues of the time and as a "propaganda" tool to promote social change. Others employed art as a medium to convey their emotions and state of mind to the world. The artistic representations provide an opportunity to reflect on the place of medicine in society then, and now, and explore what changes have occurred over time.

Figure 1. Human Confronting a Bull

In September 1940, four teenagers discovered a complex of caves located near the village of Montignac in South West France. The caves of Lascaux represent an astounding repository of paleolithic art dating back 25,000 years[1]. Among the hundreds of paintings and etchings of animals across the ceilings and walls of the caves resides the oldest artistic medical representation. The lone human figure among all the animals is a man with the head of a bird, who appears to be in some kind of trance during a confrontation with a bull (Fig 1). Beside him is a staff. It is widely believed that this figure is some sort of Shaman. The word Shaman originated from Siberia and eventually came to be applied to all medicine men and women of indigenous cultures[2] (Fig 2). Shamanism predates all established religions and involves working with the spirit or soul either to heal or to gain spiritual knowledge. For the Shaman everything is alive and carries information that can be referred to as the spirit, energy or consciousness. In order to communicate with the spirit or consciousness the Shaman will shift his or her own state of awareness. The shift of consciousness allows the Shaman to "see" what the problem is on a spiritual level and retrieve information in order to heal. Illness is perceived as a lack of power and to heal the Shaman returns power to the individual.

Figure 2. Hmong Shaman

I first learned of the practice of Shamanism when I worked at the University of Minnesota in the 1990's. A large community of Hmong had settled in Minnesota having fled Laos at the end of the Vietnam War. The Hmong were threatened by the intrusion of North Vietnamese troops into Laos so the United States encouraged them to fight and provided them with training and weapons[3]. They made tremendous sacrifices fighting for the Americans and many had to flee their country to escape genocide at the hands of the North Vietnamese when the war ended. More than 100,000 Hmong died as a result of the Vietnam war. The Hmong believe passionately in the healing power of the Shaman and it was important to understand and appreciate the role of these traditional healers in Hmong society, and work in tandem with them, to provide holistic care for this indigenous population.

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Figure 3. Rembrandt Harmenszoon van Rijn

The anatomy lesson of Dr Nicolaes Tulp has adorned the cover of many editions of Grants atlas of anatomy. The portrait is recognised as one of the earliest masterpieces of Rembrandt Harmenszoon van Rijn[4] (Fig 3). Rembrandt's painting is of great historical, artistic and sociological importance as it epitomizes the spirit of 17th century Holland. At that time group portraits of this type were an immensely popular genre. They were a social institution, the symbol of an up-and-coming middle class. It was highly desirable to be shown in the company of influential citizens to enhance career prospects and clients would pay handsomely for this privilege. Of the figures shown in Rembrandts painting only two were physicians[5] (Fig 4).

Nicolaes Tulp was one influential citizen who took centre stage in the 17th-century Amsterdam. He was a man of learning, a surgeon and an anatomist. For four years, he was Praelector Anatomiae of the Guild of Surgeons and was the first to describe the ileocaecal valve. However, Tulp was, first and foremost, a political animal: he was city treasurer eight times, and four times burgomaster of Amsterdam. The

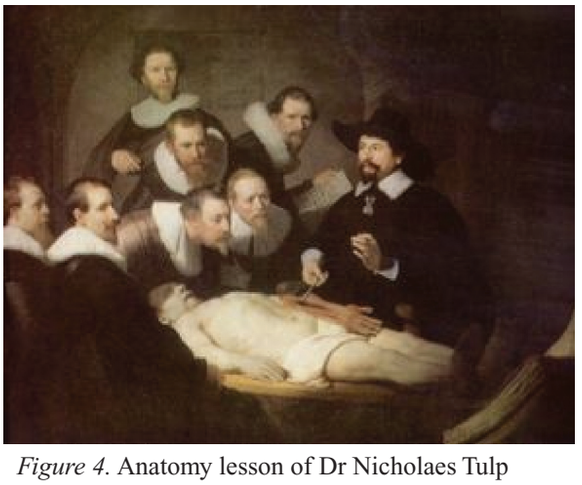

Figure 4. Anatomy lesson of Dr Nicholaes Tulp

Guild of Surgeons permitted one public dissection each year and the corpse had to be that of an executed criminal. Undoubtedly, the individual had no say in the disposition of his body after death. The lesson is being given not only for the benefit of the observers in the picture. Professor Tulp is looking beyond those crowding the dissection table towards an audience that the spectator can readily imagine.

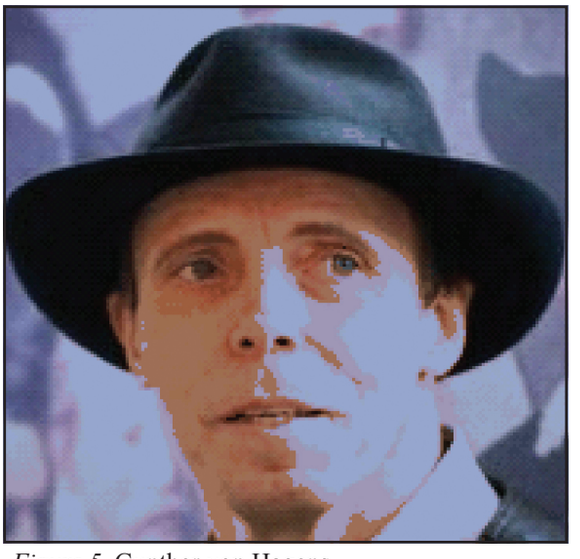

Figure 5. Gunther von Hagens

Do parallels exist between this historical perspective and the modern day display of the human body? Some insight into this question is provided by Gunther von Hagens (born Gunther Liebchen on January 10, 1945) a German anatomist who invented the plastination technique to conserve human specimens[6] (Fig 5). He developed and promotes the "Body Worlds" exhibition and display of human bodies and body parts. The exhibition has met with public interest and controversy with critics condeming the lifelike poses of the plastinated cadavers as degrading and disrespectful (Fig 6). Nevertheless, the exhibition has been a popular success having received over 15 million visitors.

In 2002 von Hagens performed the first public autopsy in the UK for 170 years, to a sell-out audience of 500 people in a London theatre. The dissection was televised on Channel 4. In 2005 Channel 4 also screened four programmes entitled "Anatomy for Beginners" that featured von Hagens. Legal proceedings have been taken against von Hagens for allegedly receiving corpses from prisons, psychiatric institutions and hospitals in Kyrgyzstan and China. The issue of personal or family consent is unlikely to have been a paramount consideration in the minds of the authorities prior to transportation of the bodies. During the hearings von Hagens denied using any of the cadavers in the body worlds exhibition. It would seem that many similarities exist linking public interest and personal ambition with the display of the human body between17th century Holland and the present day.

Alcohol abuse is not a unique 20th-century problem. William Hogarth's print *Gin Lane* depicts the results of such abuse in the 18th-century England and highlights its social consequences[7] (Fig 7). Hogarth was interested in many

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Figure 6. Figure from Body Worlds Exhibition

humanitarian projects and his zeal with regard to social and moral issues appear in many of his works. In *Gin Lane* the print illustrates the social and economic evils of alcohol abuse and was employed as a propaganda tool to effect change in society (Fig 8). In the early 18th-century gin was introduced into England by soldiers returning from the Low Countries and its popularity increased rapidly and disastrously between 1720 and 1750. It was not taxed initially because the use of fermented barley in its composition provided a market for farmers and because the distillers had a powerful political voice. With the growing problem of alcohol abuse parliamentary bills were introduced in 1729 and 1735 to limit the production and distribution of gin. The result was to suppress the distillation of good gin and to increase the production of inferior products referred to as 'Parliamentary Brandy'. The acts were unenforceable and repealed in 1743.

Figure 7. William Hogarth

Henry Fielding, a friend of Hogarth's, who became a lawyer and a Westminster magistrate in addition to pursuing his career as a dramatist and author wrote a tract in 1751 entitled *Enquiry into the causes of the late increase in robbers etc with some proposals for remedying this growing evil*. Fielding's tract and Hogarth's print of *Gin Lane* constituted part of a general attempt to reimpose legislation on the sale of spirits. They succeeded with the passage of the Tippling act in 1751. Hogarth's scene is set in the slum district of St Giles' parish, Westminster, where in 1750 at least every fourth house was a gin-shop and numerous brothels and places for receiving stolen goods existed. The only thriving establishment was the pawnbroker. The infant in the foreground with large round eyes situated between small palpebral fissures with small cheek-bones and small chin gives an "Orphan Annie" appearance to the child. Hogarth had observed the congenital defects associated with maternal alcoholism that we now recognise as the foetal alcohol syndrome that was not described in modern medical literature until 1973[8].

Figure 8. Gin Lane

In the 20th and 21st centuries, alcohol remains a major public health problem. In particular Russia's transition from a socialist to a market-led economy has been accompanied by a severe decline in the health status of the population, that in large part, can be attritubed to the effects of alcohol consumption[9,10].

In the 1980's the former soviet President Mikhail Gorbachov made a well intentioned attempt to reduce alcohol consumption driven by statistics that indicated up to 40% of the adult male population was alcoholic. Gorbachov's efforts resulted in huge revenue losses, lengthly lines and a booming black market in alcohol. It led to an increase in production of moonshine liquor that is estimated to have claimed the lives of up to 25,000 Russians from chemical poisoning. Gorbachov lost the affection he expected from the Russian people for introducing glasnost instead he only received their loathing. He reportedly told this story: "This guy", he says, "was standing in line for 10 hours to buy vodka and finally decided to go to the Kremlin to kill Gorbachev". The next day, the guy was back in the vodka line: "It didn't work", he told the others. "The line to the Kremlin is even longer". Clumsy attempts to legislate and control the sale and distribution

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Figure 9. Edvard Munch

of spirits that failed in the 18th century were replicated in 20th century Russia only to fail again.

Problems with alcohol abuse have increased in the United Kingdom with accompanying consequences for the health of the population. A plentiful supply of cheap alcohol appears to be the most important ingredient giving rise to an increase in alcoholism in society. History would suggest vulnerability to lobbying from powerful interest groups and multinational companies will play a pivotal role in determining if and when the authorities will make a concerted attempt to counteract alcohol abuse in the United Kingdom.

The Norwegian artist Edvard Munch is recognised as the pioneer of the expressionist movement in modern painting[11] (Fig 9). Munch had a tragic family and personal life. His mother died from tuberculosis when he was 5 years old as did his older sister Sophie when aged 15. His younger sister was diagnosed with mental illness at an early age and of the five siblings only one brother ever married only to die a few months after the wedding. During his life alcohol became a problem and Munch was emotionally unstable suffering from bipolar disorder. In his paintings Munch explored the themes of life, love, fear, death and melancholy. He was quoted as saying "sickness, insanity and death were the angels that surrounded my cradle and they have followed me throughout my life". His most famous painting, "The Scream", is described as the first expressionistic picture. As a representation of Munch's own "inner hell", the painting visualises a desperate aspect of anxiety and apocalypse (Fig 10).

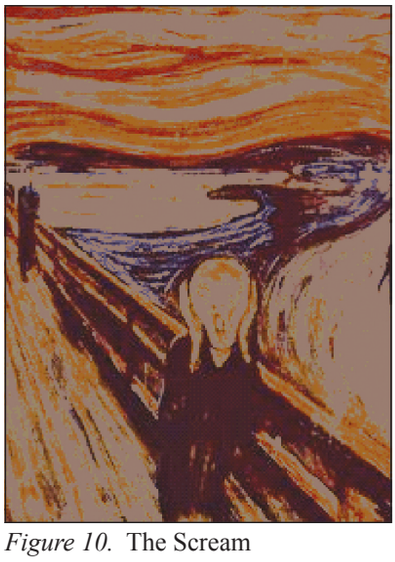

Figure 10. The Scream

It has been known for years that truly creative individuals have much higher rates of manic depression, or bipolar disorder, than do the general population. The notion that genius and insanity are linked is supported by a wealth of anecdotal evidence[12]. It may be that bipolar individuals have a wider spectrum of emotions and during their manic phase generate a great number of ideas only to highly criticise them during bouts of depression leaving only the most promising work. Or it may be the other way around. Perhaps people who are highly creative and intelligent have a greater tendency to develop bipolar disorder. Critics of the notion that individuals with bipolar disorder are more creative contend that a causal connection has never been proven and point to a number of methodological flaws and sources of bias in the evidence linking creativity and bipolar disorder[13]. Furthermore, even if a link were proven it may be relevant only to a minority of individuals. Although society as a whole may benefit from its so called "mad geniuses" this must be balanced against the cost to the individual as up to one in five sufferers attempt suicide. The excerpt below is taken from Suzanne Johnston's patient's journey article in the British Medical Journal[14]. It exemplifies the depths of despair suffered during the depressive episodes in patients with bipolar disorder and guards against romanticising this serious illness.

THE DARK SIDE

Breathing In and out. In and out. This makes no sense – it doesn't seem possible to be alive and yet feel so miserable, so wretched. I feel death parading through my body, calling out to me and mocking my feeble attempts at resistance. A black liquid oozes from my pores and covers my skin in a slick, disgusting sheen that only I can see. Darkness creeps through my veins and launches a visceral attack on my soul. I am helpless and floundering, lost in this relentless hammering of depression, with psychosis scraping its talons sickeningly against the inside of my skull.

The relationship between mental illness and extreme emotional or eccentric behaviour presents a medical diagnostic problem that is both complex and controversial[15]. The delineation and classification of mental illness has been as fiercely contested throughout the ages as it is today. Successive editions of the Diagnostic and Statistical Manual, the profession's diagnostic handbook produced by the American Psychiatric Association, show just how fluid the characterisation of mental illness continues to be. The manual is revised every few years often with incompatible and overlapping terminologies disappearing and reappearing from edition to edition. It is not only cynics that claim political, cultural, racial and gender prejudices continue to shape diagnoses of what are purportedly objective disease conditions. Homosexuality, for example, appeared in the Diagnostic and Statistical Manual as a mental affliction until 1975. It can be argued that in spite of the technological and therapeutic advances that have taken place from the time of Edvard Munch our understanding of what constitutes mental illness has not progressed significantly as the nature of the beast remains obscure.

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Historical Paper

The History of Gastric Surgery: the Contribution of the Belfast School

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INTRODUCTION:

Many aspects of the colourful history of gastric surgery are familiar to most scholars of medicine: Theodor Billroth's first gastrectomy for cancer[1], the attempts of Moynihan and Roux to develop procedures which would reduce the unwanted effects of gastrectomy for peptic ulcer[2], the contributions of Pavlov and Latarjet to the understanding of gastric physiology and anatomy respectively[3], Lester Dragstedt's application of this knowledge in performing the first therapeutic vagotomy for peptic ulcer[4]…each has been thoroughly documented in the annals of surgical history; and its associated anecdotes passed on by many a consultant surgeon to his trainees across the operating table. What is less well known is that the surgeons and physicians of Belfast also played a key role in the development of the art and science of gastric surgery, making several significant advances which will be highlighted by this paper.

COLONEL AB MITCHELL: SUCCESS IN SURGICAL TREATMENT OF PERFORATED PEPTIC ULCER

In 1886, five years after Billroth's landmark operation, Professor Thomas Sinclair performed the first Belfast gastrectomy for cancer[5]. Subsequently, the General Hospital in Frederick St, which was the forerunner of today's Royal Victoria Hospital, became one of the first centres to demonstrate success in the surgical treatment of perforated ulcer. There, Sir John Campbell, a careful surgeon credited with introducing the wearing of rubber gloves in theatre in Northern Ireland, successfully closed his first perforation in 1897[5]. His colleague, Colonel AB Mitchell, operated on a second case in the same year and by 1903 had published a series of twelve such procedures[6]. While the first three ended unhappily because of a delay in diagnosis, the success of eight of the following nine was a considerable achievement in an era when surgical repair was discouraged by sceptical physicians except as a last resort. The antagonism felt by many prominent physicians towards surgical procedures on the stomach was even greater then than it is today. For example, in 1882, following Billroth's successful gastrectomy for cancer, Ludwig Rydygier in Poland reported the first gastrectomy for gastric ulcer. When the abstract was published in Germany later that year, the editor added the famous footnote "*Hoffentlich auch Letze*" (hopefully also the last)[7].

Mitchell persevered in spite of the relatively hostile climate. Further papers followed, including an educational brief concerning 'Perforated duodenal ulcer' which was published in the British Medical Journal and read at the BMA meeting in Belfast in 1909[8]. In this narrative, Mitchell emphasized the need for early diagnosis if surgery was to be successful, deriding the contemporary insistence on 'shock' as an indicator of perforation. '*How often are we told, "I do not think there is a perforation, there is no shock.*"', he exclaimed, '*I wish this word shock had never appeared in our textbooks!*'[8]. For Mitchell, perforation was signified by the onset of rigidity, a sign he called the abdomen's '*trumpet call for help*'. He was acutely aware of the need to provide additional fluid for such patients, a phenomenon often called "third spacing" in contemporary medical parlance. He was therefore insistent on the need for continuous post-operative administration of saline per rectum, since intravenous fluid administration was not an option at that time: '*a nurse who understands the process and will not be satisfied unless she can get in at least one pint per hour is essential!*'[8]

Mitchell's final paper, giving results of 110 operations for gastric and duodenal ulcer followed in 1911. These were not excelled by any other surgeon of the time and brought great acclaim to the Belfast School of Surgery[6]. Mitchell's achievements are particularly admirable when it is considered that he was working long before the advent of antibiotics or intravenous fluid administration, and it is fitting that his contribution is commemorated annually in the AB Mitchell memorial lecture.

If Mitchell had shown that operative treatment could be effective in compromised patients with perforated ulcers, it seemed reasonable to assume that surgery would be even more successful if used to prevent perforation in patients with uncomplicated ulcer disease. Resectional procedures became commonplace but the results were not as pleasing as expected: since these patients had benign disease, they survived for long enough for the side effects – vomiting and diarrhoea, the 'dumping syndrome' and nutritional disturbances - to become

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a serious drawback. Indeed, a leading gastric surgeon of the time once exclaimed, '*If anyone wanted to cut out half of my good stomach in order to cure a little ulcer in my duodenum, I would run faster than he!*'.[9] Empirical experimentation with mechanical modifications – led by figures such as Moynihan, Roux and JP Finney, a surgeon of Ulster descent who was the first Resident Surgeon at the celebrated Johns Hopkins Hospital – led to some improvement, but it was parallel advances in the field of gastric physiology which would ultimately revolutionize peptic ulcer treatment.

JC ADAMS: LINKING HYPERACIDITY AND ULCERATION

As early as 1833, William Beaumont had demonstrated the presence of hydrochloric acid in the juices discharged from his patient's gastro-cutaneous fistula[10]. In 1910, Schwarz coined the aphorism 'no acid, no ulcer', based on his clinical observation that ulceration only occurred where gastric juice exerted its influence[9]. The definitive demonstration of a link between hyperacidity and duodenal ulceration is often attributed to Lord Moynihan; however, Moynihan himself credited the 1911 MD thesis of James C Adams of Belfast[11].

Adams was the son of a County Antrim farmer, a '*large, straight and rather stern man*' who graduated from Queen's University in 1894. He became a general practitioner at 212 Ravenhill Road, a post he retained until his death in 1951, and took no time off, conducting his research in the evenings[11]. Between 1905 and 1911 he studied twenty patients with duodenal ulcer using Ewald test meals and found that fourteen of them had hyperchlorhydria. This result was the basis for Moynihan's oft-quoted maxim that hyperacidity was a factor in 70% of duodenal ulcers[4]. Adams concluded, '*Hyperchlorhydria…is a condition of congestion, hyperaesthesia and hyperacidity…with intervals between attacks…It might be that after this condition had existed for some length of time an ulcer formed.*' He also noted another common consequence of hyperacidity, the '*continuous and copious flow of saliva which is very distressing to the patient*'[11]. It is unfortunate that Adams, a modest man, published no more of his research, but his dedication to medicine inspired many of his family to follow him into the profession[11].

If hyperacidity was an aetiological factor in peptic ulceration, it was logical for surgeons to seek a means of reducing acid secretion for therapeutic purposes. Their way had been paved by nineteenth-century physiologists who had largely elucidated the mechanism of gastric secretion. It was Ivan Pavlov who provided the first definitive evidence of the role of the vagus nerves in this process: His classic experiment demonstrated that, following the administration of a 'sham feed', gastric juice was produced in the empty stomachs of dogs with diverted oesophagi, but that this secretion was reduced after the dogs had been subjected to vagotomy[3].

In 1924, a French surgeon, Latarjet, published the first results of a series of vagotomies for the treatment of peptic ulcer in humans. However, he had added a gastro-jejunostomy in the latter patients, and many observers attributed his success to this procedure rather than the vagotomy itself[3]. It was not until the 1940s, when Lester Dragstedt arrived on the international stage of gastric surgery, that vagotomy became accepted as a mainstay of ulcer treatment. A rigorous scientist, Dragstedt believed that surgical treatment should be '*simple, straightforward and deal with the pathophysiologic root of the disease*'[12], and demonstrated that vagotomy fulfilled these criteria, performing no less than 158 such operations himself.

Even vagotomy was not without complications, however: bile vomiting, diarrhoea and dumping were all problematical, leaving Pollock to conclude in a 1952 Lancet review article that; '*Fashions in the treatment of peptic ulcer come and go, and the surgical problem remains unsolved*'[3]. Nevertheless, by the late 1950s, refinements in the technique and the combined use of vagotomy with more traditional procedures led to the publication of more favourable outcomes.

In the following decade, selective vagotomy, as first performed by Griffith and Harkins, also gained a following, the rationale being that preservation of vagal branches other than those supplying the stomach would reduce the side-effects of the surgery. A prominent Belfast surgeon, Terence Kennedy aptly summarized the dilemma, albeit with a rather quaint analogy: '*No surgeon wishing to denervate the soleus muscle for intermittent claudication would divide the sciatic nerve in the thigh; yet most surgeons using vagotomy for duodenal ulcer unthinkingly divide the whole of the vagus nerves immediately below the diaphragm, thus dividing all abdominal viscera, except the distal colon, of their para-sympathetic supply.*'[3] At the same time John Goligher (1912-98), an Ulsterman working in Leeds, suggested that a 'belt and braces' approach, using truncal vagotomy to reduce neural acid stimulation combined with antrectomy to reduce hormonal stimuli, was the optimum procedure[13]. Goligher was appointed to the chair of surgery in Leeds in 1955, a post he held until 1978, and, although his major surgical interest was in colon surgery, he nevertheless contributed hugely to the field of gastric surgery by creating an academic environment in which young surgeons could develop expertise as surgeon-investigators.

THE BELFAST TRIALS: KENNEDY LEADS THE WAY ON THE ROAD TO RATIONALISATION

By the mid-1960s, then, there were two major varieties of denervation and at least eight drainage procedures being performed in the treatment of duodenal ulcer, but little consensus as to which combination produced the best results. This situation was considered highly unsatisfactory by Terence Kennedy, who believed that surgeons were submitting patients to unnecessary and crippling side-effects (Figure 1). In Kennedy's opinion, every patient had the right to the operation with the lowest mortality, the least physiological disturbance, a recurrence rate of less than 5% and the option of reversibility should unforeseen complications occur[14]. Like Billroth, Pavlov and Dragstedt before him, Kennedy was a true devotee of rigorous scientific pursuit of facts and was one of the earliest advocates of the use of randomized, double-blind, controlled trials in surgery. He was scornful of those '*Olympians of the surgical stage*', such as Lord Moynihan, whose pronouncements regarding ulcer treatment were widely accepted on the grounds of his personal charisma and eminence, rather than on the basis of any objective evidence. Kennedy was also critical of the early trials of Goligher and Kraft, pointing to the heterogeneity of their material, absence of randomization and incomplete follow-up[15].

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Thus, together with a newly appointed colleague, George Johnston (Figure 2), and physician Dr Alistair Connell, Kennedy set out on a crusade to provide evidence which would rationalize the treatment of duodenal ulcer and improve the fortunes of patients worldwide. He began in 1966-7 with a trial designed to test claims that selective vagotomy produced less side-effects than truncal vagotomy, particularly where diarrhoea was concerned[16]. This was conducted by his own surgical team only in order to ensure that '*the techniques would be uniform and the data…more reliable*'[15], with 100 patients randomized to receive either truncal vagotomy or selective vagotomy, both with Finney pyloroplasty, and with the follow-up assessment performed by a physician unaware of which treatment the patients had received. At both the 2-year and 5-year follow-up stages there was significantly less diarrhoea in the selective vagotomy group, as well as a trend towards reduced recurrence rates, apparently verifying the suggestion that selective vagotomy was superior to the truncal procedure. As Johnston neatly put it, '*When we boil it down to the number of times patients require to go to the toilet…patients with truncal vagotomy went about five times as often as those with selective vagotomy*'[17], a consideration less likely to be overlooked by a patient than the surgeon.

However, the problems of dumping and bile vomiting still remained. This was attributed to "gastric incontinence" a term coined by another Belfast surgeon, Samuel McKelvey. Kennedy therefore decided to establish which drainage procedure would minimize these side-effects, challenging the widely held but unsubstantiated belief that pyloroplasty was superior to gastrojejunostomy. A further randomized controlled trial was commenced in 1968, with patients receiving selective vagotomy in combination with either of the above[18]. At 3.5 year follow-up there were no significant differences between the two groups but the patients with gastrojejunostomy were more satisfied and had a lower recurrence rate: further, unlike a pyloroplasty, a gastrojejunostomy could be reversed if the side-effects were intolerable. In this sense, it was noted that '*if gastrojejunostomy is a disease then pyloroplasty is an incurable disease!*'[5].

In the meantime, Amdrup in Copenhagen and David Johnston of Leeds simultaneously described the use of 'highly selective' or 'proximal gastric' vagotomy, in which the innervation of the antral pump was left intact so that normal gastric emptying could be maintained, obviating the need for a drainage procedure[3]. To establish if this method was as effective as selective vagotomy with gastrojejunostomy, and whether there was any real improvement in patient satisfaction, Kennedy and Johnston commenced a third major randomized controlled trial in 1970. This demonstrated that dumping, bile vomiting and diarrhoea were virtually eliminated by the new Highly Selective Vagotomy (HSV), but that recurrence rates were significantly greater at 12% compared with 4% in selective vagotomy[19]. When the team published a long term follow-up study of 600 patients who had undergone HSV in 1990, however, the great majority of the 11% who had experienced recurrence had achieved control with medication, while overall 92% were satisfied (Visick grade I or II), an excellent result in light of the fact that the figure for the 'normal' population is 93%[20]. The same team was quick to recognize an important but rare complication of highly selective vagotomy, namely lesser curve necrosis, which in the Belfast series only occurred when HSV was combined with Nissen fundoplication, highlighting the important risk of creating ischaemia of the upper stomach.

Figure 1: Mr Terence Kennedy

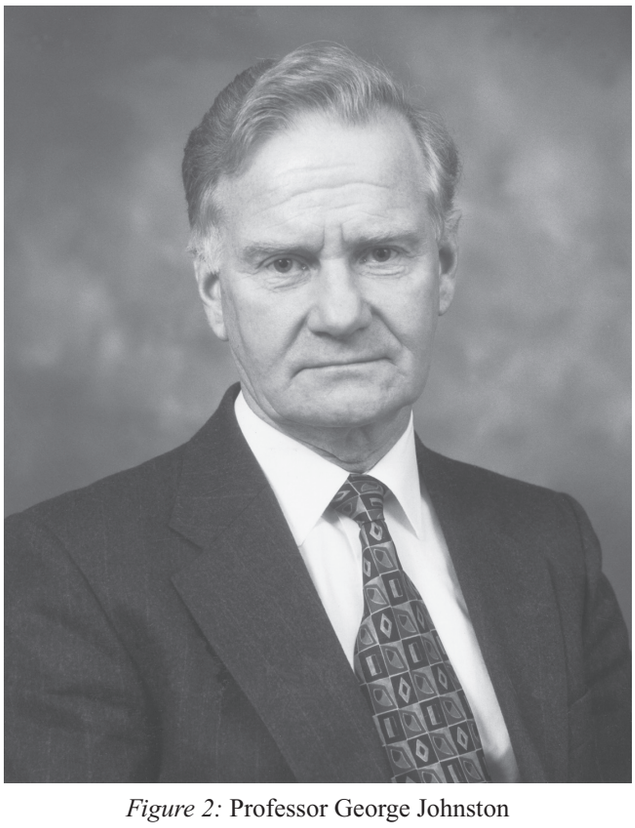

Figure 2: Professor George Johnston

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In conjunction with these central trials, Kennedy and his team conducted a variety of experiments into the physiology behind their results. They published papers on the role of gastric emptying, intestinal transit time, pancreatic and biliary dysfunction and coeliac and hepatic nerve conduction in the development of 'post-vagotomy syndrome', defined the role of the duodenum in gastrin release, described changes in antral motility after proximal gastric vagotomy and identified changes in intestinal flora after a range of anti-ulcer procedures[21-7]. They investigated the post-operative nutritional status of their patients in detail[28] and defined the place of vagotomy in the treatment of gastric ulcer with results confirming that such a procedure, previously avoided by many surgeons, was indeed satisfactory in gastric ulcers of types II and III. For type I ulcers, however, with no duodenal or antral component, it was advised that partial gastrectomy should still be carried out because of the substantial risk of malignancy[29].

Thus, by the early 1970s, these Belfast trials had provided clear answers to some of the key questions surrounding the issue of vagotomy, thanks in no small measure to the determination and character of the men concerned. Temperamentally they were very different: Kennedy was a tall and intimidating Englishman with socialist political views and a quick temper, while Johnston was a local man of short stature with a ready wit and deep Christian convictions, but they got on extremely well and developed a deep mutual respect[30]. As Johnston said of his 'sparring partner' with characteristic humour, '*It was great to work with a colleague to whom one could look up, not only literally but metaphorically!*'[31]. There is no doubt that both were extremely kind and gentle with their patients and staff, indeed Sr. Fiona Cherry on Wards 15 and 16 where he worked insisted, with some orthographic license, that the initials TLK stood for 'tender loving care'. The other characteristic which defined both surgeons was their integrity and transparency in their work and research.

One remarkable feature of their trials was the high percentage of patients followed up. This was no mean feat as the civil unrest in Northern Ireland was at its height and fear of travelling to West Belfast made patients reluctant to visit the Royal Victoria Hospital. Undeterred, Kennedy's research assistant Dr Anne Spencer would set off on foot or by car with her phlebotomy kit to visit each one at home, sometimes having to find out new addresses from neighbours if a patient had moved on. On a number of occasions when Dr Spencer had to visit a particularly dangerous area, and when she followed up patients in the security wing of Musgrave Park Hospital, Kennedy made time to accompany her personally. In one trial 99 of the 100 patients had been charted but one patient, a twenty year old man, remained elusive. It later emerged that he had been carrying a bomb into the centre of Belfast when it exploded prematurely, killing him[30]!

The contributions of Kennedy and Johnston led to international acclaim and they traveled extensively to present their findings, both being invited as visiting professors to prestigious universities in North America. Kennedy in particular wrote numerous educational articles on peptic ulceration[14, 32-5] and was honoured with many teaching opportunities, including the invitation to deliver the first Graham Coupland memorial lecture in Sydney, Australia and becoming one of few local physicians to be asked to deliver the Scott-Heron Lecture in his own hospital. His ability to communicate with colleagues, combined with his pioneering research, led to his election as President of the Association of Surgeons of Great Britain and Ireland in 1980-81, the same year George Johnston was elected secretary. Consequently, the Association Annual Meeting was held in Belfast in April 1981, an occasion which marked the zenith of Kennedy's career and perhaps of the Belfast school of gastrointestinal surgery[36].

By 1981, the basis and indications for vagotomy in its various forms had been firmly established and the debate at the meeting surrounded the management of those 10% of patients who suffered recurrent ulceration after surgery. The mid-1970s had seen the introduction of histamine receptor antagonists, notably Cimetidine, as a potential alternative to re-operation in such cases. Indeed, Kennedy, alert as always to new possibilities in optimum patient management, had conducted a randomized trial of Cimetidine versus placebo in 1978 but had found no significant differences in ulcer healing, pain or antacid consumption[37]. It appeared that, for the time being at least, a surgical solution to the problem was still important.

As part of the annual meeting of the Association of Surgeons, a special 'Billroth Symposium' was held to commemorate the centenary of the first successful gastrectomy. This was a grand occasion in the Whitla Hall at Queen's University, at which 400 delegates attended[36]. Aires Barros D'Sa, then a young vascular surgeon in the Royal Victoria Hospital, arranged for the two string quartets dedicated to Billroth by Johannes Brahms (op 51 no 1&2) to be played in the background. This artistic subtlety went completely unnoticed by the audience. It was nevertheless a fitting tribute to a man whose name had been immortalized not only through Brahms' music, but also through his own legacy of surgical innovation. It was appropriate that tribute could be paid to Billroth in Kennedy's adopted home city during a short window of peaceful opportunity. A few weeks later, the death of the hunger striker Bobby Sands and the subsequent escalation of violence in the Province would have rendered any such international meeting there unthinkable.

In that same year, Kennedy was awarded an Honorary MD from Queen's University and was elected to the Council of the Royal College of Surgeons of England. He continued his dynamic partnership with Johnston until his retirement in 1984, true as ever to his lifelong motto, 'Don't let the grass grow under your feet', or the Latin equivalent, '*Carpe Diem*' which was displayed in Wards 15 and 16 until their demolition in 2003[31]. On his last working day he performed a full theatre list as usual, quietly inscribing the word '*fini*' at the bottom of the final operation report[30]. He chose never to speak in public again as he firmly believed that medical knowledge became out of date within a day, preferring to spend his last years pursuing his interests in sailing and gardening.

A REQUIEM FOR VAGOTOMY

On the other hand, Johnston continued his work in gastric surgery while pursuing his other major interest in the management of portal hypertension[38]. The 1980s proved to be a significant era of change where the treatment of peptic ulceration was concerned: First of all, pharmacological therapy

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became more attractive as the powerful proton pump inhibitors (PPIs) were added to the physician's armamentarium. Then, Barry Marshall's revolutionary discovery of the ulcerogenic properties of *Helicobacter pylori* opened up the possibility of curing the underlying disease through an eradication regime combining Omeprazole with two antibiotics, an intervention shown to induce ulcer healing in 90% of patients[5].

Parallel to these changes in ulcer treatment, the true incidence of peptic ulceration was also shown to be declining, a phenomenon most likely due to the falling incidence of H pylori in the community[39]. The halcyon days of surgery for ulcer appeared to be over, prompting Professor J Alexander-Williams to publish his '*Requiem for Vagotomy'* in the British Medical Journal in 1991[40]. Johnston and his colleagues were not convinced, however, and composed a vigorous reply pointing to the fact that, while elective ulcer surgery had indeed declined, the number of emergency admissions for complications had remained almost constant[41]. They also suggested that long-term drug therapy invited poor compliance and gave less satisfactory Visick gradings, as well as highlighting evidence that up to 50% of medically-treated patients would require surgery at some point. Their reply concluded with the emphatic statement, '*Proximal gastric vagotomy is not dead and should not be buried*.'

However, by 1994 ulcer surgery truly was almost extinct: Professor Johnston performed only three vagotomies in his last working year. Throughout the 1980s a similar decline in cases of gastric cancer was observed, probably because it similarly was shown to be related to infection with *Helicobacter*. Epidemiological studies from many Westernised countries showed the incidence of gastric cancer to be declining steadily[39]. One could be forgiven for supposing that the time had come for gastric surgeons to relinquish their scalpels and seek new occupational horizons. However, just as quickly as ulceration declined, two other diseases became more amenable to surgical treatment, in the wake of the laparoscopic revolution.

NEW DISEASES; NEW CHALLENGES FOR GASTRIC SURGEONS

The number of cases of gastro-oesophageal reflux disease (GORD) started to rise exponentially – in Belfast as elsewhere - just as peptic ulcer surgery began its dramatic decline. It is paradoxical that these two diseases appeared to be inversely related when it is considered that both are associated with acid secretion, the pharmacological control of which had never been better. A number of prominent surgeons, notably Tom DeMeester in the USA, began to investigate the pathophysiology of GORD. They discovered that 60% of GORD patients had an incompetent lower oesophageal sphincter[42], a mechanical problem which would not respond to pharmacological acid suppression but which was potentially remediable through surgical intervention. Over the next few years, a variety of 'fundoplication' procedures were developed which were intended to restore sphincter function. In 1986, DeMeester published a report showing one such operation to be 91% effective in the control of reflux symptoms over a 10 year period, a success rate superior to that of any medical therapy[43]. Shortly afterwards, the introduction of laparoscopic surgery led to the development of laparoscopic Nissen fundoplication, an operation now well established in the armamentarium of all upper gastrointestinal surgeons, despite the enormous consumption of Proton Pump Inhibitors.

The second of the two diseases, morbid obesity, is only now gaining recognition as a surgical problem in the UK, and bariatric (anti-obesity) procedures have yet to be carried out in Belfast. In the United States, however, bariatric procedures have grown in popularity to such an extent that they have come to be described, with some irony, as the gastric surgeon's bread and butter. Some interesting parallels can be drawn between the understanding of morbid obesity and GORD: both were not initially considered to be a disease, lifestyle alterations were advocated in both conditions with little success, and medical therapies, including appetite suppressants and lipase inhibitors in the case of morbid obesity, were introduced with little effect on the growing scale of either problem. Finally, the introduction of a low risk and highly effective laparoscopic operation for both diseases led to its widespread adoption.

The earliest operations for morbid obesity did not involve the stomach at all, but were designed to bypass the small bowel. Their dangerous side effects, including liver failure, renal calculi, and extreme diarrhea, made them too hazardous to gain widespread acceptance. Surgeons then explored the possibility of restricting oral intake by operating on the stomach. Edward Mason of Iowa developed Vertical Banded Gastroplasty in the early 1970s, and though it avoided the mortality associated with intestinal bypass procedures, it was less effective and often caused refractory vomiting[44]. Many other surgeons experimented with different forms of gastric restriction, aided by the co-incidental introduction of surgical stapling into routine operative techniques. Purely restrictive procedures did not produce reliable and symptom free weight loss until the development of the adjustable gastric band, intitally in Sweden[45]. Nowadays, the most common operations performed for morbid obesity are the Roux Y Gastric Bypass and the so-called "lap band"[46]. Thanks in part to the legacy of Terence Kennedy, it is now generally accepted that such innovations must be subjected to careful scrutiny by long-term follow up, and that competing treatments must be subjected to rigorous clinical trials, ensuring that clinicians and patients alike can be sure of their validity. Given the inexorable adoption into Ulster society of patterns of eating and exercise typical of those in North America, the introduction of bariatric surgery into Northern Ireland is unlikely to be far away.

CONCLUSION

Perhaps public health measures such as 'fat taxes' and weight-based airline fares will help reduce the problem of obesity; perhaps a new pharmaceutical advance will restore a damaged Lower Oesophageal Sphincter. In either unlikely scenario it is doubtful that gastric surgeons will end up in the dole queue, for eating is one of the fundamental human activities, not just because of its nutritional function, but as the vehicle for social interactions from births and christenings to weddings, graduations, business deals, and even funerals. As Lester Dragstedt is alleged to have said, "*The stomach is a nice organ to take to dinner"*, and it is likely that gastric surgeons worldwide will continue to be needed to ensure that the stomach fulfils its role, and to provide an effective substitute if the stomach has to be removed. The medical community in Ulster can be justifiably proud of the past accomplishments of its leading surgeons in this area, and we can expect equally

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significant advances from their surgical sons – and daughters – in the future.

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Case Report

Bowel perforation caused by swallowed chicken bones – a case series

S Akhtar, N McElvanna, KR Gardiner, ST Irwin

Accepted 6 December 2006

INTRODUCTION,

Most foreign bodies pass through the gastrointestinal tract without any consequence. A very small percentage perforate the bowel, leading to acute abdomen and requiring surgical intervention. In most cases, the cause is discovered peroperatively. Foreign bodies such as dentures, fish bones, chicken bones, toothpicks and cocktail sticks have been known to cause bowel perforation. Three cases of bowel perforation caused by swallowed chicken bones within a period of one year are presented.

CASE 1

A 59 year old woman was admitted with a painful irreducible incisional hernia. There was a past history of left hemicolectomy for a diverticular stricture, hysterectomy and bilateral salpingo-oophorectomy, hypothyroidism, chronic obstructive pulmonary disease, hypertension, depression and morbid obesity. Examination revealed a tender, erythematous and irreducible large incisional hernia. It was felt that this was a strangulated incisional hernia. At operation, the hernial sac contained small bowel that had been perforated due to a chicken bone. A small bowel resection was performed with end to end anastomosis and the incisional hernia was repaired. The patient made an uncomplicated recovery (fig 1).

CASE 2

A 46 year old man was admitted as an emergency with a 12 hour history of severe colicky abdominal pain and vomiting which had become constant and aggravated by coughing. There was a past medical history of diverticular disease, chronic constipation and peptic ulcer disease. On examination there was generalised abdominal tenderness and guarding with rebound tenderness in the right iliac fossa. There was an associated leucocytosis (13,000/mm^3) and raised inflammatory markers (CRP 22mg/L). Erect chest X-ray showed free subdiaphragmatic air. A laparotomy revealed a perforation of the sigmoid colon due to a chicken bone in a diverticulum. The chicken bone was removed and the sigmoid colon was repaired. The patient made an uneventful recovery.

CASE 3

A 38 year old man with a previous end-colostomy for faecal incontinence (secondary to cauda equina syndrome) presented as an emergency with a six day history of fever, decreased stoma output and a painful parastomal swelling. On examination he was obese, pyrexic (40 ^{0}C), tachycardia and had generalised abdominal tenderness and cellulitis over a large irreducible parastomal hernia. He was thought to have a strangulated parastomal hernia and underwent emergency laparotomy. At operation he was found to have a parastomal abscess secondary to a colonic perforation within the hernia caused by a chicken bone. The stoma was revised and the parastomal hernia repaired. The patient made a full recovery.

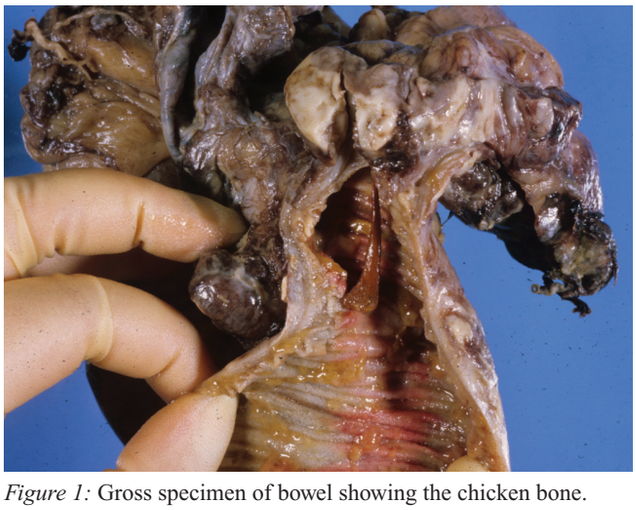

Figure 1: Gross specimen of bowel showing the chicken bone.

DISCUSSION

There are more than 300 cases[1] of bowel perforation caused by foreign bodies reported in the literature. Fish bones, chicken bones and dentures are the commonest objects followed by toothpicks and cocktail sticks.[2-11] The majority of patients do not recall ingesting the foreign body, it being discovered either on investigation (abdominal X-ray or CT scan), or during operation. The greater risk is at extremes of age,[1] in those wearing dentures (dentures cover the most tactile area of the palate and the foreign body goes unnoticed) or in patients with previous bowel pathology (diverticular disease, intestinal stricture). Alcoholics and psychiatric patients are also at increased risk. The clinical presentation may include frank peritonitis, localised abscess formation, enterovesical fistula, intestinal obstruction and intestinal hemorrhage.[1,9]

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Abdominal radiographs are rarely helpful in making a diagnosis preoperatively, however CT scan of the abdomen is considered the most useful imaging to detect foreign bodies or complications arising from them. The most common site of perforation is the terminal ileum and colon, although an increased incidence of perforation has been reported in association with Meckel's diverticulum, the appendix, and diverticular disease.[12-16] Perforation commonly occurs at the point of acute angulation and narrowing. Treatment usually involves resection of the bowel, although occasionally repair has been described.[1,13]

Two of the three cases presented in this report presented as an incarcerated hernia (one incisional and one parastomal) with perforation of the incarcerated bowel by a chicken bone. The third case presented with peritonitis. All three patients had a predisposing condition (hernia or diverticular disease). None wore dentures, and all were grossly obese. Overeating, rapid eating, or voracious appetite may be contributory factors towards ingestion of chicken bones.

CONCLUSION

Perforation of the bowel in a hernia due to an ingested foreign body may mimic strangulation. Diners should be careful when eating poultry or game and exercise due care.

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Case Report

Acute transverse myelitis following typhoid vaccination

Rabindranath N Das, J Jaykumar.

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KEYWORDS: acute transverse myelitis, vaccination

INTRODUCTION:

Transverse myelitis is an acute spinal cord demyelination giving rise to dysaesthesia across chest or abdomen with sphincter dysfunction following viral, bacterial infection or vaccination. Annually millions of active immunization with vaccines are carried out globally with occasional case reports of transverse myelitis as adverse reactions[1]. Acute transverse myelitis (ATM) following rabies,rubella,measles[2], influenza, polio, cholera, diphtheria, pertusis and tetanus[3] has been reported in the literature but typhoid vaccine (ViCPS) induced acute myelitis has not been documented in the recent literature. We report a case of typhoid vaccine induced ATM.

CASE REPORT:

A 19-year-old man presented with paraesthesia and weakness in both legs 5 days after intramuscular ViCPS typhoid vaccine [Aventis, Pasteur]. The day after vaccination he developed fever, malaise and pain and swelling at the injection site (right deltoid). On the 5th day post-injection, he developed sensory loss of all modalities (pain, touch, temperature, vibration and joint sensation) from his lower abdomen to both legs. There was gradual, progressive, symmetrical weakness of both legs - initially flaccid - followed by spastic paraplegia with retention of urine and overflow dribbling. Lower limb power was reduced to 3/5 with bilateral hypertonia after a week of onset of weakness. Abdominal reflexes were absent. Deep tendon reflexes of the lower limbs were exaggerated with a prominent ankle clonus. Both plantars were extensor. Other systems were normal. Investigations revealed a normal haemogram, biochemistry, chest skiagram and electrocardiogram. Cerebrospinal fluid: 5 lymphocytes/mm^3, 80mg/dl protein, 44mg/dl sugar [blood sugar 110mg/dl] and sterile culture. Oligoclonal bands were not detected. Spinal X-rays, nerve conduction studiey and visual evoked potentials were normal. Other relevant investigations including ANF, anti-dsDNA antibody, VDRL and p24 antigen were negative. To exclude compressive myelopathy, a magnetic resonance imaging with gadolinium contrast was done and revealed a centrally located high intensity signal in the T2 weighted film extending over several spinal segments at T12-L4 level (Fig 1a & 1b).

Intravenous pulse methylprednisolone [1000mg] was given for 3 days followed by oral prednisolone tapering over 2 weeks. The patient started feeling better after receiving active aerobic physiotherapy and was subsequently sent to a neurology centre.

DISCUSSION:

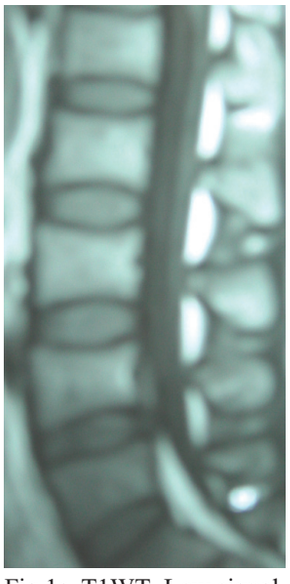

Fig 1a. T1WT: Low signal

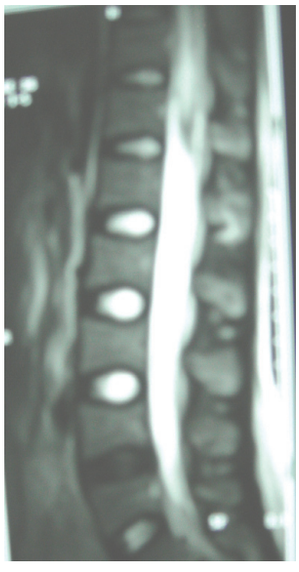

Fig 1b. T2WT: High signal

In 1990 D'Costa reported a case of ATM following cholera, typhoid and polio vaccination[4] and in 1955 McKelvy reported a case following TAB inoculation[5].

Our case is similar as evidenced by paraesthesia and leg weakness with upgoing plantars, exaggerated reflexes, loss of all modalities of sensation from lower abdomen to both feet and urinary retention. Here lower spinal demyelination involved pyramidal and lateral spinothalamic tracts, posterior column and the autonomic nervous system. Neurological complications of vaccination, namely, convulsion, coma, hemiparesis, paraparesis, blindness and even multiple cranial nerve palsies[6] mostly occurred within 24 hours of vaccination. In our case, symptoms appeared 5 days after vaccination and complete neurological deficit was established within 7 days. It fulfilled the proposed diagnostic criteria and nosology of acute transverse myelitis as described by the Transverse Myelitis Consortium Working Group[7]. Nucleus pulposus embolism (NPE) has bimodal peak of 22 and 60 years, presents with sudden, severe pain in the neck and interscapular region (70%) and rapid onset (minutes to hours) paralysis. These features distinguish it from the present ATM.

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Though influenza-like side effects are commonly seen after vaccination, there was no temporal evidence of upper respiratory viral infection at the time of vaccination. We suggest that TAB vaccination triggered the development of ATM; post-vaccination fever may have played secondary role in pathogenesis of ATM. The pathogenesis of ATM is unclear. Immunologically mediated direct insult on the central nervous system by antigen-antibody reaction has been postulated[8].

Other aetiologies of ATM (including systemic lupus, sarcoid, Sjogren syndrome, Bechet disease, syphilis, Lyme disease and HIV) have been excluded by history and laboratory tests.The spinal form of multiple sclerosis was excluded by contrast enhanced MR imaging which revealed the centrally located high signal intensity occupied more than two thirds of the cross-sectional area of the cord. There were no peripheral plaques. The peripheral contrast enhancement of high intensity signal excludes multiple sclerosis in which enhancement in the central zone of peripherally located high signal intensity on T2 weighted images are seen[9].

The best treatment often depends on a timely and accurate diagnosis. Identification of the aetiology may suggest some medical treatment, whereas no clearly established treatment currently exists for idiopathic ATM. Establishment of a diagnostic algorithm will likely lead to improved care, although it is recognized that the entire evaluation may not need to be performed for each patient. Prognosis of vaccine induced transverse myelitis is unsatisfactory and tends to linger for prolonged period with residual paralysis.

Typhoid vaccine-induced myelitis has not been reported in Nepal though the prevalence of typhoid is high. It is pertinent to mention that in this era of prevention we should be cautious about rare uncommon complication of vaccination against common diseases and to follow the universal rule of avoidance of vaccination during intercurrent illness.

ACKNOWLEDGEMENTS:

We are grateful to Prof. PVS Rana, Consultant neurologist, Manipal Teaching Hospital, Pokhara, Nepal and Dr.TK Banerjee, Senior Consultant neurologist, Peerless Superspeciality Hospital, Kolkata, India, for their valuable guidance in writing this paper.

The Authors have no conflict of interest to declare

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Letters

Profuse per rectal bleeding due to erosion of the inferior epigastric artery following a catheter tube caecostomy.

Editor,

We describe a case of profuse per rectal bleeding due to erosion of the right inferior epigastric artery, by a Foley catheter, used as a tube caecostomy, for decompression of underlying colonic pseudo-obstruction.

Case history: A sixty-four year old male was admitted to the intensive care unit with shortness of breath secondary to left ventricular failure, and chronic obstructive airways disease. He developed gross abdominal distension, which did not settle with conservative management. Imaging showed dilated loops of large bowel. Exploratory laparotomy revealed gross dilatation of the caecum and ascending colon. No mechanical cause of obstruction was evident. A 22 gauge Foley catheter was introduced through the base of the excised appendix, after decompression of the colon with a Savage's decompressor. The Foley catheter had been introduced into the peritoneal cavity through a prior stab incision in the anterior abdominal wall, overlying the right iliac fossa.

On the 9th post-operative day, the patient developed profuse fresh bleeding per rectum, associated with considerable bleeding into the caecostomy bag, from which he rapidly became shocked. Initial conservative management was abandoned in favour of a second laparotomy. Thorough examination of the colon revealed no palpable lesions. At the time of taking down the caecostomy, a copious bleed from the right inferior epigastric artery was detected, adjacent to the tract formed by the Foley catheter through the anterior abdominal wall. Following ligation of the vessel the patient's condition stabilised. No further rectal bleeding or discharge was recorded post-operatively.

Discussion: The management of pseudo-obstruction[1] is often conservative. Decompression can be accomplished by the passage of a sigmoidoscope and flatus tube, or colonoscopy. Benacci et al[2] conducted a review of patients at the Mayo clinic to determine the effectiveness of catheter tube caecostomy as a means of colonic decompression. They concluded that it was expeditious and safe, with acceptable morbidity in the majority of patients.

Gradual erosion of the right inferior epigastric artery by a caecostomy tube resulting in serious haemorrhage has not been previously documented. Computerised search of Medline and Pub Med databases did not reveal a single recorded case.

The inferior epigastric artery[3] originates from the external iliac artery just superior to the inguinal ligament, runs superiorly in the transversalis fascia, and enters the rectus sheath below the arcuate line, lying deep to the rectus abdominis. It forms the lateral boundary of Hesselbach's triangle, which is bounded inferiorly by the inguinal ligament and medially by the rectus abdominis. Ideally any catheter brought out through the anterior abdominal wall should be sited lateral to the Hesselbach's triangle, to prevent any deleterious effects to the inferior epigastric artery. In this case the Foley catheter used for the tube caecostomy had been impinging on the artery for nine days prior to eroding its wall. The resultant haemorrhage from the artery seems to have tracked down into the caecum, via the caecal-cutaneous fistula already formed by the catheter tube caecostomy. The haemorrhage, having gained access to the lumen of the large bowel, ultimately manifested as massive per rectal bleeding. Massive bleeds from a damaged inferior epigastric artery usually manifest as haematomas in the rectus abdominis muscle, but in this case the established caecal-cutaneous fistula appears to have diverted the blood into the caecal lumen.

Conclusion: This is the first documented case of severe haemorrhage associated with erosion of the right inferior epigastric artery by a tube caecostomy. Correct placement of the caecostomy tube lateral to Hesselbach's triangle should prevent this complication from occurring.

The Authors have no conflict of interest.

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Routine Rectal Biopsy?

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We describe a case of Non-Hodgkin's high grade B cell lymphoma of the rectum, which presented with a short history mimicking a perianal abscess. Careful examination under anaesthetic (EUA) and biopsies helped to clinch the diagnosis.

Case Report: A 76-year-old patient was admitted as an emergency with marked perianal pain for 1 week along with episodes of faecal incontinence during this period. The patient was being treated by the General Practitioner with antibiotics for suspected perianal infection.

On examination there was no induration around the anus but there was a point at which patient was maximally tender. The patient was examined by three senior clinicians, they all found different points of maximum tenderness. There was no obvious abscess. Investigations on admission including full blood picture, differential count, and inflammatory markers, were all within normal limits.

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The patient underwent EUA rectum; no abscess, fissure or fistula was found. Rigid sigmoidoscopy revealed diffuse non-specific redness of the rectal mucosa just beyond the dentate line. Random biopsies were taken. Post operatively the patient continued to experience severe pain and remained incontinent.

Pathology showed multiple fragments of rectal mucosa heavily infiltrated by a diffuse and sheeted proliferation of lymphoid cells with intermediate sized nuclei and little cytoplasm. The appearances were those of Non-Hodgkin's lymphoma - intermediate to high grade B-cell type. CT scan revealed significant soft tissue thickening of the anus extending into the proximal rectum. Maximum size measured 7cm. There was a suspicious lesion in the liver, which was confirmed to be lymphomatous on targeted ultrasound scan. There was no evidence of lymphadenopathy.

Due to liver involvement and infiltration around the anus the patient was started on chemotherapy (CHOP). The pain and incontinence all but disappeared after the first dose of chemotherapy and the tumour shrank significantly. Only slight thickening remained in the bowel wall at end of 2 years on repeat CT scan. The liver lesion remained unchanged. The patient remains well and asymptomatic after four years.

Discussion: Most cases of perianal pain are due to fissure in ano, perianal abscess, fistula in ano and low rectal or infiltrating carcinoma of the anal canal.

Lymphoma of the rectum is a rare condition and accounts for less than 1% of rectal malignancies. Involvement of the anal canal and the sphincters is even rarer.[1,2] Lymphoma of the rectum accounts for only 4% of GI lymphomas.[3] Primary colorectal lymphoma may present in a myriad of ways including perianal pain 9%, incontinence 2% or simply as an incidental finding 9%.[4]

This patient's perianal pain did not seem unusual at the beginning. The history of incontinence did raise the possibility of an infiltrating malignancy but the short one week history and the absence of any induration on examination led us to believe otherwise. The patient had no other constitutional symptoms to direct us towards the diagnosis of a malignancy or even abscess. The difference in the examination findings between different examiners and absence of an obvious cause such as fissure or abscess raised suspicions towards an unusual cause.

Conclusion: Careful EUA and random rectal biopsy may be indicated in all patients with acute perianal pain with no evidence of usual causes such as abscess, fissure and fistula.

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1. Perry PM, Cross RM, Morson BC. Primary malignant lymphoma of the rectum (22 cases). *Proc R Soc Med* 1972;**65(1):**72.

2. Devine RM, Beart RW, Wolff BG. Malignant lymphoma of the rectum. *Dis Colon Rectum* 1986;**29(12):**821-824.

3. Wychulis AR, Beahrs OH, Woolner LB. Malignant lymphoma of the colon. *Arch Surg* 1966;**93(2):**215-25.

4. Shepherd NA, Hall PA, Coates PJ, Levison DA. Primary malignant lymphoma of the colon and rectum. A histological and immunohistochemical analysis of 45 cases with clinicopathological correlations. *Histopathology*1988;**12(3):**235-52.

Peritoneal encapsulation: presenting as small bowel obstruction in an elderly woman.

Editor,

Small bowel obstruction is one of the common surgical emergencies. It is most often due to adhesions following previous operations or obstructed hernias. Peritoneal encapsulation is one of the very rare causes of intestinal obstruction, often diagnosed at laparotomy. This condition is largely asymptomatic and found incidentally at laparotomy or autopsy. Only a few cases have been reported in the literature and presentation as bowel obstruction is extremely rare. We report a case of peritoneal encapsulation presenting as a small bowel obstruction following herniation of the bowel loop through the sac in an elderly woman. Awareness of this condition will facilitate proper management.

Case report: An 82 yr old woman presented with three days history of lower abdominal pain, progressive abdominal distension and vomiting. She was previously investigated with barium enema for intermittent lower abdominal pain, which showed diverticular disease involving the sigmoid colon. There was no previous history of open abdominal operation, peritonitis or prolonged use of beta-blockers. Physical examination showed asymmetrical abdominal distension involving mainly right lower and mid abdomen. There was mild tenderness in the right iliac fossa with palpable bowel loops, and a reducible right femoral hernia. Abdominal X-ray showed a few dilated small bowel loops in the lower abdomen (fig 1). Inflammatory markers were mildly raised, otherwise blood investigations were unremarkable.

A provisional diagnosis of partial obstruction was made. She was treated conservatively overnight but symptoms gradually worsened. An obstructed femoral hernia was suspected and an emergency laparotomy performed. There was a shiny white peritoneal layer behind the peritoneum and bowel from the duodeno-jejunal flexure to the ileocaecal junction was found to be encased in a sac. A loop of terminal ileum was herniated through the sac with a tight constriction. The sac was excised with the release of the intestinal loop. Peritonitis developed post-operatively and at repeat laparotomy, small bowel loops were grossly distended throughout their length and were densely matted and adherent to the ischaemic terminal ileum loop and mesentery. A long segment of ileal loop was resected and a jejuno-colic anastomosis established, and a duodenal tear repaired. Postoperatively she developed pulmonary oedema, hypoproteinaemia, and hypoalbuminaemia and died from a chest infection. A post-mortem was not performed. Histology of the sac was not available but the morphological features were consistent with peritoneal encapsulation.

Discussion: Peritoneal encapsulation is a rare developmental abnormality in which part or the entire small bowel is encased in an accessory sac derived from the yolk sac. This is attached

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The patient underwent EUA rectum; no abscess, fissure or fistula was found. Rigid sigmoidoscopy revealed diffuse non-specific redness of the rectal mucosa just beyond the dentate line. Random biopsies were taken. Post operatively the patient continued to experience severe pain and remained incontinent.

Pathology showed multiple fragments of rectal mucosa heavily infiltrated by a diffuse and sheeted proliferation of lymphoid cells with intermediate sized nuclei and little cytoplasm. The appearances were those of Non-Hodgkin's lymphoma - intermediate to high grade B-cell type. CT scan revealed significant soft tissue thickening of the anus extending into the proximal rectum. Maximum size measured 7cm. There was a suspicious lesion in the liver, which was confirmed to be lymphomatous on targeted ultrasound scan. There was no evidence of lymphadenopathy.

Due to liver involvement and infiltration around the anus the patient was started on chemotherapy (CHOP). The pain and incontinence all but disappeared after the first dose of chemotherapy and the tumour shrank significantly. Only slight thickening remained in the bowel wall at end of 2 years on repeat CT scan. The liver lesion remained unchanged. The patient remains well and asymptomatic after four years.

Discussion: Most cases of perianal pain are due to fissure in ano, perianal abscess, fistula in ano and low rectal or infiltrating carcinoma of the anal canal.

Lymphoma of the rectum is a rare condition and accounts for less than 1% of rectal malignancies. Involvement of the anal canal and the sphincters is even rarer.[1,2] Lymphoma of the rectum accounts for only 4% of GI lymphomas.[3] Primary colorectal lymphoma may present in a myriad of ways including perianal pain 9%, incontinence 2% or simply as an incidental finding 9%.[4]

This patient's perianal pain did not seem unusual at the beginning. The history of incontinence did raise the possibility of an infiltrating malignancy but the short one week history and the absence of any induration on examination led us to believe otherwise. The patient had no other constitutional symptoms to direct us towards the diagnosis of a malignancy or even abscess. The difference in the examination findings between different examiners and absence of an obvious cause such as fissure or abscess raised suspicions towards an unusual cause.

Conclusion: Careful EUA and random rectal biopsy may be indicated in all patients with acute perianal pain with no evidence of usual causes such as abscess, fissure and fistula.

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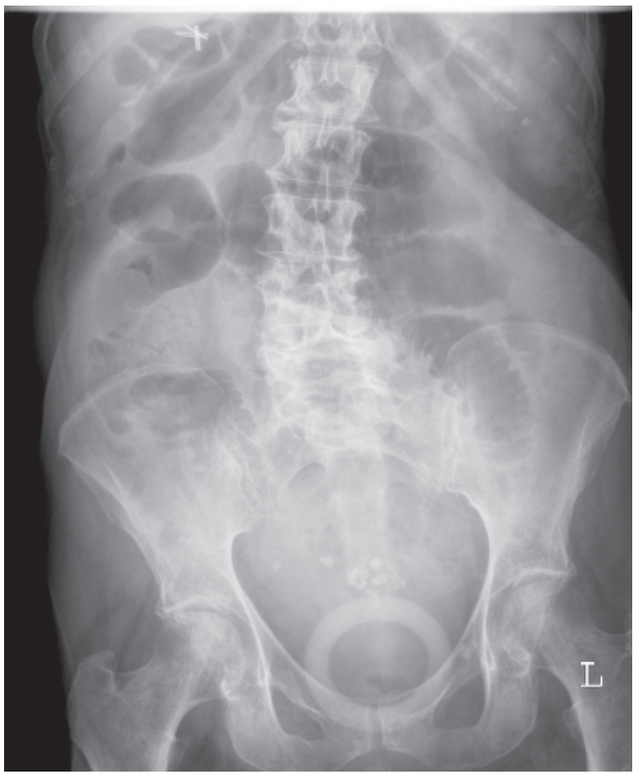

Preoperative abdominal X-ray showing dilated small bowel loops

to the ascending and descending colon laterally, the transverse mesocolon superiorly and merges with posterior parietal peritoneum inferiorly. The membrane has two openings, one around the duodenal-jejunal flexure and the other at the ileocaecal junction. Greater omentum covers the sac but is not attached to it. It was first described by Cleland in 1868. Less than 20 cases have been reported and the diagnosis was made incidentally in most of these[1]. The condition is largely asymptomatic, but some cases have presented as bowel obstruction[1].

Diagnosis may be impossible preoperatively. Naraynsingh[2] described two clinical signs, which help in diagnosis; a fixed, asymmetrical distension of the abdomen, which does not vary with peristaltic activity and a difference in the consistency of the abdominal wall to palpation. Both these findings can also be present in abdominal cocoon (Idiopathic sclerosing encapsulating peritonitis - SEP). Plain radiography in peritoneal encapsulation is usually normal or can show features of obstruction. Computed tomography may visualise the membrane. The membrane is not adhered to the inner bowel loops. When encountered during the exploration for bowel obstruction, it can be removed and excised easily.

Peritoneal encapsulation, Idiopathic SEP (abdominal cocoon) and SEP of known cause are different rare pathological conditions. Cases have been reported with features of abdominal cocoon as peritoneal encapsulation.[3] Tsunoda[4] described a case of idiopathic SEP combined with peritoneal encapsulation proposing a congenital theory for abdominal cocoon; a chronic inflammatory process of "developmental peritoneal encapsulation" which looks like a cocoon. The consistent siting of the lesion with invariable involvement of the ileocaecal junction also supports the idea of developmental abnormality in abdominal cocoon [5].

Foo[6] reported 10 cases of small bowel obstruction in young girls who had an obstruction due to a membrane covering the small intestine, which they described as "Abdominal Cocoon". The fibrous membrane showed signs of chronic inflammation and it was postulated that the condition is due to the retrograde menstruation with sub clinical viral primary peritonitis, resulting in the development of an encapsulating membrane on the intestine. Since then it has been described in all age groups and genders. It is not restricted to the tropics or subtropics.

Abdominal cocoon (Idiopathic SEP) is thought to be an acquired condition of unknown aetiology. It usually presents as bowel obstruction either by extra luminal compression by a constricting band or by torsion of the bowel. Development of sclerosing encapsulating peritonitis has also been reported from various known causes. Cases of small bowel obstruction due to sclerosing encapsulating peritonitis in patients on long-term proctolol have been described as early as 1974.[7, 8] It was a well recognized complication of proctolol and it is no longer in use. Other common causes include peritoneal dialysis and peritoneo-venous shunting. It is reported rarely in patients with tuberculosis, sarcoidosis, familial Mediterranean fever, gastro intestinal malignancy, protein-S deficiency, after liver transplantation, fibrogenic foreign material and latinised thecomas.

Various imaging findings have been described for abdominal cocoon, including delayed bowel transit, peritoneal and bowel calcification, bowel wall thickness, loculated ascites and circumscribed mass of bowel loops conglomerated in one area[9] (cauliflower sign). A thick fibrinous membrane surrounding the bowel loops can be visualised by CT scan while it also gives information on the degree of obstruction and the types of bowel loops involved[10]. In peritoneal encapsulation the membrane is free from underlying bowel loops and the histology of the sac is predominantly mesothelial with or without chronic inflammation or fibrosis[1]. A thick fibrocollaginous membrane encasing the bowel loops along with some internal adhesions characterises the sac in the abdominal cocoon. At times it may be difficult to peel it off or excise it without perforating the bowel.

The diagnosis is intra-operative in majority of cases and excision of the sac with enterolysis is all that is required. Bowel resection may be necessary if the membrane cannot be stripped atraumatically or with obvious gangrene of the bowel. Recently there have been reports of SEP secondary to chronic peritoneal dialysis treated successfully with immunosuppressive therapy and tamoxifen[9]. Both peritoneal encapsulation and idiopathic SEP are rarely documented and poorly understood surgical problems. A better awareness of these conditions will facilitate the proper management if encountered as an emergency. Distinction between these two entities is still not clear and needs further study.

The authors have no conflict of interest

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Committee on Publication Ethics (COPE) – Seminar 2007

9.30am–4.30pm Friday 16 March 2007, BMA House, London, UK

The theme of this year's seminar is "How can editors and publishers encourage ethical behaviour and transparency?", with the emphasis very much on prevention. Invited speakers will discuss authorship problems, plagiarism and image manipulation. The new features of the COPE website will be demonstrated with interactive workshops on common ethical and editorial dilemmas.

Editors, authors and all those interested in improving the standard of publication ethics are welcome.

The seminar will include:
- A publisher's perspective from Chris Graf of Blackwell Publishing Ltd
- Ana Marusic (Croatian Medical Journal) will discuss how form design affects authorship declarations
- What's in a picture? The temptation of image manipulation
- Recent developments in plagiarism detection software
- COPE's new website features – including COPE's new flow charts
- Interactive workshops on duplicate publication, authorship disputes, fabrication of data, plagiarism and unethical research.
- Opportunities to network with other editors and share your experiences and challenges

The seminar is free for COPE members and £30.00 for non-members. Numbers are limited and early booking is advisable. For registration or more information please contact the COPE Secretary at cope@bmjgroup.com or call 020 7383 6602.

For more information on COPE see www.publicationethics.org.uk

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Ulster Med J 2007; **76 (1)** 45

Interview

The new Chief Medical Officer for Northern Ireland

Claire T Lundy

Dr Michael McBride

Dr Michael McBride is the new Chief Medical Officer (CMO) for Northern Ireland. A graduate of Queens University Belfast Medical School, he also trained in St Mary's at Imperial College London. His specialist interest in HIV/AIDS suggested early on in his career that he was not afraid of working in a challenging and ever changing field. I met with him to discuss his vision of the NHS in Northern Ireland.

CL: Did you find it a struggle leaving clinical medicine behind?

CMO: Over the past number of years I have taken on a number of management roles. I took the opportunity to attend management work shops and courses that challenged my own views. I soon realised that aspects of management could actually make a difference to the medical well-being of individual patients. I was appointed a Consultant in 1994, and became Postgraduate Tutor in the Royal Group of Hospitals Trust in Belfast, for the next five years. In 2002 I was then appointed as their Medical Director. Clinical work provided me with experiences that informed my practice as a senior manager and enabled me to provide appropriate challenge to the profession. Some of the more difficult aspects of the job however included having to take responsibility for failings in the system and explain to families when things had unfortunately gone wrong.

CL: Who do you feel has been your key mentor in your career to date?

CMO: I must say that the best mentors I have had have been my patients. In all my roles throughout my career, I have always sought to remember the patient at my elbow and what they would want. I have certainly learnt from them – they are quite often so well informed and the 'experts' on their condition. We can all learn from their courage, determination and commitment.

CL: Do you think you are well prepared for your new role as Chief Medical Officer?

CMO: I am in post at a time when we are redefining how we provide the health service in Northern Ireland. I have been privileged to work in both clinical medicine and management – a good mix for the role of CMO. Both hats have enabled me to provide a well-rounded contribution to the development of health care policy. Policy decisions within the Department of Health will and do impact on the level of care that professionals can provide to their patients. As CMO, my medical background will enable me to bring a professional point of view to that table, whilst always having that patient at my elbow. My managerial background can then look to how that policy can be rolled out in practice. As professionals we must be involved in such policy discussions. We must contribute to decisions that will ultimately affect that way in which we deliver our service. We should collectively contribute to and drive change.

CL: What support team do you have in the Department of Health?

CMO: I am fortunate to have an extremely dedicated staff. I must emphasise just how passionate they are about their responsibilities. I used to think I worked hard until I started this job!

The team is a combination of administrative civil servants, doctors and public professionals. The specialist advisory committees are an important source of information and debate. The make up of these may change in the course of the review of public administration. At the present time we are working hard to maintain networks of communication with frontline professionals but also establish new links. We all work for the one system, so must work together. I also think it is important to ensure that there is an appreciation of the respective roles and challenges within the service – this could possibly be facilitated through an exchange of staff. The service could identify possible gaps in the system to inform policy. This co-operation and shared ownership could make for a more streamlined service.

CL: What do you see as the major issues in healthcare in Northern Ireland?

CMO: I think we need to engage effectively with partners' right across Government to address the many health inequalities that still exist. There are major differences between more affluent and less affluent communities in relation to issues such as smoking, obesity and mental health. In many less affluent parts of Northern Ireland, for example, a man's life expectancy will be seven years less than elsewhere. We know that lifestyle factors such as smoking are only part of the reason for this. There are wider issues such as deprivation, access to facilities and unemployment that need to be tackled. For example, the Fit Futures report recommends that we address the challenge of obesity by providing more opportunities for children and families to be physically active and by enabling them to be able to easily access affordable, healthy and nutritious food. Initiatives such as Fit Futures seek to redress the socio-economic imbalance that contributes to health disadvantage. We need to find ways to empower individuals from less well-off communities so they feel they have **real** choices.

This is a crucial time for health in Northern Ireland. The recent review of public administration (RPA) is providing us with an opportunity to drive forward further improvements in health service frameworks and quality standards.

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Ulster Med J 2007; **76 (1)** 46-47

Abstracts

Junior Members Forum, Thursday 23 November 2006

Ulster Medical Society Rooms, Whitla Medical Building, Belfast

PROGRAMME

8.00pm Introduction – Prof Dennis Johnston, UMS Junior Vice President

8.10pm Dr Ben Glover. Low tilt biphasic waveform studies

8.30pm Dr Gareth Lewis. Kidney slit diaphragm genes in type 1 diabetes.

8.50pm Dr Chris Lockhart. Waveform Analysis in Diabetes

9.10pm Discussion

9.30pm Tea and Close

The use of a low tilt biphasic waveform lowers the defibrillation threshold for the internal cardioversion of atrial fibrillation

BM Glover[1,2], CJ McCann[1,2], MJ Moore[1,2], SJ Walsh[1,2], G Manoharan[1], MJ Roberts[1], JD Allen[2], AAJ Adgey[1].

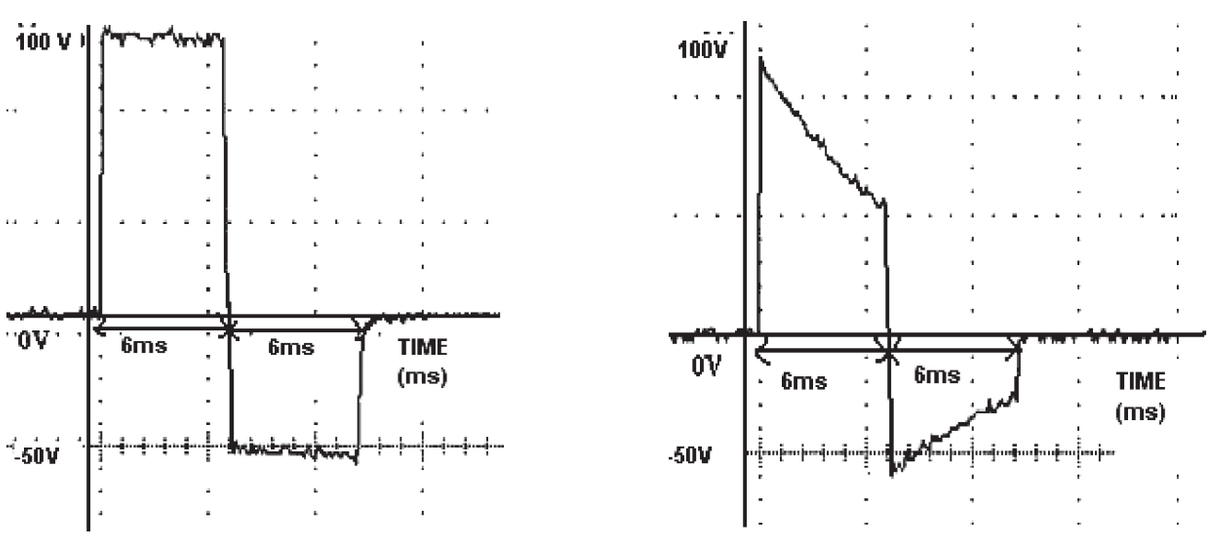
Regional Medical Cardiology Centre[1], Royal Victoria Hospital, Belfast, Queens University[2], Belfast.

Purpose: Conventional defibrillators used for the internal cardioversion of atrial fibrillation (AF) employ high tilt waveforms generated by a capacitor based discharge. We have developed a biphasic waveform with low tilt. This was compared with a conventional waveform of equivalent duration (6/6ms) and voltage.

Methods: Patients were randomised to receive either the low tilt waveform or a conventional waveform. Defibrillation electrodes were positioned in the right atrial appendage and distal coronary sinus. Peak voltage was increased in a stepwise progression from 50V to 300V. Shock success was defined as return of sinus rhythm for ≥ 30 seconds.

Results: The low tilt waveform resulted in successful termination of persistent AF in 10 of 13 cases (77%) at a mean voltage of 223V versus the conventional waveform in 2 of 12 cases (17%) at a mean voltage of 270V (p = 0.002). In patients with induced AF the mean voltage for the low tilt waveform was 90V and for the conventional waveform was 158V (p=0.005).

Conclusions: The low tilt biphasic waveform was more successful for the internal cardioversion of both persistent and induced AF. This waveform could be useful for the termination of both persistent and induced AF during ablation procedures in order to restore sinus rhythm at a low voltage.



The novel low tilt biphasic waveform (left) versus a conventional tilted biphasic waveform (right)

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Association of common gene polymorphisms in kidney slit diaphragm genes with nephropathy in type 1 diabetes.

G Lewis[1], DA Savage[1], CC Patterson[2], AP Maxwell[1].

[1]Nephrology Research Group, Queen's University Belfast, Belfast, Northern Ireland. [2]Department of Epidemiology and Public Health, Queen's University Belfast, Belfast, Northern Ireland.

Objective: Integrity of the kidney slit diaphragm (SD) is essential for proper glomerular filtration. DNA sequence mutations in genes encoding the protein components of the SD can cause severe proteinuria. It is hypothesised that common DNA polymorphisms within SD genes may predispose to the development of proteinuric renal disease such as diabetic nephropathy (DN).

Methods: The genes NPHS2, CD2AP, NPHS1, Kirrel2, ACTN4, NEPH1 and TJP1 were screened by denaturing high-performance liquid chromatography for DNA polymorphisms in 15 DN cases and 15 type 1 diabetic controls without nephropathy. All coding and regulatory regions were examined and the population frequency of the detected variants characterised in 48 healthy controls. Haplotype-tagging single nucleotide polymorphisms (htSNPs) were deduced for each gene utilising the variants occurring at 5% frequency.

Results: A total of 128 polymorphisms were detected. Thirty htSNPs and six potentially functional variants were genotyped in a case-control association study (cases=223, controls=366). All patients were Caucasians with type 1 diabetes diagnosed before 31 years. Cases had persistent proteinuria +/- renal failure, developing after at least 10 years duration of diabetes. Controls had a minimum duration of diabetes of 15 years, were not receiving any anti-hypertensive therapy and had no evidence of microalbuminuria on repeated testing. Allele and genotype frequencies for all polymorphisms, in addition to the haplotype distributions in each gene, were compared between cases and controls. Three variants and haplotypes in NPHS1, Kirrel2 and ACTN4, all located within a 3 Mb region on 19q13, were associated with DN ($P<0.05$).

Conclusions: Common variation in the SD genes studied may account for a component of the inherited predisposition to DN. Replication of these results in a separate population is necessary to confirm whether or not a susceptibility region for DN exists on 19q13.

Waveform Analysis in Diabetes - A marker for Cardiovascular Risk Stratification

CJ Lockhart[1]; PK Hamilton[1], C Quinn[1], C Agnew[2], RC McGivern[2], GE McVeigh[1].

[1]Department of Therapeutics and Pharmacology. School of Medicine. Queens University Belfast.

[2]Medical Physics Agency, Royal Victoria Hospital, Belfast.

Objectives of Research: Characteristic changes in the arterial pressure pulse contour accompany risk factors for and disease states associated with an increase in cardiovascular events. Such changes in waveform morphology, recorded by invasive and non-invasive techniques in large arteries, indirectly implicate altered structure and function in microvascular beds as the primary sites for vascular adaptations associated with ageing and disease. Dysfunction of the vascular endothelium is a hallmark of most conditions that are associated with atherosclerosis, and plays a pivotal role in the pathogenesis of atherosclerosis and its complications.

The over-arching aims of this study are:

1. To determine if quantitative analysis of velocity flow waveforms, recorded from the brachial artery, can identify and track local changes in vascular tone in response to nitric oxide modulation. We postulate that altered brachial flow waveform morphology in response to NO modulation, is apparent before a change in the arterial diameter can be detected. Furthermore, a sensitive non-invasive marker capable of detecting changes in NO bioavailability, and thus endothelial function, could have major therapeutic importance in the clinical setting.

2. To show that quantitative analysis of Doppler flow velocity waveforms, recorded in the ocular circulation, can sensitively detect and track local changes in micro vascular haemodynamics of type I diabetics; and in particular, to relate such waveforms to changes in geometry and tone of the microvasculature i.e. mapping of the retinal arteriolar circulation, in response to inhaled oxygen and carbon dioxide.

Methods: Characterisation of Doppler flow velocity waveforms by identification of the systolic and diastolic excursions of flow (or pulsatility) during the cardiac cycle have been employed to estimate vascular resistance of the microvascular networks, downstream to the measurement site. In our department we have shown that time-domain and frequency-domain analysis of Doppler flow waveform morphology recorded in the ophthalmic and central retinal artery clearly discriminates between patients with type 2 diabetes mellitus and age-and-sex matched control subjects. Analysis of waveforms recorded from the carotid artery in these patients did not discriminate between the 2 groups. Waveform analysis also sensitively detected and tracked the haemodynamic effects of the administration of donors and inhibitors of nitric oxide in the ocular microcirculation. The development of more advanced waveform analysis techniques is currently underway.

Conclusions and future work: These preliminary data suggest the ability to directly evaluate and monitor the status of specific microcirculatory beds of interest rather than inferring general changes in the microcirculation from pulse waveforms recorded from large muscular and elastic conduit arteries, identifies structural and functional abnormalities in specific target organs. If endothelial dysfunction (ED) is indeed the substrate for the development and progression of arteriosclerosis, the ability to detect ED and to monitor sub clinical vascular disease holds potential to further refine cardiovascular risk stratification and preventive therapy.

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Ulster Med J 2007; **76 (1)** 48-50

Abstracts

76th Meeting of the Ulster Society of Internal Medicine, Friday 20th October 2006

The Mater Hospital Trust, Belfast

PROGRAMME:

2.00pm Welcome - Chairman: Dr David Higginson
2.00pm Spoken Presentations I
3.10pm Invited Abstract: Cardio-Renal-Anaemia: Prevalent and treatable. Dr Damian Fogarty, Senior Lecturer and Consultant Nephrologist, Belfast City Hospital Trust.
3.40pm Afternoon Tea
4.10pm Spoken Presentations II
4.35pm Invited case from The Mater Hospital Trust
4.50pm Presentation of prize for best abstract
5.00pm Close

PRESENTED ABSTRACTS

Aquagenic wrinkling of the palms in adult patients with cystic fibrosis.

JP Tolland[1], KE McKenna[1], JS Elborn[2]

1 Department of Dermatology, Belfast City Hospital, Belfast.

2 Department of Respiratory Medicine, Belfast City Hospital, Belfast.

Aquagenic Wrinkling of the Palms (AWP) is characterised by the development of oedematous white plaques on the hands following exposure to water. To date 30 cases of AWP have been reported, 17 of which are in patients with cystic fibrosis (CF)[1]. Only two cases have been reported in males[1,2]. We have identified 45 patients out of a cohort of 102 adult CF patients who describe AWP. 24 cases are male and 21 female. 25 patients give a very good history of wrinkling of the hands when immersed in water, 13 give an average history and formal testing has been carried out in 7 patients with positive results. In most patients the whole of the hand is affected and not just the finger tips. Eight patients state that the reaction is painful. Eight of the patients report desquamation, especially at the finger tips, shortly after the hands are out of water. A similar reaction involving the feet is also described by seven patients. Fourteen describe mild to moderate hyperhidrosis of the hands. We tested seven patients by placing one hand in warm tap water; the other hand was used as comparison. After 15 minutes of immersion AWP was demonstrated in all cases. The whole of the hand appeared white in colour, oedematous and excessively wrinkled.

Conclusion: we present the clinical features of this interesting phenomenon and postulate that the incidence of AWP is likely to be much higher than the small numbers reported in the literature to date.

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Mortality following Percutaneous Endoscopic Gastrostomy: results of the National Confidential Enquiry into Patient Outcome and Death

SD Johnston[1], TCK Tham[2], M Mason[3]. Belfast City Hospital[1], Ulster Hospital Dundonald, Belfast[2] and the NCEPOD[3].

Background: Percutaneous endoscopic gastrostomy (PEG) is an accepted method of placing a feeding tube to enable enteral feeding in patients with swallowing difficulties. However the factors associated with morbidity and mortality following PEG have not been studied in detail. We describe the largest audit of mortality following PEG tube insertion.

Methods: Deaths occurring within 30 days following PEG tube insertion in the United Kingdom between April 2002 and March 2003 were identified and a questionnaire sent to the consultant endoscopist for completion.

Results: 719 patients (391 male, median age 80 yrs.; range 26-98 yrs.) who died within 30 days following PEG insertion were identified. 97% of patients had co-existent neurological disease. PEG tubes were inserted by specialised GI physicians in 522 cases (73%). Seventy-two patients (10%) required reversal agents following sedation. Following PEG tube insertion 309 patients (43%) died within one week. Death was due to cardiovascular disease (n=175), respiratory disease (n=508), central nervous system disease (n=358), renal disease (n=38) and hepatic failure (n=11). In 136 cases (19%) the NCEPOD expert panel regarded the procedure as futile.

Conclusions: Mortality and morbidity following PEG tube insertion is not insignificant. Selection of patients is paramount to good patient outcomes. Multi-disciplinary team assessment should be performed on all patients being referred for PEG tube insertion. Attention to pre-procedural baseline

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investigations may also reduce morbidity and mortality.

Elevated troponin levels in acute stroke are negatively associated with outcome at 3 months.

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Introduction: It has been suggested that raised troponin levels are associated with unfavourable outcome after acute stroke. The aim of this study was to determine the prevalence of raised troponin T levels (TnT) in a prospective cohort of patients with acute stroke and examine the relationship between TnT and outcome at 3 months.

Methods: Patients with acute stroke were assessed (including National Institutes of Health Stroke Scale, NIHSS) and had TnT measured within 72h. Outcome at 3 months was assessed using modified Rankin scale (mRs). Comparisons between troponin positive and negative groups were made using either students t-test, mann whitney u, or chi-square depending on the characteristics of each variable.

Results: 132 patients were recruited. 3 month follow-up data is currently available on 98. Elevated TnT levels were present in 14 (10.6%). Patients with raised TnT were older (mean [SD] age, 79.2 [8.68] v 72.0 [11.89], p=0.013) and had more severe strokes (median [range] NIHSS 8.5[1-19] v 4[0-25], p=0.04). At 3 months, mRs was significantly higher in the TnT positive group (median [range] 6[1-6] v 1[0-6], p=0.01), as was mortality (50% v 12%, p<0.001). In multivariate analysis, raised TnT (r= 0.27 p=0.01), age (r=0.20, p= 0.01) and NIHSS (r=0.55, p= <0.001) were independently associated with 3 month mRs.

Conclusions: In this prospective study, raised TnT levels were present in 1 in 10 acute stroke patients and were negatively associated with outcome at 3 months. Further studies are required to determine the causes of poor outcome in troponin positive patients.

Contemporory management of acute coronary syndromes: insights from the Mater hospital cardiology database

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Background: Management of acute coronary syndrome (ACS) has changed significantly in recent years. Current guidelines advise early inpatient coronary angiography for many patients. We reviewed the Mater Hospital cardiology database to determine the impact of these guidelines on the management of our patient population and the hospital outcomes in these patients.

Method and Results: Data for all patients admitted to the Mater Hospital, Cardiology Unit with ACS is entered into a database. This was analysed for the period April 2005 to September 2006. Of 598 patients with acute coronary syndrome, 100 (17%) had ST elevation myocardial infarction (STEMI), 133 (22%) had NON-STEMI and 365 (61%) had unstable angina (USA). Seventy-four of 100 (74%) STEMI patients received thrombolytic agents. Sixty of 100 (60%) STEMI patients had coronary angiography (CA) pre-discharge which resulted in revascularisation in 43 (43%), 35 percutaneous coronary intervention (PCI), 8 Coronary artery Bypass surgery (CABG). Fifty-eight of 133 (43%) NON-STEMI patients had CA which resulted in revascularisation in 34 (26%) (26 PCI, 8 CABG). Eighty-seven of 365 (24%) USA patients underwent CA followed by revascularisation 42 (12%) (34 PCI AND 8 CABG). Only 7 of 100 (7%) STEMI patients and 9/133 (8%) NON-STEMI patients underwent exercise treadmill testing prior to discharge. Rates of prescription of evidence-based secondary prevention medications for the whole study population were: aspirin 502/598 (84%), clopidogrel 434/598 (73%), beta-blocker 454/598 (76%), ACE-inhibitor or angiotensin receptor blocker 421/598 (71%) and statin 521/598 (87%). In-hospital mortality rates were 10/100 (10%) for STEMI, 3/133 (2.3%) for NSTEMI and 3/365 (0.8%) for USA patients. The mean (median) length of hospitalisation in days was 13.2 (6) for STEMI, 12.6 (6) for NSTEMI and 6.4 (3.5) for unstable angina.

Conclusions: In contemporary N. Ireland practice, mortality for unselected patients with STEMI remains significant. A large proportion of ACS patients, and particularly those with STEMI and NON-STEMI, have inpatient coronary angiography and subsequent revascularisation procedures. Consequently, few STEMI and NON-STEMI patients currently undergo exercise treadmill testing. The duration of hospitalisation for acute MI probably reflects delays before CA and revascularisation procedures can be performed.

Pseudo-hyperkalaemia and aetiology of thrombocytosis: a six-year retrospective correlation study

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Pseudohyperkalaemia is a rarely encountered event among patients with thrombocytosis. Typically, a raised serum potassium level is observed in the absence of renal failure, and it causes unnecessary anxiety among clinicians. Pseudohyperkalemia may lead to inappropriate administration of calcium resornium, insulin in 5% dextrose in an attempt to lower potassium level. The association between pseudohyperkalaemia and aetiology of thrombocytosis is unclear.

A six-year retrospective audit was conducted on 90 patients with thrombocytosis referred to the Haematology Department in Ulster Hospital Dundonald, a large district general hospital. Over two thirds of this study population had myeloproliferative disorders, and the most common diagnosis was primary thrombocythaemia (39%, n=35). In contrast, reactive thrombocytosis was observed in approximately one third of the cases (31%, n=28).

Pseudohyperkalaemia with apparent potassium level above the upper limit of the normal range (K>5 mmol/l) was observed in the majority of patients with thrombocytosis from any aetiology (66.6%, n=60). The likelihood of finding pseudohyperkalaemia was highest among patients with primary thrombocythaemia (91.4%, n=32/35), followed by polythaemia rubra vera (56%, n=9/16), and reactive

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thrombocytosis (32%, n=9/28). A significant positive correlation was observed between the platelet counts and the serum potassium level (Spearman's correlation coefficient, R=0.28, p=0.01).

The falsely raised potassium level is due to the release of intracellular potassium from platelets during clot formation in the specimen bottle (serum sample). This is a time- dependent phenomenon; the use of plasma sample in either Li-heparin or Na-heparin bottles will circumvent this phenomenon.

Systematic review: blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia

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Hypertension and cognitive impairment are prevalent in older people. Hypertension is a known risk factor for vascular dementia (VaD) and recent studies suggest hypertension impacts upon prevalence of Alzheimer's Disease (AD). The aim of this Cochrane review was to determine if treatment of hypertension lowers the rate of cognitive decline and dementia in patients without known cerebrovascular disease.

Trials included in the systematic review were randomized, double-blind, placebo-controlled trails, in which interventions to lower blood pressure (BP) were administered for ≥ 6 months to hypertensive patients. The Cochrane Dementia and Cognitive Impairment Group Specialized Register was searched from 1966-2005 to identify suitable trials. Primary outcomes were incidence of dementia and cognitive change from baseline.

Three trials were identified with 12,091 hypertensive subjects (SHEP 1991, Syst-Eur 1997 and SCOPE 2003). Analysis was performed on the combined results of all three trials.

Results of incidence of dementia outcome: There was a trend towards a significant benefit of treatment (O.R. 0.89, 95% CI 0.69, 1.16). Only Syst-Eur reached significance with results indicating a benefit.

Results of cognitive change from baseline outcome: No significant benefit from treatment (WMD=0.10, 95% CI -0.03, 0.23).

Conclusion: there was no convincing evidence that BP lowering prevents dementia or cognitive impairment in hypertensive patients without prior cerebrovascular disease. There were problems analysing the data, however, due to heterogeneity across trials, number of placebo patients given active treatment and loss to follow-up. Further placebo-controlled trails would be necessary but this raises ethical issues.

An unusual cause of abnormal thyroid function tests

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Abnormal thyroid function test results frequently pose diagnostic challenges. We report a 23 year old female who presented with fatigue. Free T_4 was 28.9pmol/L (7.6-19.7) and TSH 2.06mU/L (0.45-4.5). She had no other symptoms or signs of hyperthyroidism and on examination was clinically euthyroid with no obvious goitre. Interfering antibodies were excluded, sex hormone binding globulin (SHBG) was not elevated (18nmol/L [25-90]) and α-glycoprotein subunit was normal (<0.3IU/L). Following TRH stimulation (Protirelin 200μg), TSH rose appropriately from 1.59mU/L at baseline to 21.1mU/L at 20 minutes. The pituitary was normal on CT imaging.

Sequencing of the thyroid hormone receptor (TR) β gene, on chromosome 3, revealed a point mutation at position 460 with substitution of the normal glutamic acid by lysine (E460K), thus confirming the diagnosis of resistance to thyroid hormone (RTH). Her father and sister were found to share both the biochemical phenotype and the genetic defect, while her brother did not. Free T_4 index (6.0-10.5) and TSH (0.4-3.6mU/L), respectively, were as follows; father, 16.7 and 2.5; sister, 15.8 and 2.9; brother, 9.5 and 4.4. Affected subject also had high serum levels of T_3 and reverse T_3.

RTH is a condition of impaired tissue responsiveness to thyroid hormone. The more common forms are caused by TRβ gene mutations and inherited in a dominant fashion. Of the 170 different TRβ mutations, E460K has been identified in three other families. This mutation reduces the affinity of TRβ for T_3 to 25% that of the normal receptor. RTH should be considered in patients presenting with elevated FT_4 and unsuppressed TSH. Its identification prevents unnecessary investigation and inappropriate treatment in the patient and in other affected family members.

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Abstracts

9th Meeting of the Irish Society of Human Genetics, Thursday 7th September 2006

Trinity College, Dublin

PROGRAMME:

10.00 - 11.00	Registration / Tea and coffee
11.00 – 11.01	Welcome
11.01 – 12.00	Spoken presentations - Plenary I
12.00 – 13.00	**Keynote address:** Dr Alan Irvine - "Genetic skin barrier defects in atopy"
13.00 – 14.00	Lunch + poster viewing
14.00 – 15.15	Spoken presentations - Plenary II
15.30 – 16.00	Tea / coffee & poster viewing
16.00 – 16.15	Business meeting
16.15 – 17.15	**Plenary address:** Prof Tim Spector - "Use of twins for gene discovery"
17.15 – 18.00	Wine Reception / Presentations / Meeting Close

ABSTRACTS

SPOKEN PAPERS:

S1. An approach to therapy for retinitis pigmentosa: siRNA-mediated suppression of IMDPH1

Lawrence Tam, Anna-Sophia Kiang, Avril Kennan, Pete Humphries.

Ocular Genetics Unit, Dept of Genetics, Smurfit Institute, Trinity College Dublin, Co. Dublin, Ireland.

Inosine monophosphate dehydrogenase I (IMPDH1) has been identified as the gene responsible for the RP10 form of autosomal dominant retinitis pigmentosa (adRP). Mutations within the IMPDH1 coding region have been associated with significant conformational changes in protein structure, resulting in the formation of aggregates with concomitant depletion of GTP. In contrast, IMPDH1$^{-/-}$ mice have shown a slower and milder form of retinal degeneration than that observed in human RP10 patients. These observations suggest that the disease pathology is not caused by haploinsufficiency of normal IMPDH1, but by a dominant negative phenotypic effect exerted by mutant protein. As a result, RP10 is a potential target for therapeutic intervention where simultaneous ablation of wild type and mutant IMPDH1 alleles by siRNA molecules may decrease the rate of photoreceptor degeneration to a similar extent to that observed in the IMPDH1$^{-/-}$ mouse model. In this study, we have identified two highly efficient siRNAs and have demonstrated very successful suppression of IMPDH1 transcripts at the mRNA and protein level in mammalian cell cultures and murine retinal explants. Our results indicate the potential of these siRNAs to form the basis of a worldwide therapy for the many patients harbouring mutations in the IMPDH1 gene.

S2. Novel Retinal Expression of Beaded Filament Structural Protein 2 Observed in the C57BL/6JOlaHsd Mouse.

Alison Reynolds, Avril Kennan, Paul F. Kenna, G. Jane Farrar Pete Humphries,

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The Bfsp2 gene (also called CP49) encodes an intermediate filament protein, whose expression to date has only been reported in the eye lens fibre cell. Some substrains of the 129 strain of inbred mouse carry a 6303bp deletion within the Bfsp2 gene, which includes the start of exon 2 and results in dramatically reduced expression levels, rendering these substrains functional knockouts. The only recorded phenotype of this functional knockout is a slow but progressive loss of optical clarity with age. During the analysis of a microarray study, performed to compare retinal gene expression levels in C57BL/6JOlaHsd and 129S2/SvHsd mice, it was noted that the expression of Bfsp2 mRNA was reduced in the 129S2/SvHsd strain. We have subsequently confirmed, by diagnostic PCR, that this substrain of 129 mice also carries the known 6303bp mutation in Bfsp2. Novel retinal expression of Bfsp2 mRNA was confirmed by real time rtPCR in the C57BL/6JOlaHsd. Histological analysis was carried out to verify the real time rtPCR findings and localise the retinal location of Bfsp2 mRNA expression. The results of *in situ* hybridisation in mouse retina localise Bfsp2 expression to the photoreceptor layer, possibly within the inner segments in the C57BL/6JOlaHsd retina. These results point to a previously unknown role for Bfsp2 within the retina.

S3. Hypoxia-inducible suicide gene therapy strategy for prostate cancer.

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2 Cancer Research UK Gene Therapy Group, Paterson Institute for Cancer Research, Manchester, UK.

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Exploiting tumour hypoxia represents a novel gene therapy approach for cancer. We have cloned hypoxia response elements (HREs) from oxygen-responsive genes including vascular endothelial growth factor (VEGF) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) upstream of the cytosine deaminase (CD) gene. Constructs drive expression of this prodrug activation enzyme, converting inactive 5-fluorocytosine (5-FC) to active 5-fluorouracil (5-FU), allowing selective killing of vector containing cells. Constructs were transfected into 2 prostate cancer cell lines (DU145, 22Rv1) and exposed to oxygen concentrations of 0.5% (pO2<2mmHg). Western blot analysis indicated detectable CD at 16h with a peak at 48 hours hypoxic exposure as well as 24h after a 3h-hypoxic exposure. No expression was observed in aerobic cells, confirming the specificity of the approach. Transfected cells exposed to hypoxia for a 48h period showed a decrease in cell number and associated cell death following a 5 days aerobic 5-FC treatment at the clinically relevant dose of 1mM, when compared to untransfected as well as transfected aerobic controls. These data suggest that targeting hypoxia using a gene therapy approach has demonstrated efficacy in selective killing of prostate cancer cells. Furthermore, cells exposed to 5-FC in hypoxia appear more sensitive to the treatment than aerobic cells.

S4. Association of the IL18 gene with celiac disease in the Irish population

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2 Dept. Medicine, University of Dublin, Trinity College,

3 National University of Ireland, Galway, Ireland.

IL18 is a proinflammatory cytokine which promotes development of the Th1 lymphocyte response. IL18 is known to play an important role in inflammatory, autoimmune and infectious diseases. The aim of this study was to investigate any genetic association between IL18 and celiac disease in the Irish population.

We genotyped 395 celiac disease patients and 354 controls for 4 SNPs within IL18. SNPs were chosen to allow a haplotype tagging approach based on previously defined haplotypes consisting of 27 SNPs as characterised in a European population. SNPs were also chosen based on potential effects on protein structure or expression. Haplotypes were constructed computationally and compared between groups.

Three SNPs in IL18 (IL18_S2-137_rs187238, IL18_S3_rs5744241 and IL18_S4-607rs1946518) showed a significant association with disease either at allele frequency, genotype frequency or carrier status level prior to correction for multiple testing. IL18-137 was significantly associated with disease at the genotype level (p=0.0380). IL18_S3 was significantly associated with disease when allele frequencies (p=0.0385) and carrier status (G allele; p=0.0490) were examined. IL18_S4-607 also showed a significant association at the allele frequency level (p=0.0100), the genotype level (p=0.0265), and at the allele carrier status level. (G allele; p=0.0159). Total gene haplotype analysis was carried out using all four tSNPs. A significant association was observed for haplotype rs1946518T, rs187238G, rs2043055A, rs5744241A (p=0.0379). Analysis of the IL18 promoter SNPs (S4-607 and S2-137), which have been associated with altered IL18 expression, revealed a significant association for two promoter haplotypes (haplotype -607 G, -137 G) (p=0.0153), (haplotype -607 T, -137 G) (p = 0.0053).

In this study, we have shown that IL18 is significantly associated with disease status at the level of haplotype and functional SNP allele and genotype distribution suggesting that IL18 is involved in the pathogenesis of celiac disease.

S5. An Interesting Fragile X Family

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We describe a Fragile X family manifesting an interesting FMR1 inheritance pattern. Patient A presented with global developmental delay, speech problems and dysmorphic features not typical of Fragile X. His cousin had classic Fragile X showing a full FRAXA FMR1 expansion mutation. Patient A was found to have a 38 (CGG_n) repeat FMR1 allele. Somatic mosaicism was excluded by Southern blot analysis. Patient A's mother, grandmother and maternal aunt all have expansions in the premutation range and an unusual X inactivation pattern was detected. The size of the CGG_{38} repeat allele was confirmed by sequencing which also revealed a pure CGG tract with no AGG interruptions. This was suggestive of a regression mutation from a larger expansion. Alternative mutations around the promoter / CGG repeat region were also excluded by this analysis. Immunohistocytochemistry analysis showed FMRP was detectable in 94% of Patient A's lymphocytes, however the level of functional FMRP was not measured by this technique. Presented with these results we reported Patient A "as unlikely to be affected with Fragile X-A". Subtelomeric MLPA analysis is underway for Patient A. Microsatellite and $(CGG)_n$ repeat analysis of the FRAXA region is ongoing to trace the inheritance of the unstable FMR1 allele.

S6. Update on the complex CF mutation spectrum in the Republic of Ireland

C King,[1,2] T McDevitt,[1,2] M Rogers,[1,2] B O'hIci ,[1,2] S McQuaid,[1,2] C Le Maréchal, [3] C Férec, [3] DE Barton[1,2]

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The incidence of CF in Ireland is 1/1461.[1] The National Centre for Medical Genetics has provided a cystic fibrosis (CF) genetic testing service since its inception in 1995, using an ARMS method designed to detect the 11 most common mutations in the Irish Republic (sensitivity of 93%). A total of 3,243 patients with clinically diagnosed, classical CF or with symptoms suggestive of CF, have been tested to date. The ARMS test has provided a confirmatory genotype in

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768 of these patients (approximately 24%). A cohort of 129 probable CF patients, with one or no mutation identified by the ARMS method, were selected for comprehensive mutation screening. Small gene alterations were screened for by DGGE and dHPLC and confirmed by sequencing. QMPSF was used to identify large genomic rearrangements. This additional analysis has so far resulted in the identification of a second CFTR gene alteration in 59/129 patients, and the identification of both CFTR gene alterations in 2/129 patients. A total of nine patients have not had any mutation identified. Four novel point mutations and one *de novo* (2623-2A>G) mutation have been identified as well as two multi-exon deletions involving exons 2-4 and exons 14-15. We present details of these findings and assess their contribution to the CF mutation spectrum of the population of the Republic of Ireland. [1]Cashman *et al.* The Irish Cystic Fibrosis Database. *J Med Genet* 1995;**32:**972-975.

S7. The *MTHFR* 1298CC and 677TT genotypes have opposite associations with red cell folate levels

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Individuals homozygous for the thermolabile variant (677TT) of methylenetetrahydrofolate reductase (MTHFR) exhibit reduced folate status as evidenced by a drop in the biomarker red cell folate (RCF) compared to those who carry at least one 677C allele. The 677TT genotype is reported to protect against colon cancer when folate intake is high. We now report that a different polymorphism in the same enzyme, namely 1298A>C is associated with increased RCF levels.

Many previous studies of the 1298A>C polymorphism have been confounded by the fact that it is in linkage disequilibrium with the 677C>T variant. Our study eliminated this problem by focusing on a large number of subjects with the 1298A>C polymorphism all of whom were 677CC (wildtype) homozygotes. We studied 508 subjects, determined their genotypes at *MTHFR* positions 677 and 1298 and measured levels of plasma and red cell folate and homocysteine. Consistent with previous studies, the 49 677TT individuals had reduced RCF levels (P= 0.0001) compared to 677CC wildtype individuals (n= 231). However, among the 231 677CC wildtype individuals, the 41 1298CC homozygotes had significantly higher RCF levels compared to 1298AA (P= 0.0016). Thus, these two common polymorphisms change a metabolic phenotype in opposite directions.

Our results suggest that future studies into the relationships between MTHFR and disease should take these phenotypes into account. The association of the 1298CC genotype on RCF indicates that the reported protective role of this variant in cancer risk is by a mechanism that is different to the 677TT genotype.

S8. Examining Extracellular Domains Identifies New Candidate Genes Subject to Positive Selection in Humans and Chimpanzees.

Lilian PL Lau , Daniel G Bradley, David J Lynn.

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Genome-wide analyses of positive selection in the human genome have recently become possible with the availability of the chimpanzee genome and offer the chance to identify those genes that were of most importance during our evolution. A number of studies have investigated signatures of adaptive evolution in our genome but have uncovered relatively few cases of positive selection acting on protein coding genes. By examining a particular domain, the extracellular region, where selection is likely very prevalent due to the functions of these regions in antigen and ligand binding and pathogen interactions, we aim to identify additional candidate genes that may have been missed in previous analyses. A mouse outgroup is used, where possible, in the comparisons of human and chimpanzee extracellular encoding regions, to provide directionality to the signal of selection. 592 genes were identified with $d_N/d_S > 1$ in the extracellular domain on the lineage leading to humans. In pairwise comparisons, we have identified a dataset of more than 1,100 genes with $d_N/d_S > 1$ in this region, approximately 65% more than have been previously identified. From both these datasets we identify a set of 28 genes with roles in immunity, olfaction, neuronal development and metabolism that have robust statistical support for positive selection and discuss the potential selective forces that may be driving adaptive evolution in them.

S9. Allele frequency spectra in disease populations

AW Ryan, V Mattiangeli, DW Morris, JS Daly, D Kelleher, R McManus.

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The Ewens-Watterson (EW) test compares the within-population distribution of alleles at a locus to a theoretical distribution. If allele frequencies show a preponderance of one or a few alleles and a number of much rarer variants, directional natural selection may be inferred. This effect may be mimicked in disease population samples, where risk associated alleles may be over-represented. In order to evaluate this effect, we have analysed data from two association studies, one case-control sample with a known coeliac disease association, and a second sample of family trios with reading disability association, using a modified EW test, to account for the step-wise mutation model of microsatellite loci. Both datasets show evidence of significant allele frequency distortion at the disease associated locus in populations of affected individuals. Furthermore, there is some indication that the test may be sensitive to parent of

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origin effects. The test may, therefore, provide additional information, particularly in Transmission Disequilibrium Test studies, which consider transmission by heterozygous parents, and thus disregard some of the available data. Furthermore, the test may provide insight in situations where more than one allele at a locus is associated with disease, as the entire allele frequency spectrum is considered.

S10. SuperAIMs: Detecting Intra-Continental Population Stratification

Brian McEvoy[1] Mark D Shriver[2] Daniel G Bradley[1]

1 Smurfit Institute of Genetics, Trinity College, Dublin 2, Ireland,

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Stratification occurs in human populations when individuals within a group have varying degrees of ancestry from different sources. Knowledge of this is important in case/control association studies where a mismatch in the ancestry of the two cohorts can cause spurious false positve association between a gene and a phenotype. It can also be useful for identification of genes through admixture mapping and exploring population origin and history. Stratification is detected using genome markers whose alleles show large frequency differences between populations and consequently are informative as to ancestry. These are termed Ancestry Informative Markers (AIMs) and are well described for the differentiation of continental level ancestry. However, as diversity is less within continents, intra-continental AIMs are more difficult to identify and are rarer. We have examined up to 3.45 million SNPs typed in three populations of the HapMap project (Europe, Africa, Asia) and in a Native American cohort for population specifc F_{ST} branch lengths. Those showing exceptionally high divergence in one of these continental groups were then typed in 1052 individuals from 51 global popualtions in the Human Genome Diverstiy Panel to identify those that also show intra-continental variation. These may act as 'superAIMS' able to distinguish regional continental ancesty.

POSTER PRESENTATIONS:

P1. Towards Tissue Specific RNA interference – A Study of Novel RNAi Delivery Vectors Designed to Achieve Suppression Using a Polymerase II Transcribed Single Transcript

Danny Allen, Paul F Kenna, Pete Humphries, G Jane Farrar.

Human Molecular Genetics, Trinity College Dublin, Ireland.

RNA interference (RNAi) is a post-transcriptional, sequence-specific gene-silencing technology that utilises double stranded (dsRNA) molecules to degrade messenger RNA containing homologous sequence. A significant body of research has been undertaken in the field of suppression (utilising RNAi) *in cellulo* and *in vivo*, however the majority of these studies have utilised synthetic siRNAs or polymerase III promoter-driven shRNAs which are ubiquitously expressed. The aim of this study was to create and evaluate a polymerase II system that could be used to achieve long term expression of functional siRNAs. This approach combines PolII promoters with cis-acting hammerhead ribozymes. Potent siRNA molecules do not tolerate many over-hanging bases 5' or 3' of the double stranded region of the molecule, the cis-acting hammerhead ribozymes in the designs act to remove the extra overhanging bases created by PolII promoters. In summary, the designs produced functional siRNA and suppressed the target reporter gene (eGFP) both *in cellulo* and *in vivo*. As the promoter used in this study (CMV) is a PolII promoter, it can potentially be substituted with any PolII promoter including a range of tissue specific promoters. The benefit of an RNAi system which can potentially use any promoter type is the ability to maintain a level of control superior to traditional methods. Additionally, an increased type-1 interferon response is a risk associated with any novel siRNA delivery method; however, these constructs did not elicit a significant type-1 interferon response compared to traditional H1 transcribed shRNA.

P2. Mutation analysis of KCNQ1, KCNH2, KCNE1 and SCN1B genes in genome of patients with LQT syndrome

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LQT syndrome is a cardiovascular disorder characterized by an abnormality in cardiac repolarization leading to a prolonged QT interval on the surface ECG. There is a significant risk of syncope, *torsade de pointes* and sudden death. Inherited long QT syndrome was first clearly described in 1957. There are two variants, the autosomal dominant Romano-Ward type and the autosomal recessive Jervell and Lange-Nielsen type. Genes mutated in patients with LQT syndrome encode ion channels. Long QT is associated with two cardiac muscle ion channels: voltage-gated K^+ channels (KvLQT1-KCNQ1 gene, minK-KCNE1 gene, HERG-KCNH2 gene, MiRP1 subunit) and voltage-gated Na^+ channels (SCN1B).

The objective of this study is to identify the underlying genetic basis of patients with LQT syndrome anamnesis. In this group of patients we have identified 19 nucleotide exchanges with probable pathological influence, 14 nucleotide polymorphisms and IVSs and two amino acids polymorphisms in genes KCNQ1 (11p15.5), KCNH2 (7q35-q36) and KCNE1 (21q22). This basic set of three LQT genes has been extended about next candidate gene-SCN1B (19q13.1) gene. The mutation analysis was performed using methods multiplex-PCR, multiplex-SSCP (single strand conformation polymorphism) as the screen method, and automated sequencing. This work was supported by grants IGA MZ ČR NA 7424-3 and NR/8063-3.

P3. Polymorphisms within the Regulatory Region of the Human *MTHFD1* Gene

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The human *MTHFD1* gene encodes a trifunctional cytoplasmic enzyme involved in folate metabolism and plays an important role in the biosynthesis of DNA. A polymorphism, R653Q, within MTHFD1 has previously been identified as a maternal risk factor for the development of neural tube defects (NTDs), abruptio placentae and unexplained mid-trimester miscarriage in the Irish population (Brody *et al.,* 2002; Parle-McDermott *et al.,* 2005(a); Parle-McDermott *et al*., 2005(b)). This indicates that MTHFD1 plays an important role in normal development and, therefore, expression and regulation of the *MTHFD1* gene will be critical for the developing embryo. We sought to identify polymorphisms within the *MTHFD1* gene that influence transcriptional regulation.

We previously determined that the transcriptional initiation window of *MTHFD1* mRNA occurs between -150 and -30. SNP rs1076991 occurs within this initiation window and, therefore, is a good candidate to influence gene expression. We performed luciferase reporter gene assays to investigate the possibility that this polymorphism influences transcriptional regulation of the *MTHFD1* gene. These assays were performed using cloned fragments of the *MTHFD1* promoter (from position -600 to -6) that contained either the 'C' or the 'T' allele. The results from three separate experiments (each experiment was performed in triplicate on two consecutive days) revealed that the mean transcriptional activity of the 'T' allele is 43.3±20.9% that of the activity of the 'C' allele. This suggests that this polymorphism may have a direct functional affect on expression of the *MTHFD1* gene.

P4. Comparing Y chromosome haplogroup frequencies and surnames of Norse and Irish origins in men in Northern Ireland

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The paternally-inherited Y chromosome is widely used for studies of population diversity and human migrations. Studies have found that that nearly 90% of the Y chromosomes in Irish populations derive from haplogroup (HG) R1b3. By contrast, modern Norwegians have roughly equal proportions of HG R1b3, R1a1 and I1a. We have used this difference to examine the Viking contribution to the genetics of males in Northern Ireland (NI). Ten Single Nucleotide Polymorphisms (SNPs) were tested in 244 men from Northern Ireland. Additionally, a subset of 157 of these individuals were typed for 17 Short Tandem Repeats (STRs). Surnames were divided into four groups according to origin: Irish (n= 74), Norse (n=94), Scottish (n=34) and English/Norman (n=42). At the HG level, although the Scottish and English/Norman populations were distinct from the Norse and Irish names, the Norse and Irish showed no differentiation. Preliminary analysis of the STR variation shows little differentiation within samples in the R1b HG. Of the 21 Northern Irish samples in HG I, seven were found to be in HG I1a. All seven of these were surnames of English, Scottish or Norman origin. It appears even the minimal Viking contribution to the modern NI population likely derives from Scotland or England, rather than directly from Norway.

P5. Does Noggin cause twinning?

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We report monozygotic twin boys of a spontaneously conceived triplet pregnancy with facio-audio-symphalangism (FAS) syndrome. Their non-identical triplet brother is unaffected. In addition, to the typical dysmorphic facial features of FAS they also had hypermetropia and conductive deafness due to congenital stapes ankylosis.

In 1994 Lynch *et al* reported monozygotic twin boys of a spontaneously conceived triplet pregnancy with caudal appendage, short terminal phalanges, conductive deafness, cryptorchidism and mental retardation[1]. These boys had the typical facial appearance of facio-audio-symphalangism. Their unaffected triplet sister was not affected. It is highly probable that both these sets of monozygous twins have a Noggin mutation.

Spontaneously conceived triplet pregnancies occur in about 1 in 6500 births in the Republic of Ireland[2-4] and 1 in 8000 in the UK[5]. Noggin mutations occur in approximately 1 in 10000 births. Given the unlikely probability of FAS recurring in monoygotic twin boys from a triplet pregnancy we propose that this suggests that a Noggin mutation may predispose to twinning.

There is embryological evidence for this. In 1903, Hans Spemann divided a cleaving amphibian embryo into two halves. The dorsal half developed into a perfectly well-proportioned half-sized embryo containing both dorsal and ventral tissues. The ventral half developed into a "bauchstuck" (belly piece). It is now known that the dorsal centre or Spemann organizer is a source of secreted BMP antagonists (such as Noggin, Chordin, Follistatin and Cerberus)[6]. Mutations in Noggin could therefore theoretically predispose to twinning. Our cases add evidence to this theory. We have reviewed pedigrees of families with likely Noggin mutations and have not found an excess of twins. However, it may be that the presence of the non-identical triplet influenced the twinning process or that a certain mutation type is more prone to twinning than others. Mutational analysis on both families is pending.

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6: Regulation of ADMP and BMP2/4/7 at opposite Embryonic poles generates a self-regulating morphogenetic field. *Cell* 2005;**123:**1147-1160.

P6. Exploration Of Information Seeking Processes And Behaviours By The Parents Of Newly Referred Patients To The Northern Ireland Regional Genetics Service.

Janice Kee

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The main aim of this study was to explore the information seeking behaviours of the parents of patients who were referred to the Northern Ireland Regional Genetics Services. This exploratory study analysed themes relating to the resources parents use for information and the motivations for information seeking. The analysis revealed that healthcare professionals are the primary source of information and further information seeking depends on this interaction. Uncertainty, reassurance and responsibility were identified as the main factors contributing to health information seeking during a genetics referral. It also emerged that the need for information and the motivation for seeking information was influenced by the how long the patient had had the diagnosis and how well they were adapting and accepting the diagnosis.

Several points reported in this study are relevant to clinical practice. It is important for genetic counsellors to remain aware of patient's expectations and address information needs at an appointment. The importance of informing patients about what the genetics service can offer prior to the clinic was highlighted. The value in writing to patents after the appointment with information that was given at the appointment was also demonstrated.

P7. An Audit of Genotypes and Borderline Sweat Tests in Irish CF Patients

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The sweat test (ST) is seen as the gold standard diagnostic test for cystic fibrosis (CF). Borderline STs (i.e. 40-60 mmol/L) present particular difficulties, not only in the clinical diagnosis of a patient, but also in terms of genetic counselling. Borderline results are seen in 4% of STs; 23% of these patients will subsequently be found to have two CFTR mutations, one of which is usually "mild." We investigated CFTR mutations in 105 patients with borderline STs referred to the NCMG from 1995 to 2005. If not originally provided, ST levels were sought retrospectively. ST levels were obtained for 77/105 (73%) of referrals. 43% (33/77) of referrals with "borderline" STs actually had normal ST levels according to accepted reference ranges. None of the referrals with normal STs had two CFTR mutations. 45% of referrals (35/77) were confirmed to have borderline ST levels. Of these, 77% (27/35) had no mutation, 14% (5/35) had one classic mutation and 9% (3/35) had 2 mutations (one classic + one mild). 12% (9/77) had ST levels in the diagnostic range. The high proportion of referred "borderline" STs that actually had normal levels indicates a problem with interpretation or use of ST guidelines by clinicians. The implications for genetic testing services are: (1) data audit is required in order to maintain testing and reporting standards (2) ST levels should be sought if not provided with a query CF referral (3) a ST should be performed before comprehensive mutation screening.

P8. Association of Methylenetetrahydrofolate reductase (MTHFR) polymorphism and the risk of Squamous Cell Carcinoma in renal transplant patients.

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The relative risk of developing cutaneous squamous cell carcinoma (SCC) is significantly increased following organ transplantation.

Objective: We investigated genetic association with SCC in two pathways associated with cancer risks, with potential for modification by vitamin supplementation.

Measurements: 401 renal transplant recipients (117 with SCC and 250 without any skin cancer) were genotyped for key polymorphisms in the folate pathway (MTHFR:C677T; methylene tetrahydrofolate reductase), and the vitamin D pathway (VDR: Intron8G/T; vitamin D receptor).

Results: Individuals carrying the MTHFR 677T allele had a marked increase in risk of SCC (adjusted OR= 2.54, p=0.002, after adjustment for age, sex, skin type, sun exposure score and immunosuppression duration; lower 95% confidence boundary OR of 1.41). In contrast, VDR polymorphisms were not significantly associated.

Conclusion: Folate-sensitive pathways may play a critical role in the elevated rate of SCC in renal transplant recipients. Further studies are required to assess the impact of high levels of folate supplementation on the incidence of SCC in transplanted and nontransplanted populations.

P9. Dicentric Chromosome 15 Syndrome

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Introduction: Dic (15) syndrome is associated with developmental delay, learning difficulty, epilepsy, autism, and facial dysmorphism. Prader Willi/Angelman Critical Region (PWACR) was postulated to be responsible for the phenotype of dic (15) syndrome.

Methods: We reviewed records for 14 patients with extra structurally abnormal chromosome (ESAC) 15.

Results: 13 patients had 47,+der(15) karyotype; 1 patient with an unidentified heterochromatic segment was excluded. Six patients had involvement of the PWACR region; 4 of these had dic (15) syndrome; 1 result was on amniocentesis and the pregnancy terminated; 1 adult was diagnosed on cytogenetic investigation for recurrent miscarriages. 7 individuals were PWACR negative; 4 probands had cytogenetic analysis for concerns regarding their developmental and/or mild

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dysmorphic features, however all 4 patients were later felt to be clinically normal on follow-up. All 7 patients did not have features of dic (15) syndrome.

Discussion: Some of the patients were seen in early 1990s, Involvement of PWACR had been assumed, based on G-banding. We believe that FISH using SNRPN/UBE3A probes for PWACR is today's gold standard. The PWACR negative group did not have features of dic (15) syndrome; therefore we conclude that involvement of the PWACR region is responsible for phenotype of dic (15) syndrome.

P10. Two Cases of AML with 8p11 rearrangements and different clinical presentations

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8p11 rearrangements involving the MOZ gene in AML are rare. The most common translocation being the t(8;16) but variant rearrangements have been reported. The majority of cases are associated with haemophagocytosis. Some smaller studies have suggested that these abnormalities are associated with a poor prognosis, however, it was grouped as intermediate prognosis in the UK AML 10 cytogenetic classification, 1998. We report 2 cases of AML with different 8p11 rearrangements with the characteristic haemophagocytosis, but with very different clinical presentations. The first case is a 51 year old man who presented with DLBCL but relapsed after one year with DLBCL and AML, cytogenetic analysis at relapse showed an apparently balanced t(8;16) translocation and an add(9p). The Second patient is a 61 year old man who presented with M5 AML and an unbalanced t(8;22) translocation.

P11. A third case of a t(1;21) translocation involving AML1 in treatment related leukaemia.

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AML1 gene rearrangements have been reported extensively in the literature. In particular the t(8;21) with ETO/AML1 Fusion in M2 AML, the t(12;21) with TEL/AML1 fusion in pre B cell ALL and the t(3;21) with EVU1/AML1 fusion in blast crisis CML and treatment related AML or MDS with prior therapy with a topoisomerase II inhibitor. However, the AML1 gene at 21q22 similar to the MLL gene at 11q23 is a promiscuous gene with at least 30 partner chromosomes identified in the literature. Rare and novel AML1 rearrangements have also been reported in a number of cases with prior exposure to radiation or topoisomerase 11 inhibitors. Two cases of a t(1;21)(p36;q21) translocation involving PRDM16/AML1 gene fusion have been previously reported, one with prior exposure to radiation and one after treatment with a topoisomerase II inhibitor. Here we report a third case of a t(1;21) translocation in a patient with therapy related AML following treatment for AML four years previously. None of the drugs used were topoisomerase 11 inhibitors.

P12. Northern Irish pedigrees with familial phaechromocytoma / paraganglioma syndrome, demonstrate clinical heterogeneity and variable penetrance in addition to a founder mutation

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Paragangliomas and phaeochromocytomas are benign, highly vascularized, slow growing tumours derived from the neural crest. Inherited predisposition to the development of these tumours may occur as a result of several cancer predisposition syndromes, including von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2 and the recently described familial phaeochromocytoma paraganglioma syndrome. This rare condition is caused by mutations in genes encoding 3 of the subunits of mitochondrial complex II, succinate dehydrogenase, SDHB, SDHC and SDHD. SDHD mutations show maternal genetic imprinting, higher frequency of head and neck tumours and increased risk of tumour development at higher altitudes.

Previous reports of SDHD founder mutations have not involved UK populations. We now present data involving five apparently unrelated Northern Irish families with an identical mutation in SDHD (P81L). These families exhibit considerable clinical variability in terms of tumours present in the known heterozygotes. The families also exhibit variable penetrance, with an age range of 16-60 years in the probands and 30-87 years in non penetrant heterozygotes. This is further highlighted by an age penetrance range of 40-68 years in siblings of one pedigree. In light of this apparent founder effect, the implications for genetic testing in this rare condition will be discussed.

P13. Two patients with different deletions of 1q and a similar phenotype.

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We present two cases with deletions of chromosome 1q44. Case 1 was referred for genetic assessment at age 17m, with failure to thrive, developmental delay, seizures and normal karyotype. She was hypotonic, with brachycephaly, hypertelorism, clinodactyly, wide-spaced nipples and small puffy feet. At age 5y she was hypermetropic, had prominent lower lip pads, widely spaced uneven teeth and severe developmental delay. MLPA indicated a deletion of the 1q telomere region, confirmed by subtelomere FISH to be a terminal 1q deletion. Case 2 was referred at birth in 1993 with microcephaly, low set ears, pre-auricular tag, sloping forehead, prominent orbit, high arched palate, poor feeding, hypotonia and normal karyotype. At age 3y, brachycephaly, protuberant lower lip, wide-spaced teeth, puffy hands and feet, hypermetropia and cerebral palsy were noted. At age 12 he had severe developmental delay and repeat karyotyping identified 46,XY,del(1)(q43q44). MLPA and subtelomere FISH confirmed an interstitial deletion.

1q deletions are rare but have a recognised phenotype.

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Subtelomeric "pure" terminal deletions are extremely rare as these are usually complicated by partial trisomy for another chromosome. Our subtelomeric deletion is the 4th reported pure terminal deletion of 1q. These cases also illustrate the value of repeat chromosome analysis in cases of developmental delay and dysmorphism.

P14. Validation of a Luminex-Based Multiplex Assay for 25 Cystic Fibrosis Mutations

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New technologies for multiplex testing for single-nucleotide polymorphisms are finding applications in the diagnosis of genetic disorders. Plans for newborn screening for cystic fibrosis (CF) in Ireland and issues of sensitivity and efficiency with our current "home-brew" ARMS assay led us to look for a multiplexed CF assay which could be adapted to the mutation spectrum of the Irish population. We have an excellent knowledge of the Irish mutation spectrum, as all patients with mutations not detected by our ARMS assay are screened by DHPLC of the entire CFTR gene at the laboratory of Professor Claude Ferec in Brest, France.

Using Luminex™ Liquid Bead Array Platform (Applied Cytometry), we evaluated the Signature™ CF 2.0 ASR from Asuragen (formerly Ambion Biosciences) which tests for the 24 CF mutations included in the ACMG/ACOG CF panel .

We evaluated the assay on a variety of sample types (blood spot, buccal, CVS, amniocyte) and also on a large cohort of DNA extracted from peripheral blood samples (n=468) of known CFTR genotype, to examine the sensitivity and specificity of the assay. A total of 385 samples (82%) were genotyped correctly on initial analysis, while 18% failed to yield a genotype. Assay failures could usually be resolved by dilution of the sample such that the true number of samples that failed to yield a genotype and therefore required a rebleed was 7 (1.5%). No samples were genotyped incorrectly, indicating that the Signature™ CF 2.0 ASR is a sensitive and robust assay for CF diagnostics.

P15. Lujan syndrome: report of a possible case and consideration of diagnostic difficulties

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Lujan syndrome (also known as Lujan-Fryns syndrome) is an X-linked mental retardation syndrome, first described by Lujan in 1984 in four affected males. The patients, sons of three normal sisters, showed Marfanoid habitus, narrow face, high palate and hypernasal speech, in addition to other features. Further patients have been described over the years, some more convincing than others. The patient described here is an 18 year-old male with significant learning difficulties and epilepsy. He is the only child of non-consanguineous parents, and although his father has a brother with learning difficulties, this is not thought to be connected. He is tall and thin, with a long narrow face, high-arched palate, and markedly hypernasal voice. The thorax is narrow, and the legs and arms long. Fingers and toes are slender and hypermobile. Chromosome and Fragile X analyses were normal. This patient fits the proposed diagnostic criteria for Lujan syndrome, but it is readily apparent that there is a lack of "hard handles" to allow this diagnosis to be made with certainty, indeed to reliably differentiate Lujan syndrome from the many other causes of mental retardation in males.

P16. The angiotensin II type 2-receptor -1332G/A gene polymorphism and coronary artery disease in Ireland

Weihua Meng[1], Chris C Patterson[2], Christine Belton[1], Shafie Kamaruddin[3], Paul G Horan[3], Mark S Spence[3], Paul G McGlinchey[3], Pascal P McKeown[1,3].

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Introduction. Coronary heart disease (CHD) remains a leading cause of death worldwide. It is a complex disease resulting from interactions between multiple genetic and environmental factors. Recently, an X-linked angiotensin II type 2-receptor gene polymorphism (-1332G/A) was reported to be associated with premature CHD in a family-based study in the UK (Alfakih *et al, Eur Heart J*, 2005). We, therefore, undertook a similar approach to identify if there was an association between this polymorphism and premature CHD using an Irish family-based DNA resource.

Methods. A total of 1494 individuals from 580 families were included. Linkage disequilibrium between the polymorphism and disease status was tested using the X-linked reconstruction-combination transmission/disequilibrium test (XRC-TDT).

Results. Of the 580 families genotyped, 156 were informative. No significant association was found between this polymorphism and premature CHD in the Irish family-based collection, either in the whole study group (P=0.34) or when males (P=0.13) and females (P=0.45) were studied individually.

Conclusions. Using the XRC-TDT test, we have found no association between the X-linked angiotensin II type 2-receptor gene polymorphism (-1332G/A) and premature CHD in this Irish family-based study.

P17. Identification of tandem repeat variations using whole-genome shotgun sequences

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Tandem repeat sequence length polymorphisms have been implicated in a wide range of diseases and are also known to modulate the pathogenicity of a number of bacteria. This study describes a bioinformatics approach to detect repeat polymorphisms on a genome-wide scale. A set of 257,256 tandem repeats detected in the human genome sequence were searched against whole-genome shotgun sequences from the EnsEMBL trace archives. Results were validated using repeat polymorphisms from the CEPH genotype database, showing correlation between the heterozygosity measure of repeat

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variability with that inferred from the trace archive search (Spearman 0.172, p<0.0005). Statistics were gathered on the sequences of repeats and on sequences flanking these repeats. Statistical modelling confirmed the findings of previous reports on predictors of repeat variability but also revealed a number of novel predictors, such as a marked increase in variants with certain ranges of GC content. These finding give insight into the forces influencing repeat polymorphism and facilitate predictions of repeat polymorphisms from repeat and flanking sequence. They also enable the estimation of heterozygosity, which will be of use in genotyping studies, where a repeat can be excluded if the expected level of variability is likely to be too low to be detected.

P18. Candidate Gene Analysis of the 21q22 Bipolar Affective Disorder Susceptibility Locus

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A genome-wide scan for linkage in 60 bipolar disorder (BPAD) affected sib-pairs identified weak linkage of region 21q22 to BPAD (D21S1446, multipoint NPL=1.42, P=0.08, bipolar type I model). 21q22 is a highly replicated BPAD susceptibility locus. The location of the peak linkage marker, D21S1446, 12Kb upstream of S100B identified it as a candidate susceptibility gene. S100B is a calcium-binding, astrocytic protein that exhibits neurotrophic and neurodegenerative effects. Serum S100B protein levels are increased in schizophrenic and bipolar patients and a two marker haplotype is associated with susceptibility to schizophrenia.

We investigated whether variants within S100B are associated with BPAD in a collection of 125 Irish BPAD trios. SNPs located within the promoter (rs3788266: P=0.03) and 3' UTR (rs2839350: P=0.02) of S100B were associated with BPAD. The association increased in significance when restricted to families with psychotic traits, suggesting that S100B is a susceptibility factor for psychosis. The location of the associated variants within the promoter and 3' UTR suggests that they may directly affect expression of S100B. The results of the single- and multi-marker association tests will be presented in addition to association analyses of TRPM2, a 21q22 candidate gene previously associated with BPAD.

P19. The Use of the Gene Dossier in the UK

Fiona J Stewart (on behalf of the UK Genetic Testing Network)

One of the remits of the UKGTN is to ensure that tests being offered through the network have clinical utility. Other countries are now actively looking at methods of assessing the clinical utility of genetic tests. The method used by the UK is the assessment of Gene Dossiers. These are based on the ACCE framework and can be downloaded from the UKGTN website www.UKGTN.org.

One of the important principles is the Test-Disease-Population triad. Providers are asked to give details of the technical methodology, sensitivity and specificity. Information about the disease and, most importantly, how the test result will influence management of the individual and their family must also be provided. Details of the target population, a clear referral pathway and testing criteria should also be supplied.

The gene dossiers are assessed by the Gene Dossier Committee which is a multidisciplinary group and a decision is made on whether the dossier can be accepted.

We feel that this model enables decisions about particular genetics tests to be made in a timely, robust and transparent manner without the enormous resource implications of full scale health technology assessments.

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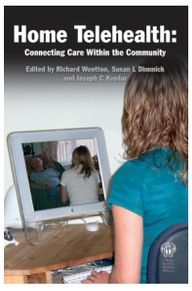
Book Reviews



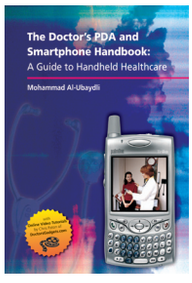
Home Telehealth: Connecting Care Within The Community. Eds Richard Wootton, Susan L Dimmick, Joseph C Kvedar. Royal Society of Medicine Press, London, April 2006.280pp. £29.95. ISBN 1-85315-657-4.

At first glance this book is a collection of chapters about a somewhat obscure subject with the usual balance between offerings of excellence and those with impenetrable prose. On closer inspection however this is a deeply subversive book which attempts to undermine the "twin towers" of healthcare in the industrialised world: that hospitals are veritable temples of healing and that community care provided by an increasing number of skilled doctors, nurses, social workers, occupational therapists, psychologists, dieticians, speech and language therapists, audiologists, physiotherapists, healthcare assistants and many, many others is a shining example of excellence. The book's editors are much too clever to state their subversive views explicitly, but they come through clearly in the book's content. There is for example a chapter which purports to show that patients actually like to be followed up at home using technology and even prefer it to being followed-up in hospital clinics or having regular visits by a nurse. Well how subversive is that?

However the real aim of this diabolical book comes in the next chapter entitled "Business models and return on investment". This claims that home telehealth is cheaper because it keeps people out of hospital. It even quotes an example from obstetrics in support of this notion. Are they saying that people having babies shouldn't all be admitted to hospital? Preposterous! No specialty or disease seems safe from the contributors' demonic rants: renal medicine, palliative care, asthma, congestive heart failure, AIDS, wound care and even cardiology are all identified as targets suitable for increased delivery of care at home using technology. Unbelievable! The jewel in the crown of these home telehealth fanatics is of course diabetes. So what, if by the year 2030 there are only two sorts of people in the UK – those with diabetes and those looking after them? So what if all the existing health real estate - hospitals, nursing homes, even Department of Health offices - will be needed to house this patient population? Surely this is better than some half-baked system where patients are encouraged to take more responsibility for their own condition, and have their disease monitored (and any adjustments in treatment made) remotely without the doctor or nurse even seeing them! They even suggest that the diabetes specialist can be thousands of miles away! How demented is that!

The final insult of this book is a chapter on "Quality of Care" (cunningly hidden between offerings on Home Dialysis and Diabetes). As doctors and health professionals, we all know that we all provide an extremely high quality service to all our patients. To suggest otherwise is nonsense and to state that factors such as *timeliness* and *patient-centeredness* should be used to assess quality is completely ludicrous. The only people who will wish to read this book are those pathetic individuals who think their existing service isn't completely perfect and are sufficiently broad-minded (weak?) to wish to look at other ways of doing things. Clearly that will leave many copies unsold and I hope that these will be publicly burnt.

Victor Patterson



The Doctor's PDA and Smartphone Handbook: Mohammad Al-Ubaydli, Chris Paton. Royal Society of Medicine Press Ltd, London, April 2006. 80pp. £12.95. ISBN 1-85315-686-8.

This is a potentially useful little book for anyone considering buying a handheld computer, personal digital assistant or smartphone. At £12.95 it is expensive for a pocket sized book of less than 80 pages with rather poor quality black and white illustrations and images. The book covers all that you would need to know in deciding which hardware best suits your needs, but could perhaps explore this important area in a little more detail in a single chapter – the information is scattered throughout the book.

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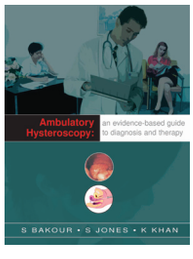

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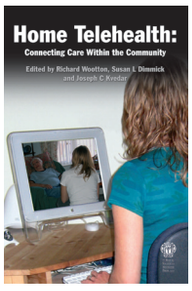

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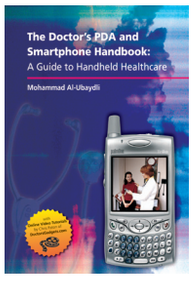

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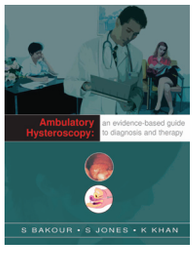

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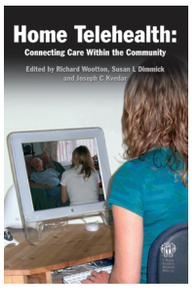

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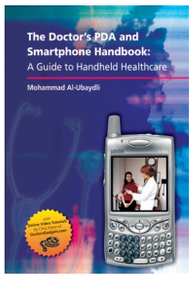

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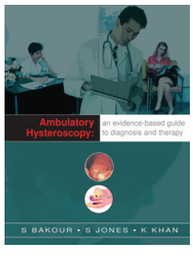

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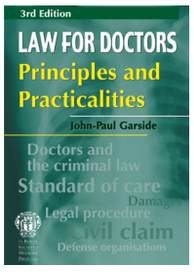

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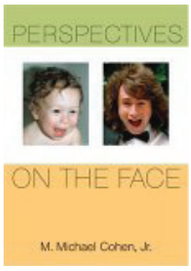

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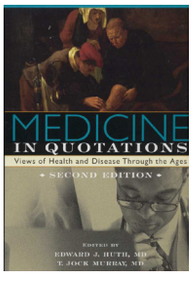

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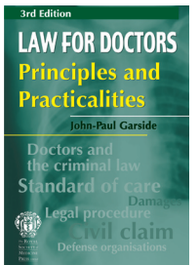

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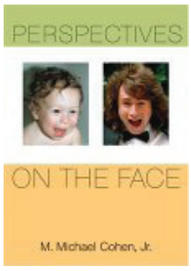

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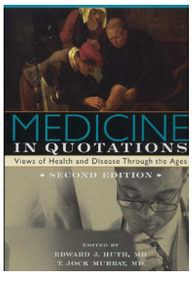

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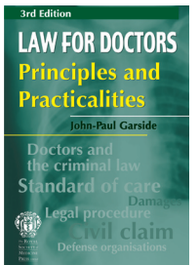

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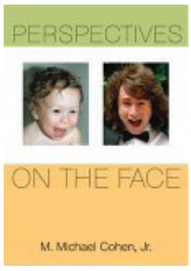

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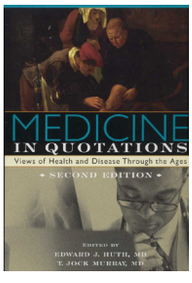

Medicine in Quotations: Views of Health and Disease Through the Ages. 2nd Edition. Eds Edward J Huth, T Jock Murray. American College of Physicians, Philadelphia, April 2006. 550pp £34.95. ISBN: 1-930513-67-4.

The second edition of Medicine in Quotations weighs 1.47 Kg and is 0.262 m high. With a BMI of 21.4 it might be regarded as a lightweight but the Book Mass Index is deceiving; the volume has been handsomely produced and there are rich pickings inside. The

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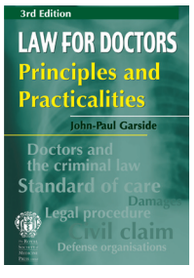
It remains the most commonly performed gynaecological procedure in the United Kingdom and is still normally carried out under general anaesthetic. There appears to be little reason why the majority can't be performed under local anaesthetic- the subject of this book. The three authors are well known and published in the field of hysteroscopic surgery. The book however has a highly practical side and contains a large number of colour photographs amongst its 141 pages.

The book is well written with chapters on how to set up an outpatient hysteroscopy service including advice on providing a business case for those interested in developing a service in their local hospital. Further chapters are provided on performing operative hysteroscopy under local anaesthetic, the accuracy of hysteroscopy using evidence based approach and risk management. In keeping with modern educational practice each chapter contains multiple-choice questions and a table of key points listed.

A personal quibble is that the book contains little information on the use of transvaginal ultrasonography to determine which women require a hysteroscopy. In conclusion, this book would be of great benefit to experienced clinicians aiming to set up a new ambulatory hysteroscopy service and to year three to five Specialist Registrars undergoing the RCOG special skills module in hysteroscopic surgery. The book is probably less relevant to trainees prior to the part II MRCOG examination.

Hans Nagar



Law for Doctors -Principles and Practicalities. John Paul Garside. 3rd Edition, The Royal Society of Medicine Press Ltd. London. June 2006. 94pp. £14.95. ISBN 1-85315-681-7.

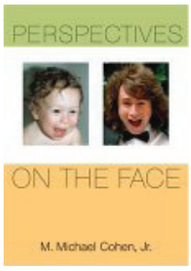
Law for Doctors is a small volume of just over ninety pages. However, encompassed within its ten short chapters is almost all the information required by today's doctors in dealing with medico-legal events, whether writing a medical report for legal procedures or taking on the role of expert medical witness. It is easy reading, and at the conclusion of each section references are cited and appropriate cases are listed for further study if required.

Probably all the sections are of equal value but the reviewer would highlight the following chapters:

"Principles of Negligence, Duty and Standard of Care", "Consent: Minors and the Mentally Incapacitated; Research; Training" and "Doctors and the Coroner's Court" as being particularly informative.

This book is a gem. It should be read by every doctor regardless of speciality. It also should be available in every hospital department and in all health centres. The reviewer wishes that it had been available twenty years ago!

Elizabeth E Mayne



Perspectives on the Face. M Michael Cohen Jr. Oxford University Press, Oxford, UK. March 2006. 288pp £43.00. ISBN 0-19-530040-8.

The first thing to say about this book is that I love the cover. It is such a great illustration of how our facial features, though changing with the passage of time, are a unique identifier of who we are. This cover should convince those who are sceptical of mothers' abilities to recognise their own child after separations of sometimes many years.

The book is very technical and gives a comprehensive overview of the development of the face and the various conditions caused when this process goes wrong. Although the 'blurb' inside the jacket mentions that it would be of interest to, amongst others, sociologists and art historians I suspect that its technical detail makes it of more interest to those involved in dealing with abnormalities of the face such as craniofacial surgeons, plastic surgeons, dentists and dysmorphologists. I am not sure that the detailed lists of the many genes expressed in craniofacial development will be of interest to non geneticists. I have to say I found the section on the evolutionary perspective quite hard going and felt more comfortable when we got on to the embryonic and developmental aspects. There are some nice descriptions and diagrams of genetic interactions and some very good 3D scan images.

Although there are bits in the sections on psychological, sociocultural and artistic perspectives that were of interest to me, they didn't seem to me to sit well next to the very technical sections on, for example, the surgical perspective. I almost had the feeling of there being two books with sections from each being interspersed.

Michael Cohen obviously has a wonderful memory for unusual facts and the book is peppered with these little gems. For me it was news to know that someone with typhoid fever is said to have a body odour akin to freshly baked brown bread and someone with typhus, one like a butcher's shop.

In summary there is a huge amount of information in this book, much of which is very interesting. However I am not sure that it entirely works as a coherent whole.

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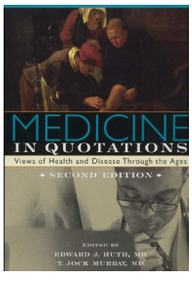

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The 3521 quotations have been grouped in perhaps 1000 topics arranged alphabetically from the "A" of *Abetalipoproteinemia* to the "Z" of *Zollinger-Ellison Syndrome*. Some topics are specific and contain only a single quotation, others such as *Patient-Physician Relations* contain many more. Within each topic the quotations are placed in order of date to allow a chronological overview of the topic's development. Confusingly, however, entries for one organ and its diseases may be distributed between a number of different topics with no direct cross-referencing between them; see, for example, *Hyperthyroidism*, *Hypothyroidism*, and *Thyroid Gland*. Some eponymous conditions such as *Colles Fracture*, *Kaposi Sarcoma*, and *Sjögren Syndrome* are listed under their eponym, while Wilson disease appears under *Hepatolenticular Degeneration (Wilson Disease)*. Some quotations (427 and 2190, and 1699 and 2447) are duplicates. The *Student BMJ* is quoted on the dust jacket as saying "One of few reference books that are worth reading from cover to cover" but perhaps this was written with tongue in cheek, and it is likely that readers will mostly browse the collection, either completely at random or concentrating on topics of interest. Those seeking a particular quotation could usefully first search the topic list but there are in addition an author-citation index and a subject index. The author-citation index is an alphabetical list of authors, each author's entry containing a list of citations for their quotations, each citation ending with the title of the topic in which the quotation appears and the quotation number. Curiously, the citations within each entry are listed alphabetically not by topic but by their first words. By and large this index seems to be satisfactory; if an author is known the quotation can be found although a large number of topics might need to be searched for oft quoted authors such as William Osler. The subject index may seem to be comprehensive but there are significant gaps. For example, "Kussmaul's breathing" cannot be found by searching for **Kussmaul**, **breathing**, **dyspnoea**, **diabetes mellitus**, **acidosis**, or **ketoacidosis**; and the quotation "There is no body cavity that cannot be reached with a #14 needle and a good strong arm" cannot be found by searching for **body**, **cavity**, **needle**, **aspiration**, or **arm**. (Both quotations, 727 and 2226 respectively, are traceable via the topics list under *Diabetes Mellitus* and *Needle Aspiration* or via the author-citation index under Kussmaul and Shem.) A quotation for what would now be called ankylosing spondylitis (2913) is to be found in the topic *Rheumatoid Spondylitis* but neither **ankylosing** nor **spondylitis** appear as headings in the subject index, and the only entry under **rheumatoid** is for the arthritis. The Oxford Dictionary of Quotations (revised fourth edition) has about four index entries to one quotation; the ratio for Medicine in Quotations is about two to one, indicating a lesser degree of cross-referencing. The claim on the back cover that the subject index is "exhaustive" seems optimistic.

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John I Logan

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AS Fitzpatrick, Marshall Riley

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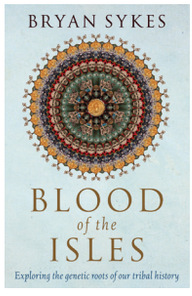

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In Sykes's first foray into the popularisation of this approach, he wrote "The Seven Daughters of Eve", a fascinating romp through the history of our maternal genetics. The reader will be familiar with the cellular role and characteristics of mitochondria, but their particular value to the genetic archaeologist lies in the property that they contain their own DNA (they are the evolutionary relics of once-free-living bacteria that engaged in a highly significant and successful alliance with the ancestors of all eukaryotic cells), and this DNA is exclusively maternally inherited. The logical upshot of this is that your mitochondrial DNA is inherited from your mother, who got it from her mother, and so on, right back through human history and prehistory - indeed back through our common ancestors with the other great apes, other primates, mammals, vertebrates, and to the very first proper eukaryotic cell itself. Although this is perhaps obvious, it is nonetheless an arresting thought, and one that clearly appeals to Sykes. Motherhood, right back to when we diverged from apple pie.

A similar principle (this time following the male line exclusively) applies to the Y chromosome, the scrappy little chunk of DNA that is really only responsible for conferring maleness to an embryo that would otherwise follow a female developmental trajectory. In "Adam's Curse", Sykes re-worked "Seven Daughters of Eve" for the boys, and identified five patriarchal "clans" to add to the seven matriarchal ones he had identified as contributing to the vast majority of extant Europeans.

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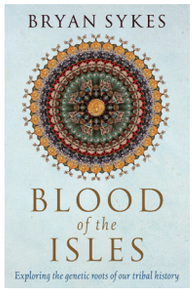

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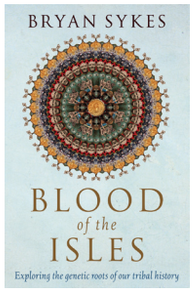
The book would be a beneficial addition to any medical ward either at the nurses' station or in the doctors' office. It offers a different perspective to most of the other pocket books on the market. However, it does not provide fundamental information critical to daily beside decision-making. We would recommend this book for consultation at ward level but not as an indispensable purchase for every junior doctor.

AS Fitzpatrick, Marshall Riley

The Blood of the Isles. Bryan Sykes. Bantam Press. September 2006. 400pp. £17.99 ISBN: 0-593056523



The human quest for our origins is as old as our species itself. It has spawned all sorts of crazy theories and legends, from the idyllic fantasies of the Garden of Eden and Noah's Ark, to the mythical Aryan racism that fuelled Nazi Germany and still persists in some quarters. The genetic history of Great Britain, Ireland, and nearby islands ("The Isles" of Professor Sykes's title) is itself associated with strong emotions, contradictory legends, and imagined histories, which may or may not have any basis in fact. Bryan Sykes is something of a legend himself - a distinguished clinical geneticist and expert on collagen disorders, he turned his hand to "genetic archaeology" - the study of ancient and modern populations by unpicking the discrete and information-laden sequences of the genes they carry.

In Sykes's first foray into the popularisation of this approach, he wrote "The Seven Daughters of Eve", a fascinating romp through the history of our maternal genetics. The reader will be familiar with the cellular role and characteristics of mitochondria, but their particular value to the genetic archaeologist lies in the property that they contain their own DNA (they are the evolutionary relics of once-free-living bacteria that engaged in a highly significant and successful alliance with the ancestors of all eukaryotic cells), and this DNA is exclusively maternally inherited. The logical upshot of this is that your mitochondrial DNA is inherited from your mother, who got it from her mother, and so on, right back through human history and prehistory - indeed back through our common ancestors with the other great apes, other primates, mammals, vertebrates, and to the very first proper eukaryotic cell itself. Although this is perhaps obvious, it is nonetheless an arresting thought, and one that clearly appeals to Sykes. Motherhood, right back to when we diverged from apple pie.

A similar principle (this time following the male line exclusively) applies to the Y chromosome, the scrappy little chunk of DNA that is really only responsible for conferring maleness to an embryo that would otherwise follow a female developmental trajectory. In "Adam's Curse", Sykes re-worked "Seven Daughters of Eve" for the boys, and identified five patriarchal "clans" to add to the seven matriarchal ones he had identified as contributing to the vast majority of extant Europeans.

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The differing activities and proclivities of males and females over the ages mean that Y-chromosomal DNA and mitochondrial DNA allow us to open a window on population histories, and put some flesh on the bare bones of legend and myth. Perhaps surprisingly, this approach is bearing significant fruit, some of which borders on the shocking. In 2003, Zerjal *et al.* reported an astonishingly high carriage rate of a recent Y-chromosome signature across the old Mongol empire - up to 8% of the Y-chromosomes appeared to show an origin from around the time of Genghis Khan - the tempting inference (which may well be correct) is that this is the genetic legacy of Genghis himself. He and his descendants were well known for their sexual voracity, and association with the ruling family would have boosted their reproductive luck somewhat.

Dan Bradley and colleagues in Trinity College Dublin have uncovered a similar "Genghis effect" apparently originating in early medieval north-west Ireland, associated with surnames connected with the *Ui Neill*, descendants of the family of the infamous Niall of the Nine Hostages. Niall's most remembered exploit was the capture of the young Roman Briton Succath, later to become St Patrick. So it's all his fault (Moore *et al.*, 2006).

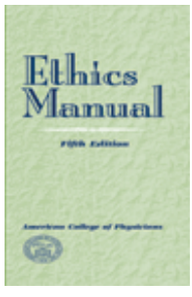
The genes seem to fit with the story, and using these principles, Sykes sets out on a genetic journey across the four regions of the Isles (England, Wales, Scotland, and Ireland), revealing the genetic signatures of the various postulated waves of conquest, immigration, raiding, etc., from the original Mesolithic colonisers of the land, to later arrivals, including Romans, Vikings, Saxons, Normans, and other assorted peoples. The detailed unpicking of the results makes fascinating reading, but the conclusion (and I hope the reader doesn't mind a bit of a "spoiler") is that the genetic signature of the original inhabitants of the Isles (who may be equated with the "Celts", albeit not genetically connected with the Celts of Europe) remains very strong - indeed vastly predominant. The conquests were primarily cultural, with much less displacement of the original populations than was previously assumed. This may well be a general principle in history, and the tales of large scale exoduses and migrations of entire populations may be a tad hyperbolic. Results from other populations will undoubtedly spark future debates.

"Blood of the Isles" is written in a similar tone to Sykes's other books, and as such it is very readable and enjoyable. The detailed genetic analysis is skimmed over, which might leave the author open to a charge of "dumbing down"; the non-technical reader, on the other hand, will probably welcome this. Occasionally the gushing references to the emotion of the whole enterprise are slightly overplayed, and certain parts of the text are a bit repetitive (or derived from the previous books). However, this does not detract from a rollicking and entertaining jaunt through the history of our little corner of Europe, in the pursuit of that most fundamental of questions: "Who are we?"

Zerjal *et al*. The Genetic Legacy of the Mongols. *Am J Hum Genet* 2003;**72:**717-721.

Moore *et al.* A Y-chromosome signature of hegemony in Gaelic Ireland. *Am J Hum Genet* 2006;**78**:334-338

Shane McKee



Ethics Manual 5th Edition Lois Snyder, Cathy Leffler. Royal Society of Medicine Press Ltd, London. May 2006, 54pp, £8.95. ISBN 1-930513-65-8.

The 5th Edition of the Ethics Manual is a very well referenced (117 references) and updated summary of professional ethics in medical practice. It attempts a truly comprehensive insight into ethics from confidentiality through consent to genetic testing as would be expected from such a manual. More unusually it touches briefly on good practice as applied to Disability Certification, boundaries and privacy and gifts from patients. Slightly more detail is applied to end-of-life decision making but again attempts to cover the entire range of dilemmas including DNR, artificial nutrition, advance care planning etc.

In reality the Ethics Manual will be of interest only to those intending to practice medicine in the USA or those who wish to study practice across the Atlantic. Not unexpectedly the four-principles (autonomy, beneficence, non-maleficence and justice) are central to the manual. However the legal and societal context ensures that the manual is of little appeal to UK or Irish doctors. A further indictment is the lack of detail in any of the myriad complex topics. Research ethics is covered in three pages!

Doctors seeking general knowledge in medical ethics can access a number of useful and very readable paperbacks published in the UK. Those seeking detailed ethical analysis in specific areas will have to be more diligent in their search but I am afraid that this publication will be unhelpful.

Bob Taylor

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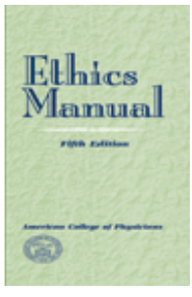

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