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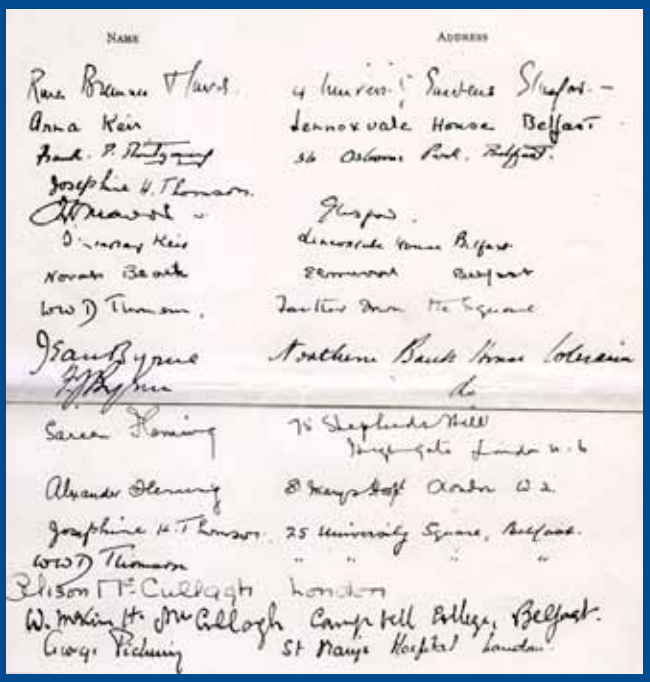

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Editorial

The future's bright, the future's now, the future's…. radiology

All decades have their focus on a particular specialty – mirrored somewhat by editors of the Ulster Medical Journal. The previous decade had great advances in neurological diagnosis when Dr Mark Gibson, a neurologist, was the editor. Similarly the decade before was a golden age for endocrine advances under the editorship of Professor David Hadden. Major advances in genetics – my own specialty – have been made in recent times. We can stretch the analogy (perhaps thin enough you may think!) to the founding editor Dr RH ('Dickie') Hunter and the advances in embryology in the 1930's[1]. The newest advance is medical imaging with radiologists now able to access every orifice in the body and withdraw fluids from therein, having often carefully looked beforehand in great detail at where to go, with sophisticated digital pictures. We have had an increase in imaging figures submitted with manuscripts, and over the next decade we can expect to see more.

My paternal grandfather was a watchmaker, and his brother - my great uncle - a photographer. They had adjacent shops in the town of Crumlin, and were affectionately known as 'Timex and Kodak'. A family history of watchmaking is handy for editing, as lots of papers often come in 'kit' form – as Professor David Hadden so perceptively recognised previously[2] - and thus need some help from the Editor to assemble. It has been a pleasure to help so many emerging authors and see papers published by medical students and young doctors rise steadily over the years. I'm not sure if photography is in the blood, but you can judge my choice of photos for yourself however, in that this editorial has less text and more pictures – I've chosen one of my favourite figures from each issue of the journal between 2005 and 2009. See if you can guess what they are.

Keep sending in your good papers (with well annotated images of course) to Dr Barry Kelly. The journal wishes him well.

Patrick J Morrison, Honorary Editor, 2005-2009.

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Fig. Collage of figures from top left, the two issues of 2005, followed by three issues of 2006-2009. The last figure is Dr Barry Kelly himself!

Ulster Med J 2009;**78(3):**142-145

Commentary

The health implications of financial crisis: A review of the evidence

David Stuckler[1,2,] Sanjay Basu[3], Marc Suhrcke[4,5,] Martin McKee[2*]

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ABSTRACT

What will the current economic crisis mean for the health of the people of Northern Ireland? We review the experience of three major economic crises in the 20th century: the Great Depression (1929), the Post-communist Depression (early 1990s) and the East Asian financial crisis (late 1990s). Available evidence suggests that health is at risk in times of rapid economic change, in both booms and busts. However the impact on mortality is exacerbated where people have easy access to the means to harm themselves and is ameliorated by the presence of strong social cohesion and social protection systems. On this basis, Northern Ireland may escape relatively unscathed in the short term but as every crisis also provides an opportunity, this is an appropriate time for the Northern Ireland Executive to reflect on whether they are making a sufficient investment in the long term health of their population.

INTRODUCTION

Northern Ireland has been hit hard by the global economic crisis. The province has suffered a sustained economic contraction, driven by falling activity in the construction and manufacturing sectors, and is now confronted by unemployment increasing from 4.0% to 6.2% between April and June 2008.[1]. The retail sector, especially in border areas, may have benefited from the decline in Sterling against the Euro, but even these gains are being dampened by the scale of recession in the Republic of Ireland.

What might the economic downturn mean for the health of Northern Ireland's population? There is extensive evidence that both unemployment and the fear of unemployment have adverse consequences for the health of individuals[2], but what is being experienced now is on an entirely different scale from usual economic swings[3]. Retired people are finding that the interest on their savings has diminished almost to zero. Families had taken advantage of cheap credit to buy houses, but now find themselves trapped in negative equity. Even those who remain in employment cannot be complacent, knowing that jobs no longer implicitly include lifetime employment guarantees.

HISTORICAL EXPERIENCES

We can look to experiences of the past to guide our expectations of the public health effects of this crisis. There have been three major international economic crises in the twentieth century: the Great Depression, the post-Communist Depression, and the East Asian financial crisis of the 1990s.

The first of these, the Great Depression that began in 1929, saw a fall in international trade of more than 50%. Unemployment rose rapidly across the industrialised world. A few countries experienced hyperinflation, with profound political consequences as the economic conditions paved the way for the emergence of fascism in Germany and Italy.

The second came in the early 1990s. Gorbachev's attempt to reform the Soviet Union was brought to an abrupt halt by an attempted coup in August 1991. Within a few days, the Soviet Union had broken apart as its constituent republics successively declared independence. Each had been part of a complex and interlinked trading system in which a single truck emerging from a factory in Kiev might contain components from ten other republics, with the whole process controlled through a system of central planning that was only possible when the state owned all the factories[4].

Many of the political leaders in the newly independent republics made a seamless transition from party apparatchiks to some form of democracy and capitalism[5, 6]. In some countries, however, the economic changes were profound. Encouraged by western advisors, who were largely motivated by the political imperative of ensuring that communism would be prevented from resurgence, they engaged – to varying degrees across countries – in what was termed "shock therapy"[7, 8], as part of which state-owned assets were given away to anyone that would take them. Often, this involved the distribution of vouchers to the public, who after 70 years of state socialism had no idea what to do with them[9]. Economic collapse ensued; unemployment rose, and savings were wiped-out by inflation.

The third economic crisis of the twentieth century took place in South East Asia. The Thai government had tied the Baht to the US Dollar but was no longer able to defend its currency

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against intense speculative pressure. Careless lending by banks created an unsustainable bubble. Once international investors realised the true state of the economy the Baht was forced to devalue by 50%. Problems spread rapidly to Thailand's neighbours, leading to mass withdrawal of capital and rapidly rising unemployment across the region.

What can we learn from the experience of these three crises as we seek to anticipate the consequences of the current recession for population health? This is more difficult than at first appears to be the case. Each crisis was different. Although popular imagery of the Great Depression is dominated by failed businessmen standing on window ledges in Wall Street contemplating a leap to their deaths, mortality rates in American cities actually fell during the crash by about 10%.

In marked contrast, the collapse of the Soviet Union, which was accompanied by economic decline on a similar scale, saw a rapid increase in death rates, by up to 20%. This equated to approximately three million excess deaths, a devastating figure in a peacetime era.

The East Asian crisis fell somewhere between these two extremes; there was no obvious change in death rates in Malaysia, but Thailand and Indonesia experienced short term increases[10-12].

LESSON LEARNING

How can we make sense of these differences? We can draw on a growing body of research, some of which has focused on the experiences of individuals and some on the experiences of entire populations. The scope of this research ranges from the international crises listed above to local crises, such as the closure of a large local employer. Certain key findings emerge.

One finding is that the rapidity of economic change appears to be a key hazard to health. The direction of change seems less important. Several studies looking at "normal" economic cycles find that deaths increase when the economy is expanding or contracting, relative to steady state[13-18]. Our research on the post-Soviet economic crisis found that those that implemented privatisation most rapidly experienced the greatest increases in deaths[19], while within Russia the increase in death rates was greatest in those regions experiencing the most rapid labour turnover[20].

However, it also seems that the extent to which economic changes impact on health depends on the extent to which people are protected from harm. Three issues are relevant: exposure to risk factors; social cohesion (informal welfare); and social protection (formal welfare).

The Great Depression began in a country that had introduced prohibition a decade earlier. Alcohol was still obtainable, with considerable variation in the extent to which states and cities enforced the law, but it was more difficult to obtain than in the past. In contrast, a culture of heavy drinking was deeply ingrained in the USSR[21]. Entrepreneurs took advantage of the new market economies to produce anything that could be sold. Some of these sales were of vodka but there was also industrial production of other forms of alcohol, such as the aftershaves that were up to 95% ethanol and which, as they were ostensibly not sold for drinking (even though it was widely known that they were drunk) were free of tax[22]. Volume for volume of alcohol, they cost about one sixth of the price of vodka[23]. In western countries, economic downturns are often associated with worsening diets, as people turn to cheap junk foods. Thus, two of the few employers increasing recruitment in the current economic crisis are McDonalds and Kentucky Fried Chicken[24,25]. Yet, some nutritional improvements may occur, as during recessions people also tend to eat out less and cook more at home overall[14,26,27]. When Cuba experienced serious economic problems after it lost its subsidies from the USSR in the early 1990s, people turned to cheap but healthy foods, in particular fruit and vegetables. The American economic blockade, designed to harm Cuba, had inadvertently protected it from exposure to American fast food chains[28].

Societies vary in the availability of social support. Our research in the former USSR showed how the adverse health effects of rapid economic change were reduced substantially where many people were members of social organisations, such as trade unions or sports clubs[19,29]. This is not surprising. In times of crisis it is important to have someone who can be turned to, whether to borrow money, food or shelter, or to get advice on where to get help.

They also vary in terms of systems of social protection. The available evidence suggests that the reason the health of Malaysians did not suffer in the East Asian economic crisis was because, unlike its neighbours, it ignored the advice of the international financial community to reduce spending on social protection[10-12]. Our work in the EU has shown that rising unemployment rates had no effect on suicides when spending on active labour market programmes, which aim to maintain jobs and quickly re-integrate workers who lose jobs into the workforce, were above US$190 per capita[13].

IMPLICATIONS FOR NORTHERN IRELAND

So what does this mean for Northern Ireland? Prediction is always difficult but a combination of social support networks, in particular the high level of membership of churches and other voluntary associations, coupled with a well developed welfare state (currently spending roughly US$150 per capita on social labour market protections), is likely to protect the population from the adverse health consequences that might be expected in many of the eastern European countries. This conclusion is supported by the experience of Iceland, which suffered a seemingly catastrophic banking and currency crisis. The Icelandic authorities had put in place an extremely detailed monitoring system and detected almost no health effects at all, except for a short-lived increase in attendances at hospital emergency departments (G Magnusson, personal communication).

Of course, even where support systems are well developed, there are individuals who fall through the gaps[30,31]. Recession may have negative health effects on those who lose their jobs, as well as slightly positive effects on those who stay in work. This would result in a neutral overall population effect but a rise in inequalities. Also, it is important to recognise that the research reviewed here has focussed on the short-term effects of economic crisis but there may also be changes in behaviour that only give rise to health problems several years in the future. Unemployment is often associated with increases in daytime drinking, with obvious long-term consequences for health. A fall in disposable income may lead people to eat

diets that are less healthy and there may also be a slowing down in the long-term decline in smoking rates. It is also likely that there will be short-term reductions in road-traffic fatalities, as traffic volume and intensity drop[32].

There is a growing body of evidence on the intimate relationships between public health and the economy that can offer some guidance to the Northern Ireland Executive. This knowledge was synthesised in a series of reports prepared for the ministerial conference on Health Systems, Health and Wealth, held in Tallinn, Estonia, which brought together health ministers from all of the countries in the European Region of the World Health Organisation[33]. These reports highlighted the importance of policies where investment in health systems feeds into sustained benefits not only in health but also in economic growth, but which by doing so reduce the future demands on those health systems. By this means it is possible to develop a virtuous circle leading to both health and wealth. From this perspective, governments should invest in the health of their population in the same way that they invest in their education and in the physical infrastructure necessary to build healthy societies and sustain economic growth.

Crucially, for Northern Ireland, this does not mean business as usual. There is a need to make the best possible use of what is likely to be a diminishing pool of public finance, given that it accounts for a much higher proportion of total economic activity than other parts of the UK[34]. At present much of this is spent on picking up the pieces of a broken society, rather than looking to the future. Although headline unemployment is still low, nearly one-third of the working age population is no longer in the labour market, the greatest rate of inactivity in the UK. There is a clear need to address this problem, addressing genuine health problems where they exist and making use of welfare-to-work programmes where they do not. Although politically highly controversial, the latter have been shown to be effective in getting people back to work and, in doing so, improving their material and mental health circumstances[35-38]. There is also a need to tackle education. Although the percentage of children achieving 5 or more GCSEs at grade C or above compares favourably to the rest of the UK, this must be interpreted in the context of the long tail of educational underachievement in the UK compared with its European neighbours[39]. Finally, there is a need to attract more inward investment, building on the work being done by bodies such as MATRIX, the Northern Ireland Science Industry Panel[40]. Policies such as these will be essential to break the cycle of deprivation and ill health that still affects too many parts of the province.

Policies such as these are, however, challenging, as they require active engagement by all parts of government, whatever their primary responsibility. Yet this is often easier at a regional level, as unlike national governments they do not have to concern themselves with matters such as defence or foreign affairs, with parts of Europe such as Catalonia, Wales, or North-Rhine Westphalia showing what can be done[41]. What is important is that politicians in Northern Ireland recognise the importance of looking to the long term, which must involve investment in the health of current and future generations.

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Presidential Address

Clouds of Unknowing

Presidential Address to the Ulster Medical Society, Thursday 9th October 2008.

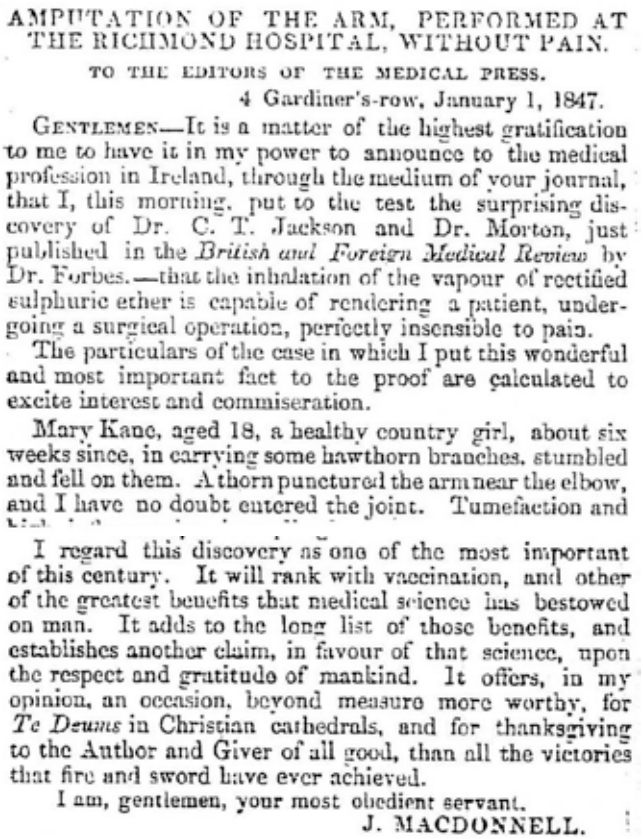
Howard Fee

Fig 1. Coat of Arms of the College of Anaesthetists

This is the Coat of Arms of the College of Anaesthetists in Dublin granted to the College in 1999 (fig 1). In central position, representing anaesthesia is a shield containing poppy heads. The cloud above represents the downwards drift to unconsciousness with the healing hand of the physician in attendance. The cloud might have another interpretation for there can hardly be a treatment in medicine which is so widely applied and yet so little understood. The supporters are unusual in heraldry taking the form of dolphins and these provide a link to one of the founders of this Society, James MacDonnell (fig 2a) whose family coat of arms also bears this heraldic symbol (fig 2b).

Fig 2. Bust (left) and coat of arms (right) of James MacDonnell

As most of you will know James was a son of the Glens and the first of a family of doctors all of whom rose to distinction in different ways. His thesis entitled 'On the Drowned' is the first formal account of resuscitation methods, and perhaps he might have been attracted to emergency medicine or even anaesthesia, had he lived a generation later. As it happened, it was his surgeon son, John, who administered the first anaesthetic to a patient in Ireland, at the Richmond Hospital in Dublin.



AMPUTATION OF THE ARM, PERFORMED AT THE RICHMOND HOSPITAL, WITHOUT PAIN.

TO THE EDITORS OF THE MEDICAL PRESS.

4 Gardiner's-row, January 1, 1847.

GENTLEMEN—It is a matter of the highest gratification to me to have it in my power to announce to the medical profession in Ireland, through the medium of your journal, that I, this morning, put to the test the surprising discovery of Dr. C. T. Jackson and Dr. Morton, just published in the *British and Foreign Medical Review* by Dr. Forbes.—that the inhalation of the vapour of rectified sulphuric ether is capable of rendering a patient, undergoing a surgical operation, perfectly insensible to pain.

The particulars of the case in which I put this wonderful and most important fact to the proof are calculated to excite interest and commiseration.

Mary Kane, aged 18, a healthy country girl, about six weeks since, in carrying some hawthorn branches, stumbled and fell on them. A thorn punctured the arm near the elbow, and I have no doubt entered the joint. Tumefaction and

I regard this discovery as one of the most important of this century. It will rank with vaccination, and other of the greatest benefits that medical science has bestowed on man. It adds to the long list of those benefits, and establishes another claim, in favour of that science, upon the respect and gratitude of mankind. It offers, in my opinion, an occasion, beyond measure more worthy, for *Te Deums* in Christian cathedrals, and for thanksgiving to the Author and Giver of all good, than all the victories that fire and sword have ever achieved.

I am, gentlemen, your most obedient servant,

J. MACDONNELL.

Fig 3. Extracts from the Medical Times letter

MacDonnell broke the news in a letter to the Medical Times on New Year's Day 1847 (fig 3a, 3b). It was not just a New Year; it was indeed a New Dawn. The details of the case were these: An 18 year old girl from the Drogheda area, Mary Kane, had been carrying hawthorn branches when she tripped and a thorn punctured her elbow. Over some weeks this became septic to the point where it threatened her life and the only recourse was amputation. MacDonnell had obviously heard about the new discovery and must have thought that Mary Kane being a strong young country girl would be an ideal subject. One or two days before administering the ether, MacDonnell decided to 'ascertain on myself', as he put it, the effects of the vapour and was assisted in this by a

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Fig 4. Henry Hickman

colleague, surgeon Alexander McDonnell. 'I rendered myself unconscious for some seconds, five or six times'. On the day of surgery itself, it took more than one attempt to get it right and we can but imagine the scene and the sense of relief, when at the end, Mary Kane opened her eyes.

Far from congratulating himself, MacDonnell concludes his letter with great humility, writing, 'It offers in my opinion an occasion beyond measure more worthy for Te Deums in Christian Cathedrals…than all the victories that fire and sword have ever achieved'. Te Deum Laudamus indeed!

The synthesis of ether was first described in modern times by the German apothecary Valerius Cordus in 1540. He called it "sweet oil of vitriol". Maybe it's too far-fetched to imagine that this gave rise to the expression 'Sweet Dreams'. Raymond Lully, a 13th Century alchemist almost certainly came across it before this and probably many others. The basic ingredients are wine and sulphuric acid. We've always had wine and sulphuric acid was synthesised by the Assyrians as early as the 7th century BC. It is, therefore, conceivable that ether was available to ancient civilisations.

In modern times, in Europe, the Swiss physician-alchemist, Paracelsus, observed the narcotic effects of ether in chickens. He noted that they "undergo prolonged sleep and awake unharmed". Unfortunately, Paracelsus failed to grasp ether's potential.

Inimical to the potential was the concept. Henry Hickman (1800-1830) was a young Shropshire GP (fig 4), who had graduated from Edinburgh about 50 years after James MacDonnell. He had no knowledge of ether but in 1825 he suggested in a letter to a local newspaper that 'suspended animation' might be used as a means of reducing pain during surgery. He had developed a technique which involved asking the patient to re-breathe from a bag. Taken to extremes re-breathing will produce narcosis and this was the basis for Hickman's suggestion, although of course he didn't know the physiological basis for it. Needless to say, his results were not entirely satisfactory and he was roundly denounced in a letter to the Lancet in September 1826, under the caption 'Surgical Humbug'[1]. Hickman's patients were described as being 'doomed to come under his care', that he was a disgrace to his profession, dishonourable, and a 'quack'. The correspondent signed himself off, not entirely honourably, as 'Antiquack'.

Crawford Long (1815-1878) was an American GP practicing in Jefferson, then a remote outpost in the southern state of Georgia. Long is now credited as being the first doctor to administer ether as a general anaesthetic to a patient for a surgical operation. It took place in 1842. Had he announced his initial case report in the literature, he might now be hailed as the discoverer of anaesthesia. On the other hand he might have attracted a torrent of abuse like Hickman, and shortened his life. For whatever reason, Dr Long left the first public demonstration of ether anaesthesia to others.

The first successful public demonstration of ether anaesthesia took place on 16th October 1846 in what has come to be known as the 'Ether Dome' in the Bulfinch Building of the Massachusetts General Hospital in Boston (fig 5). The following is a paraphrased account of what took place:

Fig 5. Mass. General Ether Dome

On Oct. 16, 1846, in the operating theater on the top floor of the building, one of the greatest moments in medicine occurred., William Morton, a Boston dentist, demonstrated the use of ether during surgery, ending the indescribable pain — and the overwhelming dread — that had been associated with the surgeon's knife.

Using a specially designed glass inhaler containing an ether-soaked sponge, Morton, administered the anesthetic to Gilbert Abbott, a printer who had come to the MGH for removal of a vascular tumor on his jaw. After several minutes, Abbott was

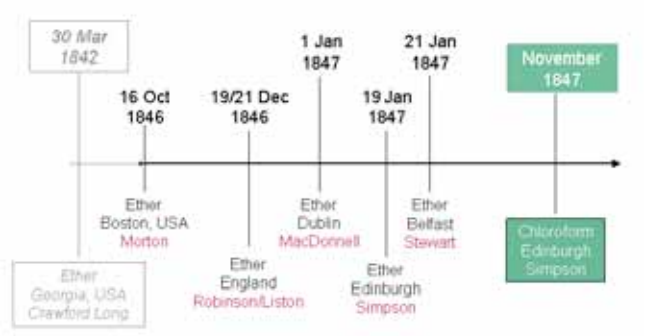

Fig 6. Early chronology of Ether and chloroform

rendered unconscious. John Collins Warren one of the most widely respected surgeons of that time, removed the tumor. Upon wakening, Abbott informed the curious and skeptical physicians and medical students in the theater that he had experienced no pain.

As the patient was carried from the operating theatre, Warren turned and faced the incredulous onlookers, remarking as he did so, "Gentlemen, this is no humbug," a suitable riposte to the scurrilous Surgical Humbug letter penned some 20 years earlier by Antiquack. News of the discovery spread quickly, and within days it was hailed in the popular press as the "greatest gift ever made to suffering humanity." In the case of ether anaesthesia, the species jump from chicken to man had taken 300 years.

The first recorded use of ether in Belfast was on 21st January 1847 for the amputation of the arm of a young woman. The next day the Belfast Newsletter published a detailed description of the proceedings in which it was stated that 'her only intelligence of the operation was being sawn through'. The ether was probably administered by Dr Horatio Stewart for surgeon Alexander Gordon who later became the first Professor of Surgery at The Queen's University[2].

Although ether may have been, in John MacDonnell's words,

Fig 7. James Young Simpson

'the greatest gift ever made to suffering humanity' it was difficult to use well. (fig 6). Stewart and Gordon would have been feeling their way, trying as best they could to avoid cyanosis without the aid of oxygen or any knowledge at all as to how to maintain a patent airway, or avoid aspiration. These early ether anaesthetics must have been sporting affairs to say the least and no doubt some patients succumbed. One surgeon, Syme, in Edinburgh said of ether: 'It will not do', preferring to do his amputations without it. His patients, had he asked them, might have taken a different view.

By way of a summary, within 10 weeks of the Boston demonstration, ether was being used London in UCL, surgeon Robert Liston remarking that 'this Yankee Dodge beats mesmerism hollow'. Within a month of this, ether had reached Dublin, Edinburgh and Belfast. The world's first chloroform anaesthetic was to follow towards the end of 1847.

Fig 8. The Lavoisiers

James 'Young' Simpson (fig 7), an Edinburgh man, entered the University at the age of 14 years, and graduated MD in 1832 at the age of 21 years. Seven years later he became Professor of Midwifery at Edinburgh University, a post he held for over 30 years. Hence he was nicknamed 'young' as in 'young Simpson'. So ubiquitous did this usage become that he incorporated 'Young' into his name. Simpson's many notable achievements in obstetrics were to be overshadowed by his discovery of the anaesthetic properties of chloroform.

Like surgeon Syme, Simpson was dissatisfied with ether, a drug he had used in obstetrics, and sought a more pleasant and more rapidly acting anaesthetic. David Waldie, a medical man and an apothecary, suggested chloroform and Simpson and his friends inhaled this at a dinner party in Simpson's house on 4th November 1847. (Just how such a party would be viewed by professional regulators these days is hardly a matter for conjecture). Not surprisingly all became unconscious and awoke delighted at their success. Within weeks Simpson published in the Lancet.

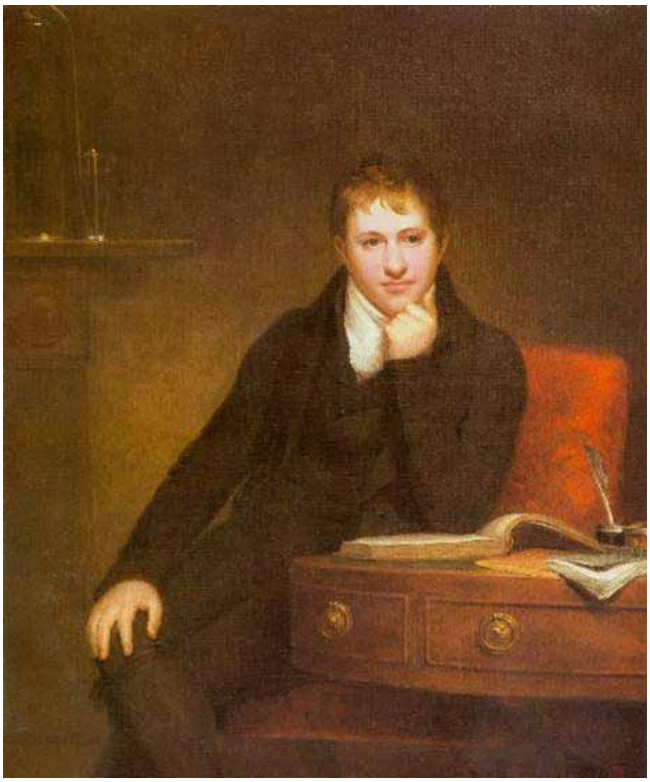

Fig 9. Humphry Davy

It is well known that Simpson was attacked for advocating general anaesthesia to relieve pain in childbirth. The Old Testament injunction that 'in sorrow shalt thou bring forth' was as strongly advocated as it was merciless. It was not until John Snow administered chloroform to Queen Victoria for the birth of Prince Leopold that anaesthesia for this purpose was accepted by the church. As Monarch she was Supreme Governor of the Church of England so the bishops were left with little option. Simpson was the first person to be knighted for services to Medicine and be became one of the most famous doctors of his day, much loved by patients and colleagues alike. At his death funding for a new maternity hospital, the Simpson Memorial Maternity Pavilion, was raised by public subscription.

In the latter years of the 18th century France was heading for Revolution. It was indeed the best of times and the worst of times. It was a time of change on many fronts in 'natural philosophy' and for those interested in the chemistry of gases in particular. Why do I show this beautiful painting by the incomparable Jacques-Louis David of Charles Lavoisier and his wife (fig 8) at a lecture like this?

Charles Lavoisier was the first to reveal the true nature of oxygen, a gas beloved of anaesthetists. In experiments on guinea-pigs he showed that respiratory gas exchange was a combustion describing it 'like a candle burning'. In so-doing he blew away the phlogiston theory of oxygen so beloved of Priestley. Secondly, he was the first to use quantitative methods in chemistry; measurement is close to the hearts of all anaesthetists. Thirdly, he introduced the double-barrelled nomenclature we use to describe inorganic salts, e.g. sodium chloride, sodium bicarbonate. Fourthly, he wrote the first chemistry book, an important book in itself and one which had an influence on an even greater scientist, Humphry Davy (fig 9).

Sadly, as an aristocrat, Lavoisier found himself on the wrong side in the years that followed. Trumped up charges were levelled against him. As Robespierre put it at the tribunal. 'The Revolution has no need of chemists'. At his execution at the age of 51 years in 1794 one of his friends remarked: 'It took but a moment to cut off his head, but it may take 100 years to produce another like it'.

Well, as is so often the case, the French underestimated the Anglo-Saxons. At the time of Lavoisier's execution, Humphry Davy (1778 – 1829) was 16 years of age and destined to become the greatest scientist of his day. Davy was a polymath. As a chemist he isolated, amongst other things, potassium, and a few days later, sodium: he was the first to show that all acids contained hydrogen; he postulated that chemical forces were fundamentally electrical, and demonstrated electromotive forces in a cell. Outside of science he was highly regarded as a poet, a friend of Wordsworth, and an archaeologist. He became famous in his own lifetime but now is remembered chiefly for two things: the indispensable miner's lamp, and discovery of the analgesic properties of nitrous oxide. Unaccountably, for as a young man he had been a surgical assistant, Davy failed to grasp the potential of nitrous oxide as a means of alleviating the pain of surgery. What an irony that at the very time the much maligned Dr Hickman, only 50 or so miles away, was experimenting with carbon dioxide narcosis, Humphry was administering nitrous oxide to treat 'hysteria' in his Medical Pneumatic Institution in Bristol.

On 11th December 1844, Gardner Quincy Colton (1814-1898) an erstwhile medical student, administered nitrous oxide as a general anaesthetic for the removal of a tooth. The patient was a Connecticut dentist called Horace Wells (1815-1848) who, on waking up afterwards, proclaimed: 'a new era in tooth pulling'. The experiment was performed at Wells' suggestion, a fact which Colton was always careful to acknowledge.

A few weeks later in January 1845, at the Massachusetts General Hospital, Wells himself attempted to repeat Colton's experiment. Unfortunately, the patient moved and then cried out and Wells became a subject of ridicule. It is not clear what went wrong, if they rushed, or if the patient held his breath, or the gas mixture was dilute. Whatever the reason, the failure affected Wells very deeply and although he continued as a dentist for a time, he became profoundly depressed and ended up taking his own life. Although Wells failed in one sense, he was the first person to submit to the only 19th century anaesthetic drug still in use in 2008. In that sense both he and Colton should be remembered as important pioneers of anaesthesia. When the flamboyant and entrepreneurial Colton returned empty handed from the Californian Gold Rush, he set up dental 'offices' in many American cities. The photograph (fig 10) shows an example of one of these with the cylinder of nitrous oxide on a bench to the left.

In 1867 Colton visited Paris to attend the First International Medical Congress. At that meeting he met a dentist, TW Evans. Evans, a Philadelphian émigré was by 1867 a fashionable Parisian practitioner numbering amongst his patients the President of the 2nd Republic himself, Louis Napoleon. Colton instructed Evans in the use of nitrous oxide

Fig 10. A Colton dental office

and soon after the Paris Congress, Evans travelled to London where he, in turn, demonstrated nitrous oxide at the London Dental Hospital.

Nitrous oxide quickly found a place in obstetric practice and the Russian, Stanislav Klikovitch in St. Petersburg, was amongst the first to advocate it for self-administration by women in labour. Klikowitch's methods were taken up by an eminent obstetrician, Paul Zweifel in Leipzig, and by one of his juniors, Albert Doderlein. Doderlein saw the need for some form of monitoring and was the first to measure blood pressure during administration. He also recognised the potential for hypoxia and checked the oxygen content of whole blood using a new spectrometric method recently developed by Felix Hoppe-Seyler (1885).

Doderlein's prescience was well judged as the risk of hypoxia has always been a major concern during nitrous oxide administration. It was not until the 1930s that machines were constructed which were capable of giving fixed percentages of nitrous oxide in air to women in labour. Ralph Minnitt of Liverpool gave his name to the most widely known of these. Another was named after Lucy Baldwin, later Countess Baldwin of Bewdley, wife of British Prime Minister, Stanley Baldwin (fig 11a,b). She was a forceful advocate for pain relief in labour in the 1930s, possibly not unconnected with the fact that she gave birth to six children.

Fig 11. The Minnitt (left) and the Lucy Baldwin (right) apparatus

I have digressed. Important as obstetric analgesia was and is, it is only a small part of anaesthesia. So we will return to the 1850s to see something of how anaesthesia developed as a specialty.

John Snow (1813-1858) of Broad Street pump fame (fig 12), was the first professional anaesthetist in these islands and was a powerful advocate of the physician anaesthetist. He was the first to apply scientific method to the administration of volatile drugs. He calculated dosages and kept detailed records of all his cases. Most remarkably he established that the potency of an inhaled anaesthetic is inversely related to its solubility in the blood. The opposite of what, at first sight, might be expected.

Fig 12. John Snow

Following Snow's early death at the age of 45 years, leadership of the embryonic specialty in England fell to another remarkable man. Joseph Clover (1825-1882) was an innovator par excellence who would find the straightjacket of modern research governance incomprehensible (fig 13). He experimented with combinations of nitrous oxide/ether in air and he designed many different types of breathing apparatus to facilitate this, including means by which concentrations could be adjusted.

Here he is inducing anaesthesia with chloroform, with a finger on the patient's pulse (fig 13). [When I started as an SHO in the main theatres in the Royal Victoria Hospital in 1973, palpation of the pulse, careful observation of colour and temperature, and a sphygmomanometer were the only forms of monitoring available for routine surgery. ECG monitors

Fig 13. Clover – hand on pulse

(single lead) were rare, unreliable and highly susceptible to diathermy interference]. In the photograph he is using his famous inhaler which remained in use, in its various modifications, right up to the Second World War.

During the 100 years from 1850 to the mid 1950s, ether and chloroform were the only volatile anaesthetics in general use. Of the two, ether was the more widely used, because it was relatively safe and, by the standards of the time, its administration could be entrusted to young doctors, medical students or even nurses.

In contrast, chloroform was intrinsically hazardous. It induced dangerous cardiac arrhythmias and was associated with fulminant liver failure. However, it provided excellent anaesthesia and was certainly preferred in Scotland and Ireland. It was never popular in USA probably because of a shortage of doctors; the administration of chloroform could not be entrusted to medical students and nurses.

Despite the higher risk of death with chloroform (estimated at 1 in 4,500 compared to 1 in 21,000 with ether) its popularity soared in the UK and in many other European countries. Such a situation could not be allowed to continue and the Hyderabad Commission 1890 concluded that it caused hypoxia. This was the beginning of the end for chloroform. It was the correct result but for entirely the wrong reasons.

You may have noticed that I've drifted across the Atlantic Ocean – the last American I mentioned was the 'American Dentist' who brought the good news from Paris to the London Dental Hospital. The fact is that during all of this time, not

Fig 14. Sir Frederick Hewitt

only did Britain rule the waves, but British anaesthesia ruled as well. Its pre-eminence up to the beginning of World War II was largely the result of the efforts of three men, Snow, Clover and Frederick Hewitt. Writing of them, the late Rod Calverley of University of California had no doubt that they were exceptional. Not only was that indeed the case, but British anaesthesia, indeed British surgery too, was fortunate that the professional lives of these three overlapped in such a way as to provide continuity.

It is not generally known that Clover (who died in 1882) was the first to perform an emergency cricothyroidotomy. He averted disaster by inserting a curved cannula of his own design through the cricothyroid membrane, thereby by-passing a large oral tumour. He remarked afterwards that 'I never used it before although it has been my companion at some thousands of cases'. That was Clover, obsessed with patient safety, and unusually for his time, well prepared for trouble. Frederick Hewitt was a man of like mind.

The successor to Snow and Clover, Hewitt (1857 – 1916) was the leading English anaesthetist of his day and an outstanding clinician (fig 14). We might remember him for a dozen things. He perfected Clover's portable inhalers, and most importantly invented the first apparatus capable of delivering oxygen and nitrous oxide in variable proportions. Apart from his clinical contributions Hewitt should be remembered for his contributions to anaesthetic training and education. It was on

his insistence that anaesthesia became part of the curriculum in all British medical schools. In 1893 he wrote the first anaesthetic textbook, a book which subsequently ran to five editions.

Hewitt was the first anaesthetist to be knighted, possibly on account of his ministrations to the future King Edward VII whom he anaesthetised for a perforated appendix on the eve of his planned Coronation. The future King, and here he is in his Coronation robes (fig 15), was not an ideal anaesthetic subject, being obese, bearded and much given to tobacco and strong drink. Most of us today would baulk at anaesthetising him. To do it with open-drop ether without any form of airway protection would have been a considerable challenge, even for a clinician of Hewitt's skill.

The subsequent reigns of Edward VII and his son George V saw great upheavals in the world and everything was caught up in them. The years from 1914 - 1934 saw advances in anaesthetic equipment, notably Henry Boyle's machine and the arrival of Ulsterman, Sir Ivan Magill's tracheal tube. But why 1934? To understand that we must go back to another era, to another starting point, a starting point which was central to the evolution of modern anaesthesia.

Sir Christopher Wren's Royal Chelsea Hospital was completed in 1692 and is still in use for the purpose for which it was built. With its magnificent chapel, it stands in stark contrast to the inhuman designs of modern hospitals (fig 16). Wren gave patients, their relatives and the staff something to lift their spirits, perhaps even their souls. The earliest

Fig 15. King Edward VII

Fig 16. The Royal Chelsea Hospital chapel

intravenous administrations of substances were performed in the neighbourhood of Oxford around 1656 and were attributed to Wren. What a polymath he was! Robert Hooke said of him:

'Since the time of Archimedes there scarce ever met in

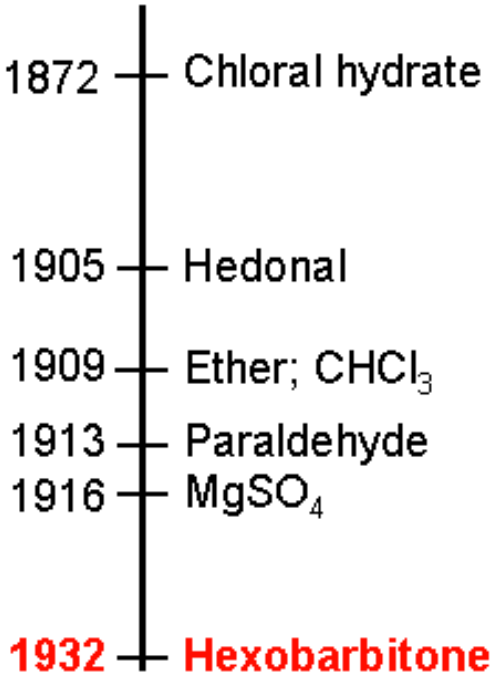

Fig 17. Intravenous 'anaesthetics'

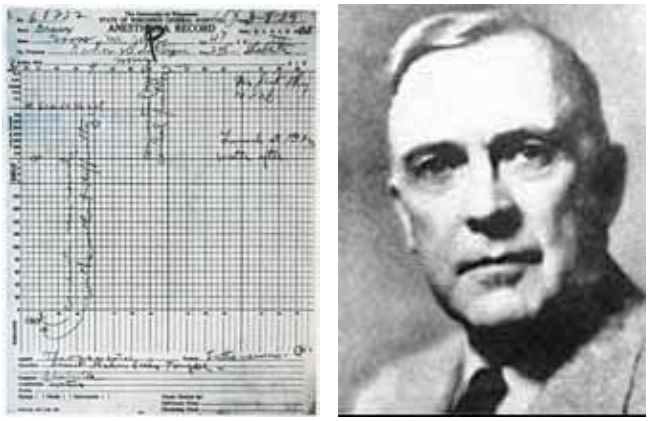

Fig 18. Reproduction (left) of the anaesthetic record of the first administration of Thiopentone, 8th March 1934 by Ralph Waters (right)

one man so great perfection, such mechanical hand and philosophic mind'.

He injected opium and other substances into dogs to see if substances could be given directly into the circulation and still exert their characteristic effects. If they did it would explain the rapid collapse following bites by venomous snakes.

Henry Oldenburg, a civil servant associate who was present at the time recorded:

'he thought he could easily contrive a way to conveigh any liquid thing to the blood by making ligatures on the veins… and putting into them slender syringes...fastened to bladders containing the matter to be injected'.

Oldenburg went on to say that they used 'big, lean dogges that the vessels might be large enough and easily accessible'. Given opium in this way the dogs were temporarily stupefied, but they survived, though probably not for long.

What excitement there must have been in the minds of Wren, Harvey, Hooke, Willis and others, as they began to uncloak these secrets right at the beginning of the scientific age. Those who wish to read more can find refer to Norman Bergman's paper[3] or enjoy Iain Pears' very well researched historical novel, 'An Instance of the Fingerpost'[4].

Many circumstances had to change before intravenous drug administration could become a reality, including the concept of aseptic technique. An early hypodermic syringe, dating from 1860 and described as English, can be seen in the Science Museum in London. It was designed by an Irish physician (Francis Rynd) and made in Dublin by an Austrian silversmith. Rynd had already invented the hollow needle in 1844.

Dr Alexander Wood was the first physician to use a hypodermic syringe to inject narcotic drugs into a patient. In 1853 he injected morphine into 'painful points' and published a report in the Edinburgh Medical and Surgical Journal. So far as we know he did not inject morphine intravenously (fig 17).

Intravenous anaesthesia was very slow to establish itself, partly due to the absence of suitable drugs, partly due to the difficulty of preventing sepsis. The arrival of barbiturates in the 1930s revolutionised anaesthesia. For the first time there was a drug which could induce anaesthesia in one arm-brain circulation time – normally around ten seconds. Hexobarbitone was the first of these drugs to achieve popularity and in the twelve years following its introduction it was used to anaesthetise approximately 10 million patients.

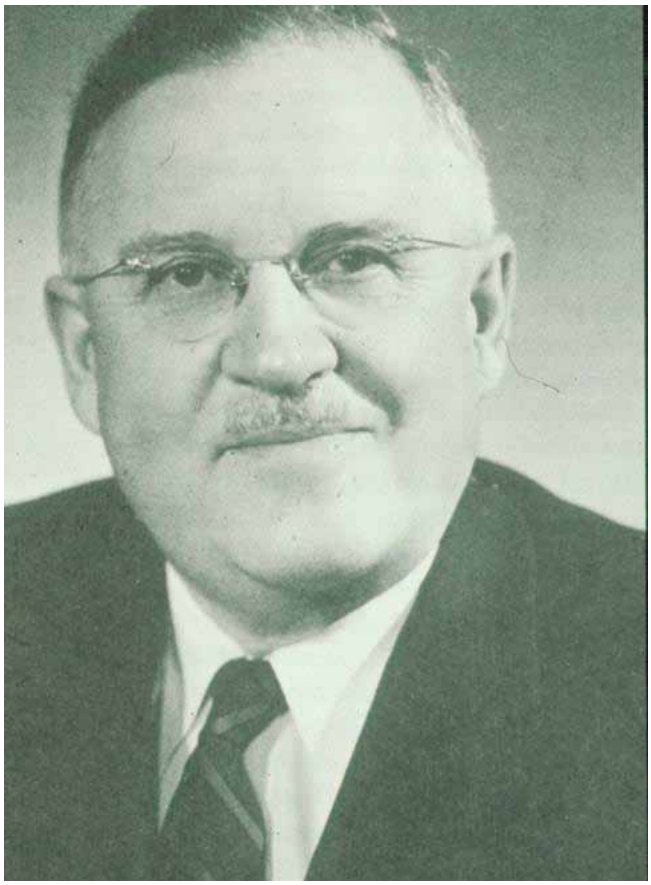

Fig 19. Harold Griffith

However, the barbiturate which would be the gold standard for the next 60 years or so, was yet to come.

This is a record of the first administration of thiopentone (Pentothal). It took place on 8th March 1934 at the University of Wisconsin Hospital and the anaesthetist was Dr Ralph Waters (fig 18a,b). He was another exceptionally gifted doctor and went on to become the world's first University Professor of Anaesthesia. Waters was a strong believer in the concept of research-led teaching and did much to encourage the development of academic anaesthesia in Britain. It is notable that a man of Waters' stature could, almost 80 years after the death of John Snow, write this about that great man:

'He is my idol, the more I try to do various things, the more respect I have for him. We need not hesitate to say that John Snow was and remains the greatest anaesthetist as well as the first'.

The use of ether to induce anaesthesia declined rapidly after 1934 and thiopentone was soon the standard method. Of course, ether, and if you were brave, chloroform, remained the only means of maintaining general anaesthesia.

The next great advance in anaesthesia originated in the jungles of Ecuador. The first medical uses of curare were

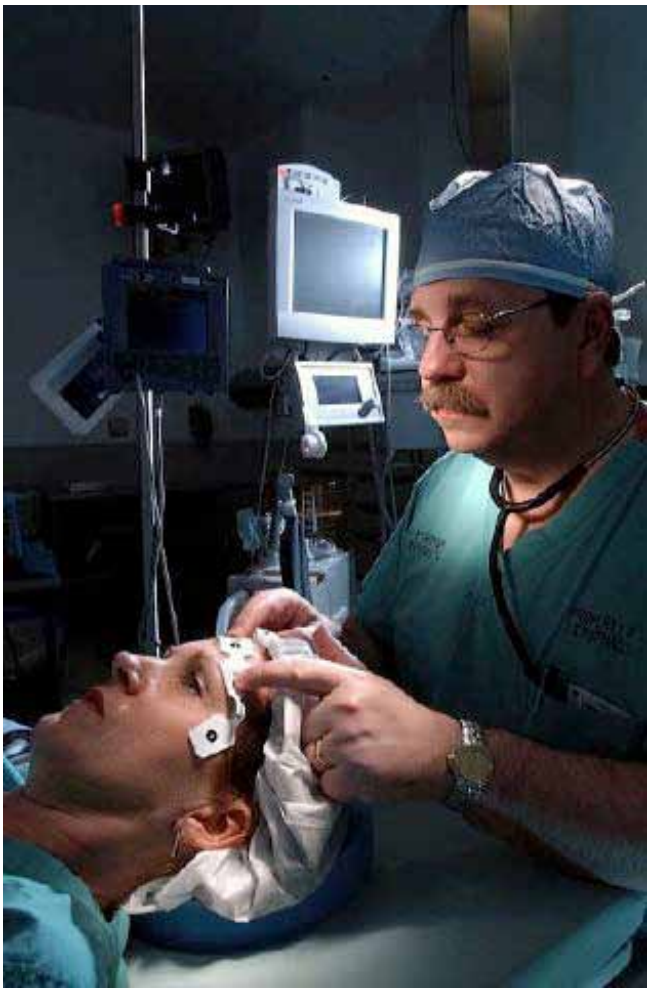

Fig 20. The BIS monitor

for relieving muscular spasms due to disease, or the spasms induced by EEG in psychiatric patients. Drs Manny Papper and Stuart Cullen were the first to use curare in anaesthesia. They gave it to two patients in Bellevue Hospital, New York City, in 1941. After the operation they were horrified to be confronted by two patients who could not breathe, and who had to be resuscitated overnight. Apnoea was not regarded as lightly then as it is now, and the concept of reversal was some way off. Papper, who later became the first anaesthesiologist Dean of an American Medical School was so shocked by the whole experience that he went so far as to say that curare had no place in anaesthesia.

Papper may have thought curare had no place in anaesthesia, but Harold Griffith in Montreal was confident that he could deal with respiratory paralysis if it occurred (fig 19). In July 1942, Griffith and Johnston reported the successful use of curare in a series of 25 cases performed in the Homeopathic Hospital, Montreal[5]. This series marked a second revolution in anaesthetic practice. Combined with tracheal intubation, which it facilitated, curare transformed surgical operating conditions.

The third revolution, had to wait for the Second World War and the Manhattan Project. In order to generate sufficient quantities of fissionable uranium for the atom bomb, Ur^{238} had to be enriched using uranium hexafluoride. The researches in fluorine chemistry which were necessary to bring this about were the springboard which gave rise to our modern heavily fluorinated anaesthetic drugs.

Halothane was first synthesised in 1951 in the laboratories of ICI by Charles Suckling. He began by asking anaesthetists what they wanted and it is a measure of his knowledge of organic fluorines that halothane was one of the first six anaesthetic compounds he synthesised. Halothane was revolutionary in being non-flammable, non-irritant, and much more potent than ether. Initial studies confirmed that it was rapidly acting with rapid recovery characteristics.

Revolutionary as it was, halothane was not perfect. Being similar to chloroform structurally, it had similar side-effects although generally these were much less pronounced. Fulminant liver failure on repeat administrations, although rare, became a growing concern in the 1970s, and a quest for better alternatives gained pace. Ross Terrell synthesised over 700 fluorinated ethers, of which just three, enflurane, isoflurane and desflurane became available for routine practice. Of these three only isoflurane and desflurane remain in regular use today. Terrell remains largely unknown to the general public despite the great service he rendered to mankind.

Sevoflurane was not one of Ross Terrell's ethers. It was discovered in the 1960s, not long after halothane, and was initially promoted in Japan. For regulatory reasons it was not licensed in the UK until 1995. Its properties are close to ideal although it has been associated with toxic degradation products when used in closed circuits with standard soda lime. This possible disadvantage can be circumvented by using carbon dioxide absorbents which do not contain strong alkalis. Sevoflurane has become the standard volatile agent for most purposes in the UK and much of Western Europe.

The question now is, has anaesthesia reached such a state of perfection that nothing more remains to be done? I do not think so. Whilst time does not permit me to delve into local anaesthetics, or the newer generations of opiates, non-opiate

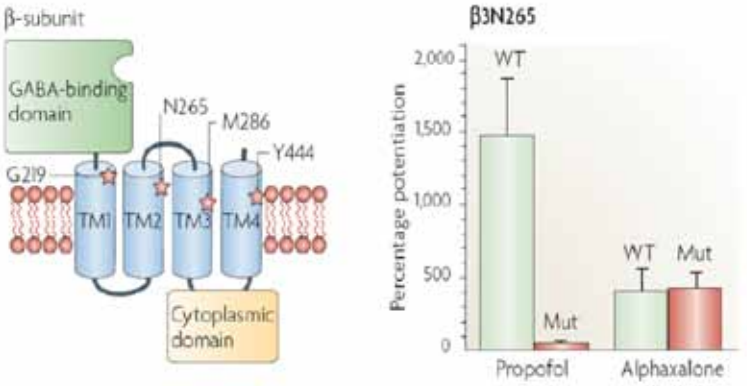

Fig 21. GABA mutation. Reproduced by permission from Macmillan Publishers Ltd NRN (from reference 13). Copyright 2009.

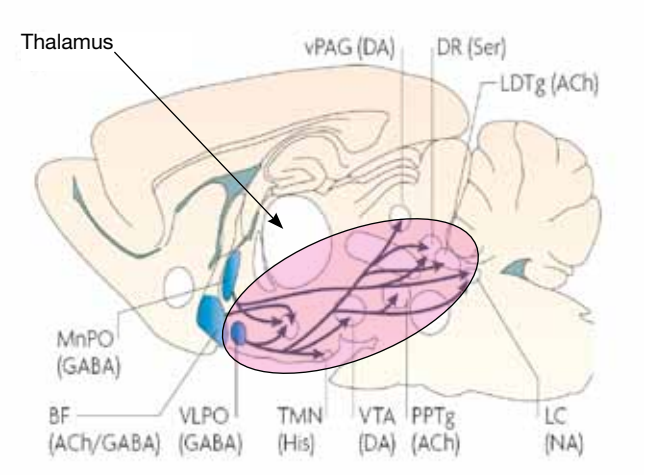

Fig 22. Thalamic projections. Reproduced by permission from Macmillan Publishers Ltd NRN (from reference 13). Copyright 2009.

analgesics, muscle relaxants or relaxant reversal drugs, the fact remains that we are still heavily reliant on opiates, with all their pharmacological baggage, to control severe pain. Our understanding of pain mechanisms, and of anaesthesia itself remains superficial. Our ability to control postoperative emetic symptoms is often ineffective and whilst we can keep people alive in intensive care units, we often lack any depth of understanding of the therapies we apply. Worse still, and surely the most serious gap in our knowledge, is that we cannot tell for sure if our patients are anaesthetised or not. We perform certain manoeuvres which we know from experience will in most cases result in an anaesthetic state, but we do not have a reliable, quantitative measure of 'depth' or even an adequate definition of what is meant by the term.

A large prospective trial of over 11,000 adult patients reported in the Lancet eight years ago quoted a figure for explicit awareness of 1 in 1000 overall, but almost twice this when muscle relaxants were used[6]. This year, an alarmingly high incidence of 1 in 100 was reported in a very carefully performed study of 4001 adult patients in the University Hospital in Valencia[7]. This group excluded patients most at risk so even this high figure may underestimate the true incidence. A prospective study of 184 children aged 5 -18 years this year revealed no explicit recall but two children responded positively under the modified isolated forearm technique, an incidence of around 1 in 100[8].

The risk factors are well known and include: caesarean section, absence of benzodiazepine premedication, emergencies, young patients, cardiac surgery and difficult intubation. The consequences include nightmares, post traumatic stress, depression, anxiety and flashbacks. One third of the patients in the Valencia study experienced one or more of these.

Can anything be done? At present the adequacy of anaesthesia is either deduced from end-tidal concentration values in the case of volatile anaesthesia, or indirectly from algorithms used to calculate target infusion dosage in the case of total intravenous techniques.

The bispectral index (BIS) monitor (fig 20) displays a real-time electroencephalography (EEG) trace, sampled from the fronto-temporal area. It generates a dimensionless number with 100 representing normal activity. Studies have shown that the probability of awareness is very low when the BIS is kept <60 intraoperatively but there are serious problems in applying this universally. Firstly, there is no gold-standard against which the bispectral index can be measured and judged. Secondly, there is marked patient variability. Thirdly, there is no clear-cut transition value which can be used to differentiate between sleep and awake. Finally, our current knowledge of the primary sites of action of anaesthetics suggests that these are distant from the fronto-temporal cortex.

Furthermore, there is no agreement on the value of BIS as a means of reducing anaesthetic awareness. A Cochrane Review last year[9] reported that when intravenous or volatile-based anaesthesia was guided by bispectral index monitoring, there was less awareness, and there were significant improvements in the quality of the anaesthetic overall. In contrast, a more recent US study reporting a comparison of bispectral and end-tidal agent monitoring concluded that BIS monitoring conferred no advantage[10]. Nor could the Cochrane review have examined a recent Australian study[11]. This showed that during anaesthesia, the EEG in infants is fundamentally different from the EEG in older children. The authors concluded that we lacked the necessary information to allow us to use anaesthetic depth monitors in infants.

So, I come back to the original question. What, if anything, can be done?

The problem for anaesthetists is that if we adopt protocol-driven methods based on bispectral indices, then in order to keep the monitor reading where it should be, we will inevitably administer higher concentrations of potent drugs than are necessary, or safe, for some patients. We do not have data which would allow us to develop patient-specific or condition-specific protocols. These we need.

In a recent editorial, Beverly Orser, from the University of Toronto, spelled out the obstacles to a reliable depth of anaesthesia monitor[12]. Anaesthetics have complex actions involving memory, pain, consciousness, vascular autonomic responses, etc. These responses require specific drugs for their suppression and the doses used are often very critical. Orser warns of the dangers of handing over critical elements of patient care to a 'black box' and concluded that we won't get anywhere until we knew a lot more about how and where anaesthetics work.

Although our knowledge of the mechanism of anaesthesia is sketchy it is advancing rapidly[13]. For example, we know with certainty that the β3 subunit of the $GABA_A$ receptor mediates both volatile and intravenous anaesthesia.

By creating mutations in the beta sub unit, we can produce mice which are resistant to specific anaesthetics. Figure 21 represents a beta subunit of a $GABA_A$ receptor. The N265 mutation shown here renders an affected mouse completely resistant to propofol, a modern day thiopentone (Pentothal). This particular mutation had no effect on other intravenous anaesthetics.

Second, we are reasonably sure that the thalamus and its

projections (fig 22) are important in the anaesthetic state. The neuronal pathways within the pink shaded oval are all GABA-ergic and are more active during sleep. We know that the ventrolateral preoptic nucleus (VLPO) is activated by anaesthesia and we hypothesise that it in turn activates sleep promoting pathways to the basal forebrain and anterior hypothalamus.

Thirdly, from PET studies it would seem that anaesthesia resembles normal sleep. As in normal sleep the largest decreases in blood flow during anaesthesia are in the thalamus, brainstem and basal ganglia. The precuneus appears to be involved in a range of highly complex tasks, including the monitoring of the world around us. It is profoundly de-activated both in deep sleep and anaesthetic-induced unconsciousness.

As I come to the end of the lecture and look forward, it is hard to know if doctors of my generation are labouring in the twilight of a golden age of medical practice, or witnessing some new dawn. There are many dark clouds including the likelihood of economic decline in the next 50 years, climate change and burgeoning population growth. The profession itself will be challenged by part-time practice, increasing patient expectations and ever more intrusive regulation and control.

What will be the consequences of the current decline in traditional research-led education and training of medical students? What a tragedy it is that the intellectual freedoms which in the past have delivered so much are now so undervalued. How regrettable it is that the freedoms which allowed generations of my clinical colleagues to conduct small research projects on the basis of a clinical observation, or even a hunch, have effectively been lost. It is worth remembering that it was those very freedoms which gave us modern anaesthesia, not million pound research grants or research strategies.

We have travelled a long way from the clouds of vapour and gas which first induced a state of unknowing in 1846. I've mentioned our lack of knowing as we struggled to find safe drugs, and good methods of administration. I've referred to our ignorance when it comes to patient awareness and the mechanisms of anaesthesia. I've alluded to storm clouds on the horizon. But I would like to end on a positive note, not just because it is a better way to end, but because I believe that there is always the potential for good, no matter how trying the circumstances.

And as this child struggles, in very trying circumstances, against the choking cloud of ether the words of the English poet clergyman, William Cowper, would seem to resonate, for her, and for us: (fig 23)

Ye fearful Saints, fresh Courage take
The Clouds ye so much Dread
Are Big with mercy, and shall Break
In Blessings on your Head.

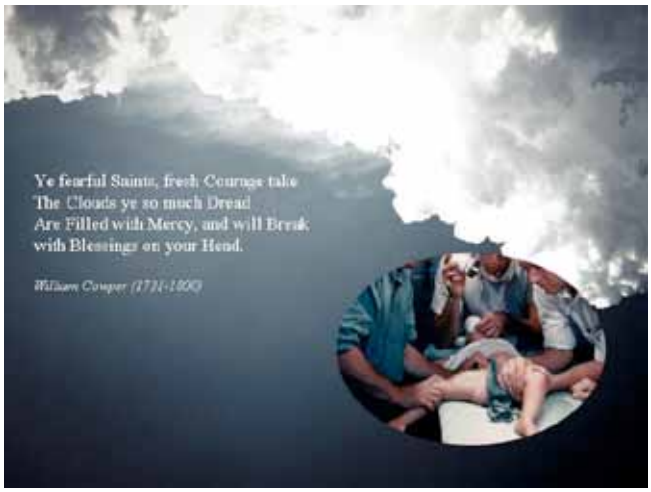

Fig 23. Clouds of Unknowing

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Review

Treating complex movement disorders in children with cerebral palsy

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INTRODUCTION

Cerebral palsy is common, affecting about 2-3 per 1000 children[1]. These children may have a motor disorder characterised by spasticity, dystonia or both. This can result in significant difficulty with activities of daily living, pain and long term joint deformity[2]. There are a number of treatments available for the management of spasticity and dystonia. This review will examine indications and practical issues for some of the common treatment options used in the paediatric population such as botulinum toxin and intrathecal baclofen and the newer therapy for dystonia management, deep brain stimulation.

Spasticity management in childhood cerebral palsy

A definition of spasticity was provided by Lance in 1980, 'Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neurone syndrome'.

Spasticity results from a lack of descending impulses that normally stimulate the release of the inhibitory neurotransmitter GABA which acts presynaptically to inhibit the release of excitatory neurotransmitters. Two of the most common causes of spasticity are cerebral palsy and acquired brain injury. Spasticity can result in functional problems with daily activities such as gait, feeding, washing and dressing. Over time it may result in joint contracture and hip dislocation in more severely affected individuals. It is recognised that a painful hip joint can result in poor tolerance of the seated position and may result in the need for frequent turning at night. The discomfort and lack of sleep can exacerbate seizures, dystonic posturing and spasms, the child can present as irritable and unsettled, in some the manifestations of pain include teeth grinding, biting and head banging. Identifying the source of pain and treating it can reduce the need for changes in anticonvulsants and tone modifying agents. However spasticity can also be helping the child to maintain posture and function as underlying muscle strength may be low. Therefore it is important for any treatment to be titratable in order to maintain functional benefits whilst reducing spasticity.

Treatment options for spasticity

Baclofen is a GABA agonist that is used to reduce muscle tone. Baclofen crosses the blood-brain barrier and binds at the GABA-B receptors of the laminae I-IV of the spinal cord, where primary sensory fibres end. It may be used for both oral and intrathecal administration. Baclofen can produce sedation when administered orally (that is, dose-related – table I); this may be minimized by initiating treatment at a low dose. This drug may also cause impairments of cognitive functions, hypotonia and may lower the seizure threshold. Maintenance doses are titrated to individual need and the titration should be done slowly, ideally incremental increases should be three days apart.

INTRATHECAL BACLOFEN

Intrathecal baclofen is a treatment used in adults and children since the mid 1980's. It can be considered in two groups: older ambulatory children or patients with severe spasticity in the upper and lower extremities. It has advantages in that it is titratable and reversible.

Mechanism

Intrathecal baclofen is delivered via an implantable pump. By infusing baclofen directly into the subarachnoid space around the spinal cord, potentiation of GABA-mediated inhibition of spasticity can be achieved while minimizing side effects secondary to high levels of baclofen in the brain. Intrathecal infusion of baclofen may be varied through the day to accommodate the patient's activities[3]. Many studies have demonstrated that intrathecal baclofen therapy is useful in the management of spasticity with cerebral palsy and spinal origin[4,5]. In patients with spasticity of cerebral origin reduction in spasticity in the upper and lower extremities after six months of therapy has been reported[5]. ITB produces levels greater than four times the oral dose facilitating the use of much smaller doses for example 0.05-1.2mg per day

Patient management generally takes place in three phases: patient selection, patients and family education, and screening.

Patient Selection

Clinically severe spasticity which impairs function in:

- Older ambulatory children

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Table I:

Guide to the oral baclofen dose range in childhood:

1 month – 2 years	**2 - 12 years**	**12 - 18 years**	Notes
1-2mg	2mg	5mg	Initial dose gradually increasing every three days
> 1year 5mg	**2-6 years** 10mg **6-12 years** 15mg	20-30mg. Max daily dose 100mg	Maintenance three times daily

- Patients with severe spasticity in upper and lower extremities
- Patients with a combination of spasticity + dystonia
- Spinal injury

Ideally patients should have been tried on oral tone modifying medications first and have had some response to baclofen and no adverse reaction.

Patient and family education

It is imperative that families have a clear understanding not only of the surgical procedure required but of the long term commitment in terms of pump maintenance and refilling. Patients should undergo functional assessments during the process of consideration for a baclofen pump. This facilitates a greater understanding of the level of ability and allows a clearer explanation of what might be improved using intrathecal baclofen. Local therapy teams can provide useful background information which assists the process. Written information should be provided explaining the assessment process, surgical procedure and follow up arrangements. Families and local teams should have access to protocols for emergency management. All of the information should be available in a child friendly format and accessible for young people with a learning disability.

Table II.

ITB withdrawal.

Clinical signs of ITB withdrawal
Increased spasticity
Agitation
Hallucinations
Severe itching
Hyperthermia
Seizures

Baclofen screening trial

A dose of baclofen is delivered via an intra thecal bolus using the standard lumbar puncture technique. Generally a dose of 50µg of baclofen is given in this intrathecal injection. The aim is to observe a demonstrable reduction in spasticity. There are a variety of techniques used in different centres to reliably assess this change in muscle tone, examples include a pre and post comparison of Ashworth scores, and change in range of hip abduction. It is important to explain to patients and families that the effect produced by the trial dose is not predictive of functional changes or the impact on upper limb tone which may be experienced following pump insertion.

Practical issues

Insertion of the baclofen pump is undertaken by the neurosurgical team. The procedure for insertion of an intrathecal baclofen pump lasts 1-1.5 hours. The pump is inserted under the covering of the abdominal muscles while the patient is under a general anaesthetic. A small catheter is inserted through a needle into the spinal fluid and is threaded upward toward the neck. The catheter is tunnelled under the skin to the abdomen and is connected to the pump. The pump is filled with the drug baclofen and is programmed by a computer to continuously release a specified dose. Patients usually remain in hospital for five days after pump insertion. During that time, their baclofen dose is increased every day as needed. The pump needs to be refilled every two to six months, depending on the pump size, concentration and dose. Refills are done using a syringe and needle and take approximately thirty minutes to complete. At that time, baclofen doses are adjusted depending on the effects that are being seen. Doses typically increase slowly during the first year, and then remain at that level for years thereafter. The drug dose is not related to age or weight, and a gradual increase during the first six to nine months is required. Generally, patients with ventriculoperitoneal shunts require lower doses. The battery in the pump lasts up to eight years at which time the pump needs to be replaced[6].

Problems with baclofen pumps

Empty pump reservoir, catheter leaks or displacement, pump malfunction, programming error and refill of pump with improper drug concentration are the possible mechanisms which could lead to an ITB withdrawal syndrome (table II) which can lead to muscle breakdown and multi system failure. Management includes an early recognition of syndrome, proper intensive care management, high-dose benzodiazepines and prompt analysis of intrathecal pump with reinstitution of baclofen.

Outcomes following intrathecal baclofen therapy

Reduction in use of oral medication for children with spasticity has been described, with improvements in comfort and function; decreased tone and spasms also observed[5].

Some aspects of speech, communication, and saliva control seem to have improved, with bowel movement frequency decreased in some children receiving intrathecal baclofen. Few changes in feeding and nutritional status have been reported. The majority of patients will sustain improved range of motion, decreased painful muscle spasm, and improvement in measures of independent function[3-5]. Finally, this treatment may be associated with possible complications, some studies suggest that children of younger age, as well as those with gastrostomy tubes and non-ambulatory status, were more likely to encounter complications necessitating removal of the pump such as pump pocket collections and infections[7,8]. Infection may remain isolated to the pump pocket or may track along the catheter, with consequent meningitis[5].

TABLE III.

ITB overdose.

Signs of ITB overdose
Excessive hypotonia
Drowsiness/reduced arousal
Respiratory depression requiring ventilation

Vloeberghs group demonstrated that ITB has a role in children with a combination of spasticity and dystonia. Interestingly they concluded that it was safe and effective to have both ITB and DBS together in selected patients with primary dystonias[9]. The American Academy reviewed all the trials for ITB available by 2000 and concluded that in a total of twenty-five trials seventeen had shown clear statistically significant improvements in areas such as moving and handling, pain, spasms, social participation and reducing the need for orthopaedic procedures. They commented that the other smaller trials had no power calculations therefore they could only be termed inconclusive rather than negative[10]. Other potential benefits that have been less extensively studied are benefits to sleep and respiratory function in patients with spasticity (table IV). One trial demonstrated significant improvements in these areas; however this clearly needs more investigation[11].

TABLE IV.

Benefits of ITB.

Positive results with Intrathecal baclofen
Reduced pain
Improved QOL
Improved seating tolerance
Improved transfers
Ambulatory patients improving capacity to walk
Ease of care / level of support
Reduction in orthopaedic surgery

BOTULINUM TOXIN THERAPY IN THE MANAGEMENT OF CHILDHOOD SPASTICITY

Prior to the late 1990's we were extremely limited in the focal medical management of movement disorders in children. A so called 'birthday syndrome' of almost annual Orthopaedic interventions overcame the functional difficulties associated with tightening at the ankle dorsiflexors, knee and hip flexors. In 1998 Botulinum Toxin type A became licensed for use in children over the age of two for management of dynamic equinus foot deformity caused by spasticity in ambulant children with cerebral palsy. This remains the only on license indication, however there is a wide range of accepted 'off license' use for children, as outlined in summary documents such as the European Consensus Statements. Targeted injections to skeletal muscles (table V) in areas including the neck, upper limb, spine, hip and lower limb have been shown to reduce problems associated with increased muscle tone as part of the upper motor neurone syndrome[12-15].

There are seven different naturally occurring serotypes of Botulinum Toxin, each acting at the nerve terminal end plate

TABLE V.

Author centre uses of Botulinum Toxin type A in movement disorders

Area	**Problems**
Head and neck	Sialorrhoea, Retro, lateral or rotatory torticollis
Shoulder	Axillary hygiene, retraction, protraction, abduction, focal dystonia
Elbow	Flexion, Extension
Wrist, thumb and hand	Flexion, hand hygiene/ hyperhydrosis, thumb adduction and flexion
Back	Opisthotonus, extension, pain
Hip	Pain secondary to spasm, flexion, adduction/scissoring, activities of daily living (toileting, dressing, changing), postural adaptation – comfort in sitting
Knee	Pain, quadriceps spasticity, flexion, crouch/jump gait patterns
Ankle	Equinus gait, inversion, pain
Foot, toe	Claw toe, hitchhiker toe, dynamic toe and foot deformities

to block the release of Acetylcholine at the neuro-muscular junction, abolishing motor end plate potential. Botulinum Toxin type A (e.g. Botox, Dysport, Xeomin) has the widest international clinical use as it causes the longest duration of muscle relaxation. It is taken up into the end plate via the high affinity synaptic vesicle protein 2 (SV2) which is up regulated in active neurons. It then irreversibly stops exocytosis of Acetylcholine by targeting the SNAP-25 protein element of the synaptic vesicle release complex. This is clinically vital as active toxin works on active synapses, those muscles with over activation causing clinical problems are specifically targeted. The terminal end plate ceases to function and regresses over the next couple of months to the end of the axonal sheath. Resprouting then occurs from this point with the growth of a new neuro-muscular junction. This leads to the duration of action within the targeted nerve-muscle of between three to four months. Clinical gain is often seen for far longer than

this however with functional benefits lasting up to twelve to eighteen months[16,17].

Different preparations have different pharmacokinetic and pharmacodynamic properties. Dose ranges are provided in Consensus documents and it is vital to remember to adhere to them as Botulinum Toxin type A is the most potent neurotoxin known to man. There is no direct correlation between doses of the preparations. Maximum doses of 12-14iu/kg of Botox or 25-30iu/kg of Dysport are recommended[18].

The core of successful focal or global management in movement therapy is a multidisciplinary team assessment that works out functional goals for interventional therapy. Specific evaluation tools are necessary dependent on the possible site of intervention, the individual's level of functional ability and age. A range of treatments are appropriate at different times of growth and development. As with Orthopaedic interventions it is important to consider a multi-level functional approach rather than injections to a single muscle body[19].

Careful explanation of effects and side effects of the Botulinum Toxin injections should be given and informed written consent obtained. Rare local haematoma is the most common observed effect. There is no published report of localized infection or inflammation, though the authors have observed this twice in over 8,000 courses. More serious adverse events have been reported if dosing and/or dilution guidelines are not respected. These include excessive muscle weakness and local spread to other muscle groups. If the injections occur at the hip level then transient bowel or bladder incontinence has been observed, generally at the peak of effect one month following administration. There are two reported international fatalities over the last twelve years, potentially linked to Botulinum Toxin type A injections. Both of these had considerable confounding factors and though dilution and dosing guidelines were vastly exceeded in both cases neither had proven systemic spread of toxin on immunoassay of distal neuro-muscular junctions.

The Botulinum Toxin injections should be administered by an experienced team in a child friendly setting. The injections themselves should take place with care to minimize trauma for the child and family. Local anaesthetic and inhaled or oral sedation or even general anaesthetic should be considered. It is generally accepted now that guidance beyond clinical palpation is needed for needle placement. In children the use of ultrasonography to localize muscles is widely used, though some centres use electrical stimulation or EMG.

Re-evaluation is necessary at the peak of potential benefit and at the time of terminal re-sprouting. Botulinum Toxin injections are not a stand alone treatment modality and once again it should be stressed that it they are used as part of an integrated therapeutic approach in Paediatric Neurodisability. A post injection management programme is necessary. It may be necessary to repeat the course of injections and continuation or discontinuation as a therapeutic modality is dependent on functional gains, improved posture and/or improved comfort in the individual child. Secondary non-response due to muscular fibrosis or the formation of neutralizing antibodies against Botulinum Toxin A is rarely seen. When benefits are no longer observed onward referral to other elements of movement therapy services may be necessary.

DYSTONIA IN CHILDREN WITH CEREBRAL PALSY

Dystonia is physiologically characterised by the involuntary co-contraction of agonist and antagonist muscle groups at a joint and an overflow flow into muscles or limbs not normally involved with intended movement, resulting in abnormalities in posture and twisting movements. Dyskinetic cerebral palsy has an estimated prevalence of 0.27 per 1000 live births[20]. In dystonia muscle tone typically fluctuates, varying from normal or low to extreme hypertonia. It can be precipitated or worsened by attempts to move and can vary according to emotional state. Dystonia typically diminishes or disappears with distraction and sleep

There are numerous systems for the classification of dystonia. Considering the underlying pathological process, dystonia may be defined as (i) *Primary*, (ii) *Secondary* or (iii) *Heredodegenerative*. Primary dystonias are unaccompanied by other neurologic abnormalities, except tremor and occasionally myoclonus. Primary dystonias are often attributable to a genetic cause[21]. To date over 20 such dystonic syndromes have been identified, with mutations denoted DYT[21-24]. Secondary dystonia can be considered symptomatic, due to identifiable brain lesions or metabolic abnormalities. Dyskinetic cerebral palsies fall into this category. Dystonia may also be classified as *focal*, *segmental* or *generalised* depending upon the extent and distribution of muscle involvement.

The basal ganglia have long been implicated in the pathophysiology of dystonia[25,26]. Considerable evidence from electrophysiological studies in patients with primary dystonia suggests that abnormalities in the central nervous system are more widespread. These abnormalities include a loss of inhibition at various levels of the nervous system, abnormalities in sensory-motor integration and abnormal neuroplasticity[27]. The basal ganglia connect to the cortex and thalamus and organize muscle-driven "motor" movements of the body. The major divisions of the basal ganglia are the caudate nucleus, putamen, globus pallidus and substantia nigra. The globus pallidus can be further divided into two subsections, the globus pallidus interna (GPi) and globus pallidus externa (GPe). Microelectrode recordings of GPi neurons taken during neurosurgical procedures on patients with primary and secondary dystonias have demonstrated low discharge rates, with irregular firing patterns[6,28,29]. Local field potentials recorded from the GPi have also demonstrated a prominent and abnormal oscillation in the 3-12 Hz band, synchronising with discharges from local neurons[30]. Further studies have demonstrated correlation between these abnormal local field potential oscillations and oscillations in EMG recordings in dystonic patients[31]. This coupling is bi-directional, though the drive from the GPi to peripheral muscle outweighs that in the reverse direction[32]. Secondary Dystonia has been hypothesised as deriving from a reduced and disordered GPi output, with a pathological low frequency oscillation.

TREATMENT OF DYSTONIA

Treatment options in dystonia include oral medications, botulinum toxin for focal dystonia, intrathecal baclofen and neurosurgical interventions. In this latter category, surgical

pallidotomy has been largely replaced with DBS to the GPi.

Oral medications:

Numerous medications have been used in the management of dystonia, including anti-cholinergic medications (e.g. trihexiphenidyl), tetrabenazine, benzodiazepines (e.g. diazepam) and baclofen.

Trihexyphenidyl has an anticholinergic effect, reducing striated muscle contractions and parasympathetic activity. It has been widely used in the treatment of both primary and secondary dystonias for more then 20 years[33]. Retrospective data has suggested a beneficial effect in the management of dystonic cerebral palsy[34]. A more recent open-labelled study in children with CP suggested an improvement in arm function with its use[35], though robust prospective data is lacking. A starting dose of 0.5 mg (infant), 1 mg (child) or 2 mg (adolescent) three times a day is generally used by the authors, increasing by 0.5, 1 or 2mg per day each week until either an effect is seen. In children and young adults doses can be increased until side effects occur or a total daily dose of 9, 30 or 90 mg is reached. The main side effects of trihexyphenidyl include dry eyes and mouth, gastrointestinal disturbances, urinary retention and behavioural disturbances. Pupil dilatation should not be considered a dose limiting side effect. These doses are in excess of the dose guidance in the British National Formulary. Use of these medications should only be considered in the context of ongoing specialist neurodisability follow up.

Tetrabenazine is a benzoquinolone that depletes synaptic dopamine transmission by a dual action, reducing vesicular monoamine uptake by binding to vesicular monoamine transporters, and also by acting as a post-synaptic dopamine receptor antagonist. Tetrabenazine is more widely used in the treatment of chorea in adult Huntington's disease. Its use in children is less common, though a number of case reports have suggested efficacy. A retrospective study of 31 paediatric patients with hyperkinetic movement disorders refractory to other medications suggested a symptomatic improvement in 24 (77%) patients[36]. In this study relatively high doses of tetrabenazine were required, over 100mg/day in three divided doses compared to an average of 70mg/day reported in adult studies.

Parkinsonism is recognised as a common side effect of tetrabenazine use in the adult population[37]. It is not possible to estimate the incidence in the paediatric population, but it has been hypothesised that this should be seen less frequently given the decline in dopamine function seen with age[38].

DEEP BRAIN STIMULATION

In recent years Deep Brain Stimulation (DBS)[39] has increasingly been used in the treatment of dystonia in both the paediatric and adult age group[40-44]. The technique utilises quadripolar electrodes implanted within the deep nuclei of the brain to deliver a continuous electrical signal. The GPi has become the established target in the treatment of dystonia (figure 1). The implanted electrodes are linked by an extension lead to a remote stimulator unit that is implanted in a similar fashion to a cardiac pacemaker into the subcutaneous tissue in the supraclavicular region or the abdomen. This unit may control either one or both of the implanted electrodes.

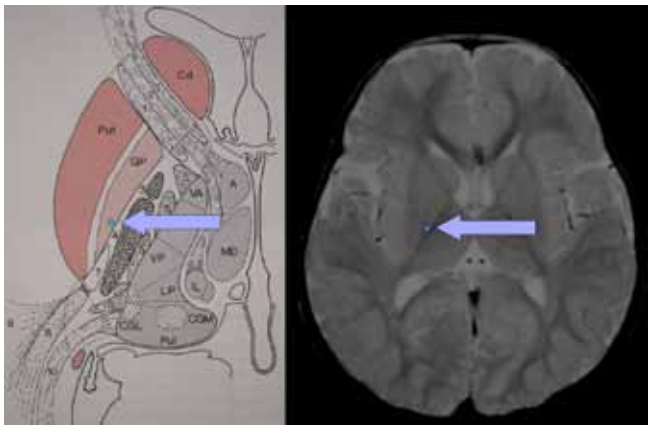

Fig 1. Anatomical location of the Globus Pallidus Internus (GPi)

Medtronic are currently the only manufacturer of approved devices. In paediatric patients, the contacts on the implanted electrodes are separated by 0.5 mm.

The Complex Motor Disorder Service (CMDS) at the Evelina Children's Hospital, London, in conjunction with the Functional Neurosurgery service at King's College Hospital, London, currently provides the only dedicated paediatric DBS service in the UK. Patients with dystonia would be considered suitable for referral where conventional therapies (i.e. medications) do not adequately control symptoms or where side effects can not be tolerated by patients (figure 2).

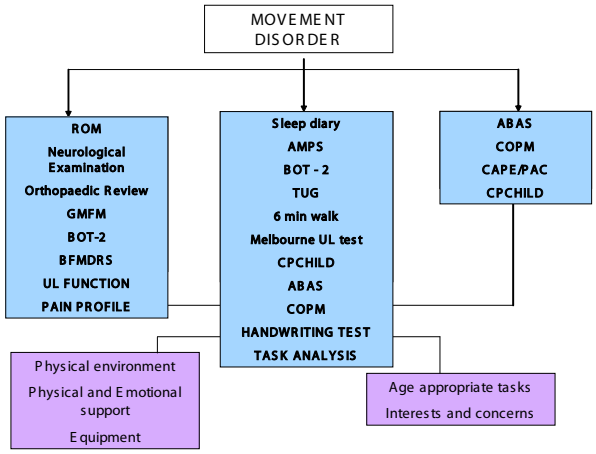

Fig 2. Assessment techniques in children with movement disorders

Pre-Operative Assessment

Following referral to the CMDS, patients receive a comprehensive baseline assessment by the multi-disciplinary therapy team. MRI of the brain allows detailed anatomical pictures of structures of interest, which is useful in determining diagnosis, location and extent of visible lesions, presence of co-morbidities or other abnormalities. This is particularly important in determining whether there is an intact GPi target site for DBS. Transcranial Magnetic Stimulation (TMS), also termed "Magstim" testing, is a non invasive and painless method of exciting neurons using strong magnetic fields held over the cortex. Electromyogram (EMG) recorded over hands and feet are used to measure nerve conduction and velocity to ensure the corticospinal tract is

intact. Extensive corticospinal damage would be considered a relative contraindication to DBS. Such patients would instead be considered for ITB.

DBS Surgery

Pallidal DBS should be considered a reversible procedure, in contrast to the pallidotomy it has largely superseded. The implanted neurostimulator is often described as a brain "pace maker" (figure 3). The surgery is performed in awake adults, but in children a general anaesthetic is used.

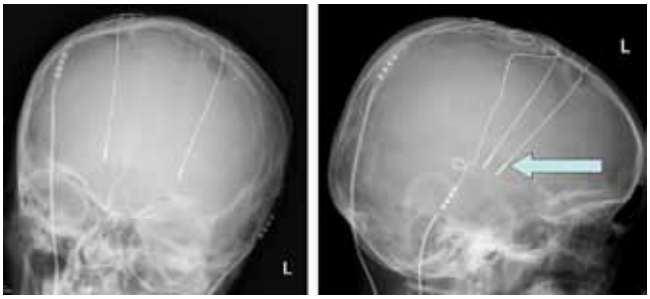

Fig 3. X-rays demonstrating the position of DBS wires

Mechanism and efficacy of DBS

The precise mechanism of action of DBS is far from clear. In broad terms, stimulation either creates a "functional lesion" in the target nuclei or replaces an aberrant output from the target nuclei with a more physiological signal[45-47]. A functional lesioning mechanism would be consistent with the comparable effect of pallidal DBS and surgical pallidotomy.

Most studies of DBS in the treatment of dystonia have used the Burke-Fahn-Marsden Dystonia Rating scale as a measure of the severity of dystonic symptoms[48]. Primary dystonia is more responsive to Pallidal DBS then secondary dystonia[49]. In Secondary dystonia, improvements in BFMDRS compared to baseline of 5-40% have been reported. This contrasts with the up to 80% improvement seen in Primary dystonia. A minimum response of 25% is often defined as a "success". It important to note that reduction in dystonia does not always equate to improvements in function, but quality of life, comfort and carer burden issues can be much improved both for the child and their carers.

The range of treatments available for children with motor disorders has expanded considerably in recent years. The best outcomes are obtained in the setting of an experienced multiprofessional team where children and families have the opportunity to learn about treatment options and have access to the right intervention at the right time. Treatment is more likely to be successful in the context of a child who is not in pain, has comfortable and appropriate equipment and is able to communicate.

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Review

Eye Abnormalities in Fetal Alcohol Syndrome

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BACKGROUND

Fetal alcohol syndrome (FAS) – a condition caused by chronic maternal alcohol consumption during pregnancy[1] – is important both in terms of its prevalence and its effects: it is estimated to be the commonest non-inherited cause of learning disability[1]. Diagnosis is based on the presence of characteristic facial dysmorphism, postnatal growth retardation and functional or structural central nervous system deficits[1]. In this review, however, we propose that the eye is a sensitive and reliable marker of teratogenesis and provides a useful adjunct to the diagnosis of FAS, with eye abnormalities having been shown to occur in over 90% of children with the condition[2]. It is our objective, then, to describe the effects of prenatal alcohol exposure on the eye, quantify their incidence and comment on their importance in diagnosis of children with FAS.

METHODS

We searched the electronic library Medline from its inception to March 2009 for original research and review articles relating to prenatal alcohol exposure, using combinations of the terms 'fetal alcohol', 'eye', 'ophthalmic' and 'alcohol teratogenesis'. We applied no language restrictions. We also searched reference lists of identified articles. Whilst this is not an exhaustive review, we have attempted to make it representative of the literature in this field.

RESULTS

Short palpebral fissures: A shortened distance between the inner and outer corners of each eye, defined as a length two or more standard deviations below the mean. Normal measurements for palpebral fissure length are provided by the Hall Caucasian Charts[3]. Measurement can be easily performed with a small ruler, although the examiner must ensure that the patient's eye is fully open. The presence of short palpebral fissures is of particular discriminant value in FAS[4].

Epicanthus: This is a lateral extension of the skin of the bridge of the nose over the endocanthion. It is important to remember that epicanthal folds may occur naturally in some races and are more commonly noted in childhood. A study found 80% of children prenatally exposed to ethanol had epicanthus; degree of epicanthus may be quantified with a Likert scale[1].

Ocular hypertelorism: Defined as an increased interorbital distance, and may be measured as the distance from right endocanthion to left endocanthion. It is a commonly reported finding in FAS, although not pathognomonic of the condition[5].

Photo courtesy of Mick Stephenson

Coloboma: Normally the choroid fissure closes during the seventh week of development - failure of closure results in the formation of a distinctive cleft in the iris known as coloboma iridis[6]. This is one of the key extensive malformations that may be found in children with FAS.

Strabismus: An abnormal alignment of the two eyes. While it is a non-specific finding, it is common in FAS and may be diagnostically useful in conjunction with other features; Strömland found that of thirty children with FAS, 13 had strabismus, 12 of which had a horizontal convergent form (esotropia)[2].

Blepharoptosis: (or ptosis), is drooping of the upper eyelid. Although it is a non-specific sign, Strömland found that 20% of children with FAS had blepharoptosis[2].

Microphthalmia: An abnormally small eye – is a frequent finding in FAS and was included in the Fetal Alcohol Study Group diagnostic criteria. However, the diagnostic usefulness of this condition is limited by difficulty in detection, particularly in the presence of confounding factors such

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as microcephaly and short palpebral fissures. Objective methods such as ocular axial length measurement under ultrasonography may be necessary[2,7].

Abnormalities of the fundus: The fundus may be affected by various abnormalities - the most common findings are hypoplasia of the optic nerve and increased tortuosity of the retinal vessels[8,9]. In a cohort of Swedish children with FAS, Strömland found optic nerve hypoplasia in 48% and increased tortuosity in 49%[2]. More recently, Hug *et al* suggested that prenatal alcohol exposure leads to disturbed retinal function on the basis of abnormal electroretinograms in ten children with FAS[10]. These conditions are important primarily because of their association with visual loss, but also because they may be useful diagnostically via ophthalmoscopic examination of the fundus.

DISCUSSION

The detrimental effects of alcohol on the fetal eye are perhaps less well recognised than its other manifestations, but are common and important from the perspective of both diagnosis and management.

While the relationship between alcohol and teratogenesis is not disputed, there is conflicting evidence on the effect of very small amounts of alcohol on mother and baby. Consequently, the threshold of safe alcohol consumption during pregnancy is unclear. The Royal College of Obstetricians and Gynaecologists (RCOG) states that women should avoid drinking excessive amounts of alcohol when pregnant but there is no definite evidence that drinking 1 to 2 units once or twice a week is actually harmful[11].

To this end, we recommend a full ophthalmic examination in all children suspected of having a fetal alcohol spectrum disorder, whether this is on the basis of developmental concerns or the possibility of maternal alcohol consumption during pregnancy. This should comprise:

- Inspection for periocular features, possibly supplemented by morphometric analysis
- Measurement of visual acuity (using visual evoked potentials), visual fields and eye movements
- Slit lamp examination of anterior segment and media
- Ophthalmoscopic examination with particular attention paid to the optic disc

Not only is this examination useful diagnostically, but it also allows timely and appropriate management of problems, which may cause profound visual loss and contribute significantly to the handicap of those affected.

We recognize that, aside from those described here, a myriad of other eye abnormalities have been described in FAS. Nevertheless, it is our hope that this review raises awareness of the effects of alcohol on the developing eye and their clinical importance.

The authors have no conflict of interest. Abdelmageed Abdelrahman and Richard Conn are final year medical students at Queen's University Belfast, Northern Ireland

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Paper

Evaluation of angiography as the sole imaging study for the proximal aortic neck prior to EVAR

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ABSTRACT

Background: Angiographic assessment is an alternative to computerised tomography (CT) prior to endovascular aneurysm repair (EVAR). We evaluated angiography in aortic neck morphology assessment as an alternative investigation.

Methods: Patients admitted for elective or emergency EVAR were assessed by pre-operative CT and intra-operative angiography. The proximal and distal aortic neck diameters, and neck length were measured. Measurements were expressed as median (95% CI).

Results: 35 patients (20 male) were assessed from August 2003 to January 2005 for elective (26) and emergency (9) EVAR. In the overall group, the proximal neck diameter was 22.0mm (21.0-23.0) on CT, and 20.7mm (19.3-22.3) on angiography. The distal neck diameter was 23.0mm (22.0-24.0) on CT, and 22.3mm (20.3-24.6) on angiography, while the neck length was only slightly greater on angiography [23.0mm (17.5-28.4)] relative to CT [23.0mm (20.0-28.0)]. The stent-grafts deployed were oversized by 26.8% (± 14.8%) relative to the CT measurements, and 33.7% (± 15.6%) relative to angiographic measurements. Good correlation was found for all three measurements between CT and angiography.

Conclusions: Angiography alone is inadequate for endovascular aneurysm repair. Although it has timesaving potential, the accuracy achieved is not sufficient to use alone.

Key words: Angiography, computerised tomography, endovascular, aneurysm repair

INTRODUCTION

Endovascular repair (EVAR) of an abdominal aortic aneurysm (AAA) has become an acceptable alternative to conventional open repair in both the elective and emergency situation. Although the effectiveness of EVAR in fit elective patients has been confirmed, the same has not been demonstrated for ruptured AAA (rAAA) patients. This is despite a few specialist centres reporting significantly better results in comparison to conventional open repair[1-3]. However, these results are based on the use of EVAR in treating stable contained ruptured AAA, with benefits in the unstable patients remaining ambiguous[4]. It is in the latter group of patients, where mortality is highest, that the value of EVAR should be evaluated.

A major trepidation with the use of EVAR in unstable rAAA patients is how to assess anatomical suitability and calculate accurate sizing of the stent-graft. Contrast enhanced computerised tomography (CT) scanning is the investigation of choice for many, with the additional advantage of revealing other abdominal pathology causing symptoms. But this investigation will lead to unnecessary delay in haemorrhage control, which is vital to the survival of these patients. On-table angiography has been suggested as an alternative, although it only provides luminal dimensions with possible underestimation of the true vessel diameter[1,3].

Since commencing a policy of assessing all ruptured AAA for endovascular repair, angiographic measurements of neck dimensions have become an integral part of our practice. The aim of this study therefore, was to evaluate whether angiographic measurements of the aneurysm neck are accurate enough to complement or replace CT measurements for EVAR, particularly with unstable emergency patients in view.

PATIENTS AND METHODS

Patient recruitment

Patients were prospectively assessed when admitted for elective and emergency endovascular repair of their aneurysm. All elective patients had AAA over 55mm in maximum diameter, while emergency patients were defined as those with a definite leaking or ruptured AAA. Emergency

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aneurysm repair was considered on all-comers, except in the presence of advanced dementia, terminal cancer, end-stage cardiorespiratory or renal disease and by patient choice. Assessment and analysis was performed upon consecutive elective and emergency patients, who had repair conducted jointly by one particular consultant vascular surgeon and one consultant interventional radiologist, both of whom had considerable experience in EVAR over several years.

The patients had morphological assessment made by both pre-operative CT and intra-operative angiography. Three morphological measurements were compared. The proximal neck diameter was measured immediately below the lowest renal artery, from adventitia to adventitia. The distal neck position was taken as the transition between parallel vessel walls and diverging walls. This is by its nature slightly subjective, but is a relatively identifiable reference point and was identified with good reliability, as there was very little inter-observer variation in bottom neck measurements. The neck length was taken as the distance between proximal and distal neck. Two experienced consultants in the endovascular team, blinded to the CT results, independently made the measurements of the angiogram. All endovascular aneurysm repairs, in this study, were performed using a Talent (Medtronic, Watford, UK) stent-graft, sized according to the pre-operative CT measurements. The normal unit protocol is to oversize the stent-graft by 20%, based on CT proximal neck diameter. However, this may prove to be slightly increased in the emergency setting, due to a limited stock of stent-graft sizes[5].

Computerised tomography angiography measurements

CT scans were performed using a Philips MX8000 four-slice helical scanner (Philips Medical Systems, Eindhoven, Netherlands). Non-ionic intravenous contrast was injected at 3ml per second by preference at the ante-cubital fossa. An automatic bolus tracking system was used to ensure optimum vessel opacification. Axial images were reconstructed at 1.6mm intervals. Measurements of orthogonal (perpendicular to the scan axis) diameter were performed on helical CT scan data sets on a Brilliance workstation (Philips Medical Systems, Eindhoven, Netherlands).

The shortest diameter was measured to avoid the distortion caused by vessels turning in relation to plane of the scan. It is possible to reconstruct images axial to a curved portion on the aorta, although the accuracy of this is not verified. At present we prefer to use the scan plane axial images to eliminate a source of potential variability. All measurements were made at the same workstation using the same measurement software and optimum windowing to reduce any artefact.

Angiographic measurements

Angiography was performed using a Philips Integris V5000 system (Philips Medical Systems, Eindhoven, Netherlands) and either Iomeron 270 or Visipaque 270 contrast solution, depending on the patient's renal function according to our institutional protocol. Measurements were performed using integrated software on the angiography system, following calibration with a graduated pigtail catheter. Measurements were made across the aortic neck, perpendicular to the aortic neck axis, at sites comparable to the proximal and distal neck measurements taken at CT. In an attempt to simulate the extreme urgency of dealing with unstable ruptured aneurysm patients, only one angiogram was made in postero-anterior projection. While an automatic measurement package is available on the angiography system, it is not reliable in detecting the aortic wall in the presence of stent-graft delivery systems and catheters. Measurements were therefore limited to those taken by manually positioning cursors on a digitally subtracted image. A measurement of the neck length was also made and taken to be the distance between the proximal and distal neck. Additional measurements, such as iliac and aneurysm sac diameters were not included in this study.

Statistical analysis

Statistical analysis was performed using SPSS (Version 13, SPSS Inc, Chicago, Il, USA). The age of the patients was described in terms of mean age in years (± standard deviation). The aortic neck measurements in mm was expressed as median and 95% confidence intervals (CI). Correlation between the two investigative modalities for the measurements was determined using Spearman's rank correlation coefficient, with a p value of less than 0.05 considered significant.

RESULTS

Patient profile

Thirty-five patients (20 male) were assessed, prior to EVAR, by CT and angiography, from August 2003 and January 2005. These included both elective (26) and emergency (9) patients and the overall mean age was 77.7 (± 6.75) years old.

Comparison of neck dimensions of the overall group

The median proximal neck diameter on CT was 22.0mm (21.0 – 23.0mm), while angiographic measurement was 20.7mm (19.3 – 22.3mm). When assessed by statistical correlation, there was a close relationship of results for the proximal neck diameter ($r = 0.71$, $p<0.0001$) (Figure 1). The median diameter of the distal neck was 23.0mm (22.0 – 24.0mm) on CT, while that by angiography was 22.3mm (20.3 – 24.6mm; $p = 0.29$). Correlation of these measurements was also significant ($r = 0.65$, $p<0.0001$) (Figure 2). The median neck length was 23.0mm (20.0 – 28.0mm) on CT and by angiography was 23.0mm (17.5 – 28.4mm; $p = 0.76$). The correlation between the measurement for the neck length, as demonstrated in Figure 3, although significant was weaker, reflecting possible apparent foreshortening on X-ray ($r = 0.55$, $p=0.004$) (Figure 3).

Comparison of neck dimensions of the elective cases

The median proximal neck diameter on CT was 21.5mm (20.0 – 23.0), while the angiographic measurement was 20.0 (18.5 – 21.5). Close correlation was found in this group of patients ($r = 0.70$, $p<0.0001$). The median diameter of the distal neck was 24.0mm (23.0 – 25.0) on CT, while by angiography was 22.3mm (19.6 – 25.1). Significant correlation was calculated ($r = 0.77$, $p<0.0001$). The neck length in this cohort was 22.0mm (19.0 – 26.0) on CT and 23.2mm (15.1 – 29.6) by angiography. Correlation for neck length remained significant ($r = 0.63$, $p = 0.004$).

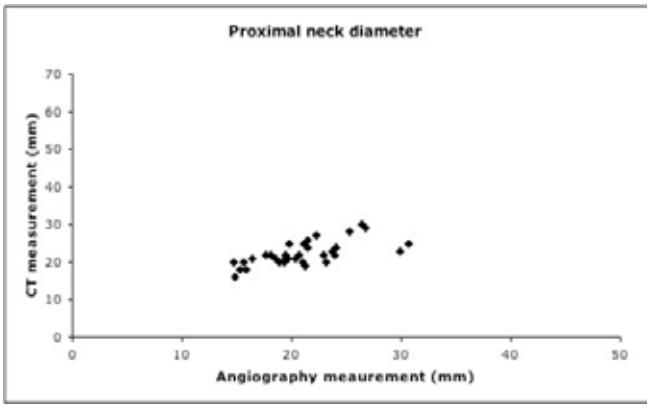

Fig 1: Scatterplot of proximal neck diameter measurements.

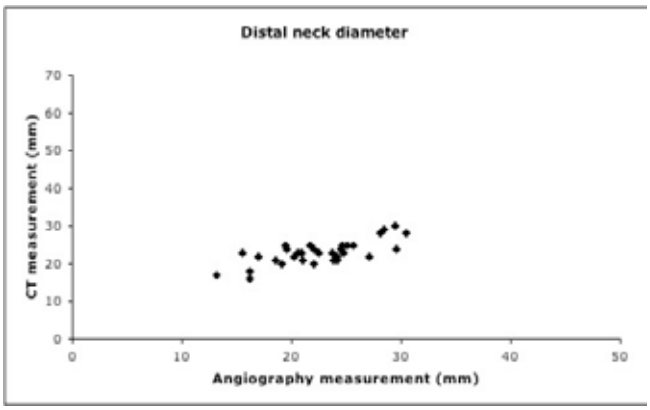

Fig 2: Scatterplot of distal neck diameter measurements.

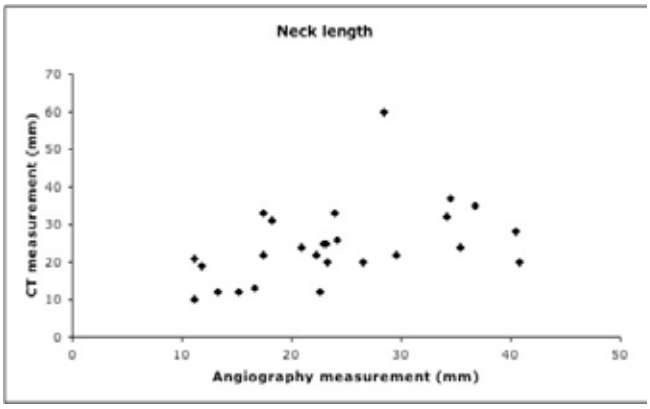

Fig 3: Scatterplot of neck length measurements.

Comparison of neck dimensions of the emergency cases

In the smaller emergency group, the proximal neck diameter was 22.0mm (20.0 – 30.0) on CT and 24.0mm (18.1 – 30.6) on angiography. Significant correlation was demonstrated ($r = 0.80$, $p = 0.03$). The median distal neck diameter was 21.0mm (17.0 – 23.0) on CT, while angiography measured it at 23.9mm (16.2 – 27.0), with correlation found to be significant ($r = 0.92$, $p = 0.0004$). The neck length was measured to be 28.0mm (12.0 – 35.0) on CT and 22.9mm (17.5 – 40.4) on angiography. Correlation was not demonstrated in this ($r = -0.04$, $p = 0.94$).

Stent-graft sizing

The mean size of the stent-grafts used was calculated as 28.2mm (± 3.6mm). They were oversized by 26.8% (± 14.8%) relative to the CT measurements, and by 33.7% (± 15.6%) based on the angiographic methods. If an approximate oversizing of 35% were used for angiographic measurements, no patients would have had a smaller stent-graft than the CT measurement, while only three patients would have had a stent-graft size within 1mm of the CT measurement.

Outcome

In the follow-up period to 2007, one stent-graft migrated in an emergency patient, although without any requirement for secondary intervention. One elective patient had a Type I endoleak, while five elective patients had a Type II endoleak, although only one required lumbar embolisation.

DISCUSSION

The speed with which a ruptured AAA (rAAA) can be effectively excluded from the circulation and haemorrhage stopped, is of utmost importance to the outcome of the patient. However, one of the most vital steps in determining the ultimate success of EVAR for the treatment of rAAA depends upon the ease and accuracy of assessing suitability and sizing the stent-graft. Although ultrasound is the cheapest and simplest diagnostic procedure of AAA, it is not suitable for pre-operative assessment of the aneurysm morphology[6]. Magnetic resonance angiography is becoming increasingly popular for the elective patient, but is unlikely to be useful in emergency settings, because of its restricted availability. CT remains the investigation of choice for both elective and emergency AAA patients. It provides accurate information on the neck length and diameter, neck shape, iliac vessels, as well as providing diagnostic confirmation of a rAAA. CT can also exclude the presence of a ruptured AAA, while angiography may not confirm a clinically suspicious diagnosis.

It has been shown that there usually is sufficient time to assess the average, relatively stable, patient with rAAA by CT scan, prior to proceeding to surgery[7]. Workers at the Southampton General Hospital have found that the median time delay to operation was 159 (16-1450) minutes, with neither the delay nor CT scan influencing the outcome. However, rAAA patients are unpredictable and unstable patients should be offered immediate life-saving surgery, whenever feasible.

The use of contrast angiography to evaluate the anatomical suitability for EVAR, and to size the stent-graft, has been proposed as an option. Nevertheless, most practitioners remain sceptical in view of its limitations. Firstly the magnification artefact, which is determined by the distance from X-ray source to receiver, and body habitus will adversely affect the accuracy of the measurements[8]. The use of calibrated catheters may minimise this artefact by allowing patient-specific determination. Secondly, tortuosity in the plane of the angiogram will cause a foreshortened appearance and diminish the apparent length of the vessel. This is partly illustrated by the weaker correlation of neck length measurements in this study especially in the ruptured cases[9]. The subgroup analysis results in an inconsistent picture with regard to the neck length correlation, but this is due to the smaller numbers in the subgroups. Thirdly, presence of thrombus, may affect the true diameter of the vessel[10,11]. Finally the presence of iliac stenotic disease may

be underestimated by projection errors. This however, may be reduced with oblique views[9].

CT overcomes many of these problems, in particular the thrombus effect. However diameter measurements with CT may suffer from methodology errors and observer variability[12,13]. This variability is regardless of the measurement plane used[13]. The elliptical shape of a tortuous vessel on axial CT can result in a cylindrical stent-graft being deployed in a non-cylindrical aortic neck, with the risk of endoleak[14]. However helical CT at small slices, as used in this series, with post-procedure reformatting produces excellent images, not unlike the real object, with the generation of 3D images and linear data along the axis of blood flow[15,16]. Although better results may be gained from 3D images than traditional axial CT, and may be ideal especially for elective EVAR planning, it is impractical in assessing emergency patients[17].

The assessment of the proximal neck morphology is crucial to the success of EVAR. Rose *et al*[18] demonstrated that 80% of rAAA were deemed to be anatomically unsuitable, with 48% having more than two adverse features. Unsuitable neck morphology was the primary reason for exclusion in 76%. This was supported by Wilson *et al* who found that the neck morphology of rAAA was significantly shorter than a similar cohort of elective patients[19].

Our comparative observation demonstrated that angiographic measurements of the neck length are similar. However, the measurements of the neck diameter by angiography are almost 7% smaller than the CT measurements. This resulted in 7% difference in the degree of stent-graft oversizing. Nevertheless, the fact that none of the patients would have received a stent-graft smaller that their CT diameter is encouraging. Accurate sizing of the stent-graft is crucial to successful aneurysm exclusion, future endoleaks and neck dilatation, but a less than perfect fit may reasonably be deemed acceptable in unstable patients who have mortality rates of nearly 100%.

While other investigators have compared angiography and CT, no conclusions have been made regarding stent-graft sizes. Beebe *et al* in 1995 retrospectively studied 50 patients who had either AAA or aorto-iliac-occlusive disease[20]. The conclusions were limited by the magnification artefact and the 8mm CT slices. Resch *et al* in 1999 found that the neck diameter was consistently smaller on angiography, but concluded that neither modality was sufficient alone[21]. Recently Diehm *et al* made the comparison in 21 patients[22]. Unlike this study the main conclusions were centred on intra and inter-observer variation in vessel measurements.

Our data, although based upon small patient numbers, suggests that angiography alone will underestimate the diameter of the aneurysm neck, and is therefore inadequate for elective cases. However, it may be argued that in the emergency situation, especially with an unstable patient, it can be used if the stent-graft is oversized by a greater margin. In addition, the poor correlation of neck length measurements may result in patients inappropriately being offered EVAR. There is no doubt that the time delay in obtaining CT scans to assess unstable patients with suspected rAAA has been a major disconcerting factor in offering EVAR as a treatment of choice. By avoiding this time delay, angiography may allow patients to be assessed quicker on the operating table. In addition, angiography can be performed with the patient fully prepared for surgery and an occlusion balloon in place for those deemed very unstable. The caveat to this lies in the fact noted earlier that 80% of rAAA patients are thought to be EVAR unsuitable. However, after performing the angiogram, surgery can proceed either as EVAR or open repair. Unfortunately, despite these theoretical attractions, our results would indicate that angiography is less than ideal for assessing aortic anatomy and cannot be justified in its current state to determine EVAR suitability and in sizing stent-grafts, particularly when most patients can undergo CT scan, even in the emergency situation.

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Corrections.

1. In Hedley Whyte J, Milamed D. Lobar Pneumonia treated by Musgrave Park Physicians. *Ulster Med J* 2009;**78(2):**119-128, there was a small typographical error: on page 125, the first line of the legend to Fig. 9, the year of Prof Maxwell Finland's death was shown as 1982. The correct year is 1987.
2. In Johnston PC, Donnelly DK, Morrison PJ, Hunter SJ. DiGeorge syndrome presenting as late onset hypocalcaemia in adulthood. *Ulster Med J* 2008;**77(3):**201-2, there was a typographical error in the second author's middle initial. It should have read Donnelly DE.
3. In O'Donnell ME, McCavert M, Carson J, Mullan FJ, Whiteside MW, Garstin WI. Non-epithelial malignancies and metastatic tumours of the breast. *Ulster Med J* 2009;**78(2):**105-112, the figure legends for figs 2-4 were transposed and incorrectly printed in the print edition and are reproduced correctly below. The figures are correct, and the online edition has the correct legends.

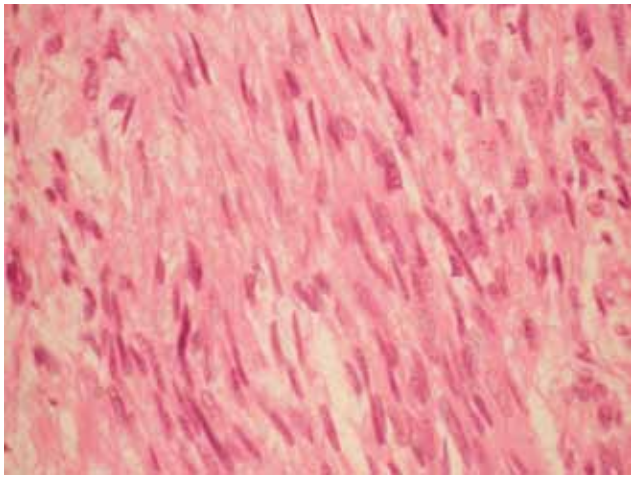

Fig 2. Breast sarcoma (H&E x 200). This field shows large spindle shaped cells with nuclear pleomorphism and eosinophilic cytoplasm. There is no differentiation which would indicate the cell of origin.

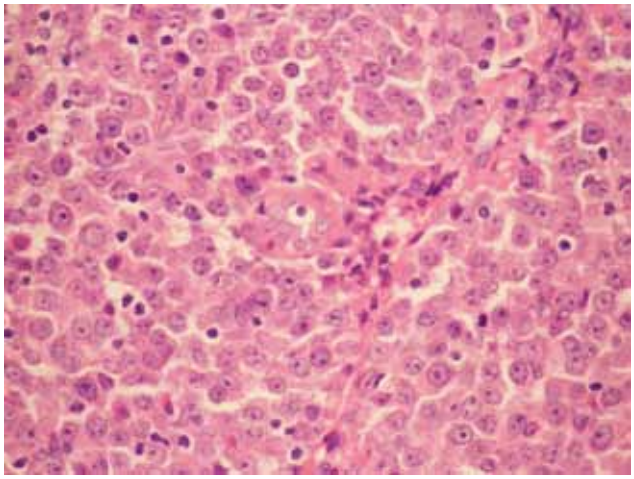

Fig 4. Multiple myeloma deposit right breast (H&E x 200). This field shows large atypical plasma cells many of which are showing immunoblastic differentiation with large central nucleoli.

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Medical History

Aspects of Vitamin A

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SUMMARY

Musgrave Park Hospital in 1942 was the site of an Anglo-American Vitamin A caper. A threatened court-martial was pre-empted. Subsequently the Queen's lecturer in Anatomy, JW Millen, who was the other lecturer to the first editor of this journal, RH Hunter, did much distinguished work. The neurological effects of Vitamin A were elucidated. Further work on cerebrospinal fluid (CSF), placenta, thalidomide and poliomyelitis led to the pre-eminence in applied anatomy and teratology of now Reader James Wilson Millen and Professors JD Boyd and WJ Hamilton, all Queen's Medical School graduates. Training of RH Hunter, JH Biggart and JD Boyd at Johns Hopkins University profoundly influenced these seminal discoveries. The Garretts, a family of Lisburn, County Down origin, saved Johns Hopkins Hospital and Medical School from financial disaster. The Garretts founded a commercial and mercantile empire that took control of the Baltimore and Ohio (B and O) Railroad and enabled the Garretts to dictate that women should be admitted to the Hopkins Medical School and Hospital on exactly the same terms as men. All women and men should already be university honours graduates. Winston S Churchill on his progress up and down the B and O main line in March 1946, recounted to President Harry S Truman and Harry Hopkins his mother's tales of the Garrett boys' adventures.

Key words: Hydrocephalus, Poliomyelitis, Teratology

INTRODUCTION

As a Christmas present in 1941, I* received from my parents a copy of *British Medicine*[1], which cost 3s 6d. I was told it might be taken back on Boxing Day for the Yanks. A fortnight before, Hitler had declared war on the United States. Benjamin Rycroft, since November my brother's godfather[2], was frequently in Windy Ridge, our rented Dunmurry Lane house. Ben read my temporary Christmas present with me. He was horrified when we reached pages 42 and 43 where the discovery of vitamins A and D is ascribed solely to Gowland Hopkins and the Mellanbys[1]. Ben told me that this simply was not true—a Kansan Hopkins Professor of Biochemistry had made these discoveries[3-6]. Moreover, he had been appointed to the Section on Research of the US National Conference on Nutrition in Defense, which advised the lend-lease program[7]. "He was not mean like Sir Edward Mellanby[8] who controlled lots of money and would not give any away, not even to make the penicillin which had run out for your pneumonia" [9].

My father, Angus, was confronted by Ben in my presence. Ben said the book was "ill-informed and provocative". "Maybe", said my father, but it should go back to Musgrave Park to show the Harvard doctors that they must educate and treat with tact those divided by a common language[10].

* All first-person references in this paper are to the first author.

Fig 1. The 31st British General Hospital and US 5th General (Harvard) Hospital combined senior staff physicians and surgeons at the time of the vitamin A caper just before the epidemic traced to contaminated US yellow fever vaccine. Angus Hedley-Whyte, Commanding Officer 31st, and Professor Thomas Lanman, Chief surgeon 5th and Professor Theodore (Ted) Badger, chief of Medicine, 5th [10], are in the front row. Benjamin Rycroft, later knighted[2,9], is in the back row. *Photo courtesy of Col Magnus Smedal, Head of Radiology, 5th General Hospital, gift to John Hedley-Whyte.*

The book was repossessed and was replaced with a crash helmet. Hugh Cairns was insisting that every military motor-bike rider wear one[11]. I was not allowed to drive my pony and trap unless I was wearing the helmet firmly strapped up.

In March 1942, Ted Badger (Fig. 1) arrived from Harvard to be chief of Medicine at Musgrave Park for Harvard's Fifth General Hospital[10]. He read *British Medicine* which was now in "Hut 1" (Officers), Musgrave Park, Belfast. Ted had graduated from Yale. As a tuberculosis specialist and a Boston City Hospital disciple of Max Finland[9], he knew all about Elmer McCollum, PhD, Yale, 1904 (Fig. 2), and the Hopkinses, both Johns and Gowland (Fig. 3). Moreover, he had sailed a small boat across the Atlantic and knew all about nutrition.

Then started the food wars and the intrusive behaviour of the US and UK authorities. The enforcers were chiefly US

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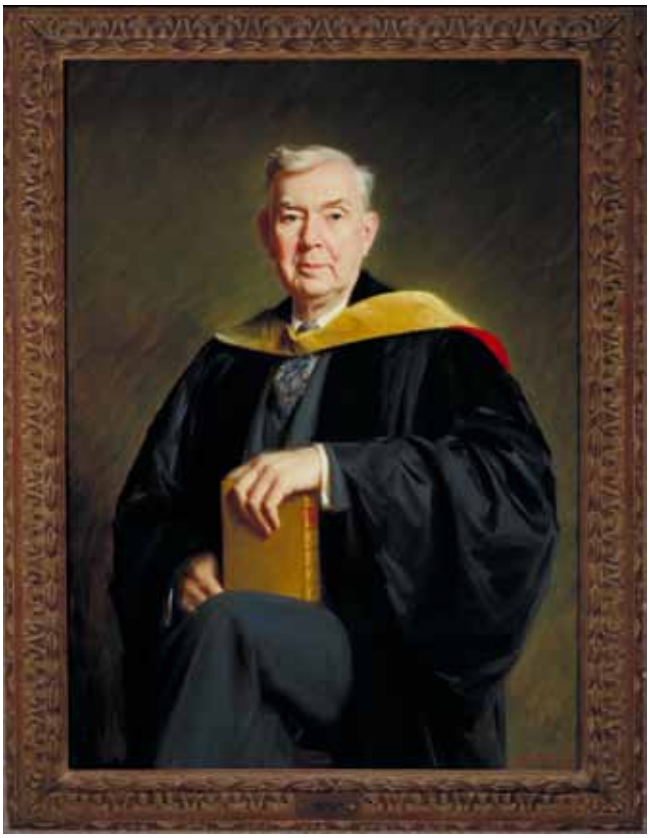

Fig 2. Elmer V McCollum by Paul Trebilcock, oil on canvas, 1954. Courtesy of the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions, photograph by Aaron Levin. Professor Elmer Verner McCollum, PhD, ScD, LLD, DHL, NAS, FRS (1879-1967), was the discoverer together with Marguerite Davis, of Vitamin A[3-6]. Later McCollum discovered Vitamin D[6,12-15]. Born of an illiterate mother in a rural Kansas pioneer family, McCollum initially supported himself, his parents and siblings by becoming a lamp lighter in Lawrence, Kansas. On this regime, lights were lit at dusk and doused at 1:30 am. McCollum developed techniques so that he could become an analyst of wild-cat Kansas oil. His father developed tuberculosis of the spine, but despite these misfortunes, his mother was taught to read and write and all five children graduated from University[7,16,17]. Having obtained a BA and MA from the University of Kansas, Elmer was called to Yale to pursue a PhD in Nutrition. In 1917, having already discovered Vitamin A, while he was on the faculty at the University of Wisconsin, he was appointed Professor of Chemical Hygiene at Johns Hopkins: later his chair was changed to Biochemistry. McCollum served Johns Hopkins from 1917 until his death in 1967. He was elected to the National Academy of Sciences of the United States in 1920[16] and to an FRS in 1961[17]. McCollum succeeded William H Welch[18] as senior mentor of young researchers in the biological sciences at Johns Hopkins. In 1921, at Hopkins, McCollum sponsored the Herter Lecture of Frederick Gowland Hopkins MD, DSc, FRS of Cambridge University[19]. Subsequently McCollum taught Dicky Hunter[20], JH Biggart[21] and JD Boyd[22] from Queen's.

military policemen with bemused sporadic cooperation by the Garda on both sides of the Éire border[28]. British regiments were given considerable latitude in what foods they procured within a certain supplementable budget. Food from Éire and near the border was effectively proscribed for British troops

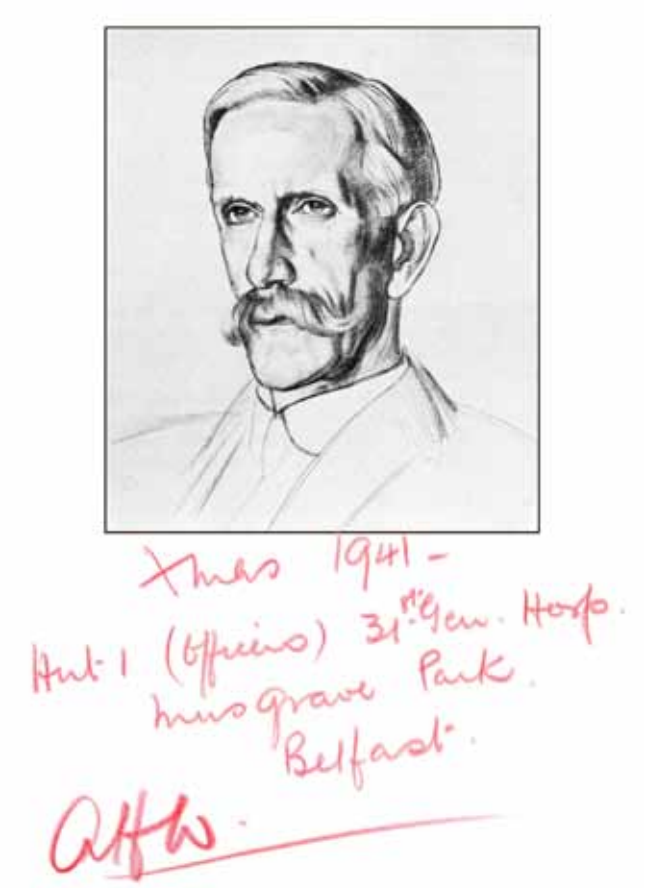

Fig 3. Sir Frederick Gowland Hopkins, OM, MD, FRS. Drawing by Eric Kennington, reproduced by permission of the Master and Fellows of Trinity College, Cambridge[1]. "Hoppy" was the first Professor of Biochemistry at Cambridge, Herter Lecturer, Johns Hopkins 1921, 1929 Nobel Laureate together with Professor Eijkman[19,23]. GM Trevelyan said of Hopkins, "He only thought of others. And so he was loved no less than he was admired"[24]. Hopkins' Department included JBS Haldane (1923-32), Joseph and Dorothy Needham and FJW Roughton[19,24,25]. The Massachusetts General Hospital called FJW Roughton to Harvard to aid with muscle physiology during prolonged cardio-pulmonary bypass[26,27]. My father's inscription is reproduced from the frontspiece of my "temporary" present[1].

- the rationale was that the Nazis, having allegedly infiltrated Éire, would poison Ulster - preferably starting with a "soft" target. The American forces were even stricter. Wherever possible, American forces were to be given only American food[29,30]. The U-boats in 1942 prevented this, but my sister and I were fed bananas by the Harvard doctors and nurses—our first memories of a banana or a tangerine.

VITAMIN A

My father was, in spring 1942, charged as commanding officer of Musgrave Park with contravening the UK food regulations. He was sent an Official Letter of Reprimand. A court-martial was threatened. This gambit did not please the Musgrave Park physicians. Rycroft and his good friend and fellow zoo consultant, Dicky Hunter[9] launched the Vitamin A reprisal. They tested patients and physicians for night-blindness and looked at the records of many previous tests. Not surprisingly, quite a few cases were found. It was

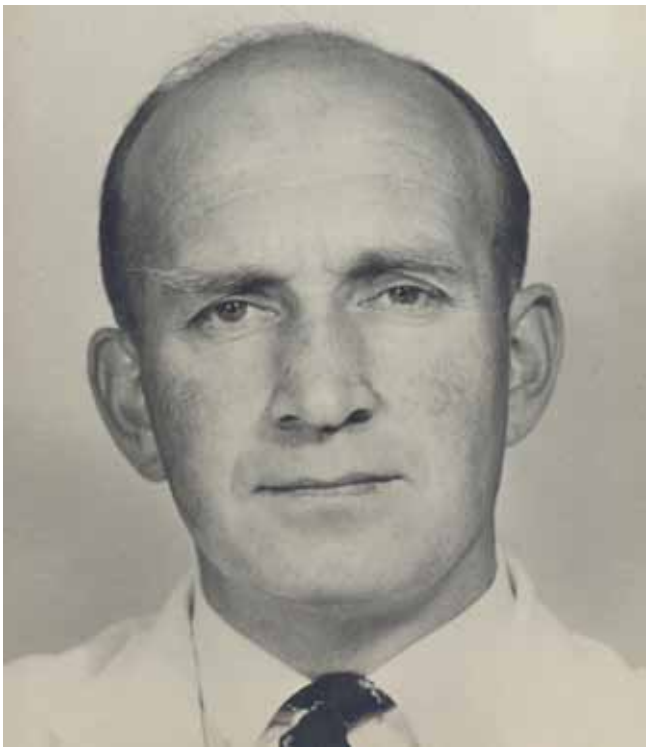

Fig 4. James Wilson Millen, MD, DSc (Queen's), ScD (Cantab), 1915-66, photograph reproduced by permission of the Master and Fellows of St. John's College, Cambridge. JWM was Demonstrator, Lecturer then Senior Lecturer in Anatomy, Queen's University, Belfast; Demonstrator, Lecturer then Reader in Anatomy, Cambridge University. My tutor in Anatomy, Clare College, Cambridge, 1952-55, JWM was born in Bangor, Co. Down. In 1932, having been Head Boy at Bangor Grammar School, he became a medical student at Queen's and Malcolm Clinical Scholar. Resident posts followed at the Royal Victoria Hospital. From 1941-48 the two lecturers under Professor Thomas Walmsley were Millen and RH Hunter, Founding Editor of this Journal[20,31]. Millen, in 1944, was appointed Medical Registrar for Queen's University and thus, ex officio, a member of all faculty committees. From 1945-47 he was President of the Queen's University Rugby Football Club[32,33].

suggested the cause was a less than optimal vitamin A intake, supposedly due to adherence to regulations.

During the years 1941-43, consumption of the United States Armed Forces C and K rations led to symptoms of vitamin deficiency[7,29]. This was corrected by McCollum's appointment in 1941 to the US Committees on Nutrition in Defense and Coordination of Information on Food and Nutrition[7]. These appointments were known at Musgrave Park. My father was thus enabled to contact Whitehall and Washington that his food control discrepancies were aimed at preventing vitamin A deficiency. The jaundice epidemic in the US troops in Ulster started[10]. For several weeks the possibility of vitamin A deficiency exacerbating the jaundice led to my father being cleared of wrong-doing. My sister and I were, thereafter, not allowed to eat bananas in public.

MILLEN AND CAMBRIDGE

When I arrived at Clare College, Cambridge for the Michaelmas Term in 1952, James Wilson Millen (Fig. 4) was assigned as my Anatomy Supervisor. We met weekly for an hour or more for three years. Millen's chief thrust was that anatomy was not useful knowledge without knowing form, function and integration in man and other animals from amoeba up the phylogenetic tree. Millen knew I had been in Belfast from 1940-42[2,9,10]. I knew he had been the other lecturer to Dicky Hunter from 1941 until he came to Clare in1948 via a short stop in Professor Sir Wilfred LeGros Clark's Oxford Department of Anatomy[33]. I also knew that Dicky Hunter was a great and long-time friend of my hero Benjamin Rycroft[9]. Millen's starter reading list was Hamilton, Boyd and Mossman's *Human Embryology,* 2nd edition[34], an edition of Millen and Hunter's Belfast boss, Professor Thomas Walmsley's[35] *Elements of Anatomy*[36] and *Cunningham's Manual of Practical Anatomy*, eleventh edition, revised by JC Brash[37]; four authors of the six, Queen's Belfast or Trinity College Dublin (TCD). In October 1952, Millen said he had heard via Rycroft that his Musgrave Park boss Angus thought that surgeons' children should learn to read using Gray's *Anatomy*. Which edition had I learned on? The correct answer, which I had to look up back in my rooms in Clare Memorial court, was the 18th, 1913, edited by Robert Howden, Professor of Anatomy in the University of Durham. The copy which I still have is inscribed, "Mr. Martin, not to be removed from Wards 5 and 5A"[38]. In 1953 Millen suggested I read McCollum's *Newer Knowledge of Nutrition,* 1929, about the vitamin A and D discoveries[6]. Then we read JH Biggart's *Pathology of the Nervous System*[39] and the *Lancet* galleys of Millen's papers on Vitamin A deficiency and the production of hydrocephalus[40,41] and other neurological malformations. Millen became well-known[42-50]. Soon after I went down to Bart's, Millen went down the Backs as Johnian Praelector and Reader in Anatomy in the University of Cambridge[33].

Fig 5. The Carnegie Institution of Washington, Department of Embryology, 1929, photograph of departmental working scientists courtesy of the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions.From left: Warren H Lewis, George L Streeter, the director since 1918, Martin Nordmann, Emanuel Fauré-Fremiet, Zygmunt Grodzinski, RH "Dicky" Hunter, later founding editor of the *Ulster Medical Journal* and long-time Secretary of Queen's University, Chester H Heuser, Carl G Hartman and Otto Leif Tinklepaugh. This Department and Institution constituted a separate legal entity adjacent to the Johns Hopkins Hospital campus[60].

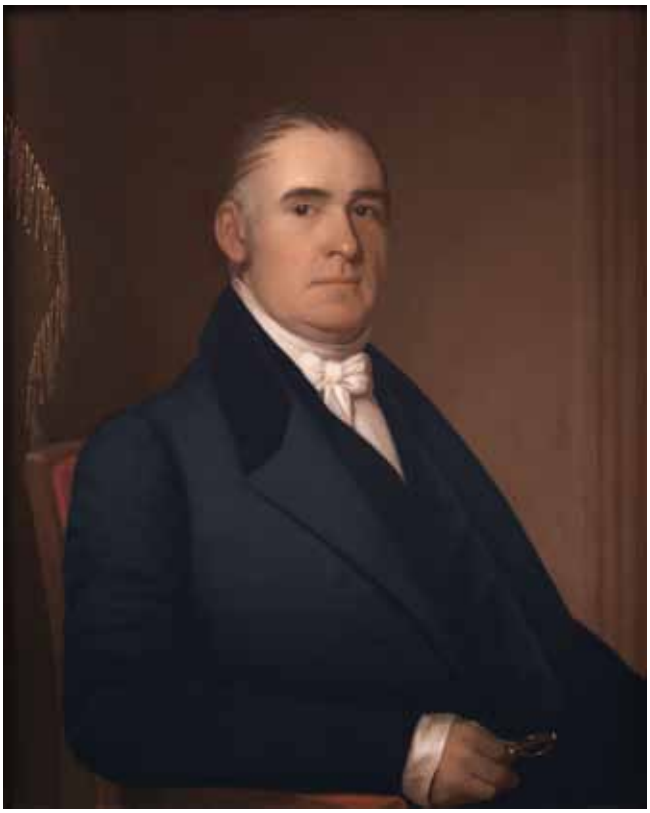

Fig 6. Robert Garrett, 1783-1857, oil on canvas, artist unknown. Reproduced courtesy of the Evergreen Museum and Library, Johns Hopkins University Museums.

On February 28, 1827, at the instigation of Robert Garrett, and other Baltimore businessmen the Act of Incorporation of the Baltimore and Ohio Railroad (B and O) was passed by the Maryland Legislature[66]. In 1830, on the B and O, Tom Thumb one-ton locomotives started replacing horses. By 1834 Grasshopper four-wheeled vertical boiler engines had become standard. In the 1840s, Garrett and B and O interests melded, and the Garretts promoted, sold and bought B and O stock. Robert's eldest son Henry was elected to the B and O Board in 1852. In 1854, second son John W Garrett was elected a director. On a 16-14 vote sponsored and promoted by Johns Hopkins, a bachelor, he became president of the B and O in 1858 and served as the first Garrett B and O Railroad president until his death in 1884[64,65].

Fig 7. Mary Elizabeth Garrett, 1854-1915, by John Singer Sargent, oil on canvas, 1904, unveiled October 4, 1904, in the rotunda of the Johns Hopkins Hospital. Courtesy of the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions, photograph by Aaron Levin.

Grand-daughter of Lisburn-born Robert Garrett, Mary Elizabeth was her father John W Garrett's only daughter and amanuensis. As such she became an eminencée grise of the Baltimore and Ohio Railroad[65] whose stock climbed from 50 to over 170 during her father's presidency[66]. The will of Johns Hopkins, who died on Christmas Eve 1873, left a seven million dollar estate, $130 million today, to found a University. Johns Hopkins's Baltimore and Ohio shares were over half the estate. Half the shares were deeded to maintain the University without encroaching on the capital of the shares. The other half of Johns Hopkins's estate was willed to found the Johns Hopkins Hospital[65]. Mary, in 1884 inherited from her father to become the wealthiest spinster in America[65] and a past-master of coercional philanthropy. She gave to Johns Hopkins School of Medicine and the Hospital on condition that women be admitted on the same terms as men and that the school be graduate level. William H Welch[18] was enabled by the Garrett gifts to become the first Professor of Pathology, a eulogist at Miss Garrett's Memorial Service in 1915[65] and the teacher together with Rich, his subsequent successor, of John Henry Biggart, who in 1931-32 was on a Harkness Fellowship from Queen's University Belfast[21].

When I started experimental studies, Millen's teaching on the necessity to control the milieu interieur of experimental animals was invaluable[51]. His teaching on the use of electron microscopy in biology aided my research colleagues when we studied the blood-brain barrier[52,53] and the lung and haemoglobin[54-58]. Millen's monograph on the cerebrospinal fluid with his long-time collaborator David Woollam, also a great teacher, was a most useful reference[59].

I asked Dr Millen why Queen's Belfast graduates had such leading roles in Teratology, Embryology and Applied Anatomy. Millen replied Dicky Hunter and Hopkins (Fig. 5). I thought he meant Gowland, not Johns. Millen politely suggested I read Gowland Hopkins's 1929 Nobel Oration[23] as well as his now classic 1906 address to the Society of Public Analysts[61], and George L Streeter's recent posthumously published *Apologia pro vita mea*[62]. Millen regretted he had not gone to Hopkins from Queen's like Hunter, Biggart and Boyd, but at least we were working next to the Hopkins building for Biochemistry at Cambridge. Millen also introduced me to his collaborators in Sir Joseph Barcroft's adjacent Physiology department. Millen had worked with Sir Joseph Barcroft's son Henry when they were both at Queen's. Henry got his FRS in 1953. I was also introduced to the biochemists in Francis Young's Department in the Hopkins Building.

Fig 8. Winston S Churchill and President Harry S Truman wave from the special Baltimore and Ohio train on their way to Westminster College, Missouri. From the Collections of the B & O Railroad Museum, Baltimore, Maryland. They "exchanged information about the American Civil War as they looked at the West Virginia and Maryland sites of famous battles…The discussion started when Mr Truman told Mr. Churchill their train was passing through Harpers Ferry. 'I know' Mr Churchill said, 'that's where Jackson seized McClellan's stores'. Mr Churchill also recounted how he had motored through Frederick, Maryland with the late President and Mrs. Roosevelt and Harry Hopkins en route to "Shangri-La"[67]. Harry Hopkins, also on the B and O train, confirmed the details of that war time journey.

THE LISBURN GARRETTS

On the 10th April 1790, Robert Garrett sailed from Belfast on the American-owned brig, the *Brothers*[63]. Born near Lisburn, County Down, on the 2nd May, 1783, Robert was the youngest of the six children of John and Margaret MacMechen Garrett[64,65]. The family arrived in Wilmington, Delaware in May 1790. His father died on the voyage or soon after but his mother was able to buy a farm in Cumberland County, Pennsylvania. As a Scottish Calvinist mother, she worked the family hard[66]. At sixteen, Robert wintered with Ohio Indians. In 1801 he first visited Baltimore, Maryland. By 1814, Wallace and Garrett was prospering. He dissolved the partnership on the death of his first wife, Martha, but married in May 1817 Elizabeth Stouffer, daughter of a Baltimore merchant. By 1819 Robert Garrett and Company were doing business with the rest of the United States and the British Empire.

The family of Robert Garrett Senior rescued Johns Hopkins Medical School and enabled its Hospital to be completed after the crash of 1873 - a rail-road financial bubble from which it took the US economy a decade to recover[65]. The B and O and Johns Hopkins were saved by Robert Garrett's (Fig 6) son and grand-daughter (Fig. 7) travelling to London and raising over $200 million in today's money from Barings just prior to the crash[66]. That was what Winston Churchill told us on 7th December 1951[10] when we dined with him, and we Harrow Monitors discussed the American Civil War. In response to a question about his 1946 Fulton, Missouri trip on the B and O, Churchill (Fig. 8) said Harry Truman was "an astute card player who had won my money." "Never criticize the office of the President of the United States. Remember, young men, he is Commander-in-Chief".

The New York Times had a slightly different take on the journey. Along the main line of the B and O the route passed many Civil War sites. Churchill was known to be extremely knowledgeable[67] about this horrendous first modern war in which 630,000 were killed[68]. President Truman and his military aides were taught much. After his Iron Curtain speech at Westminster College[69], Churchill took his B and O Railroad carriage back to Washington, stopping en route to visit Civil War memorials. Truman and his entourage flew back sans Winston[69] and his mother Jennie Jerome's stories of the Garrett boys: in the Athens Olympic Games of '96, Robert Garrett III was the winner of both the discus throw and the shot put. He placed second in the high jump and the long jump. For each first place medal he received an olive branch and for each second place medal a branch of laurel, along with their respective diplomata[70].

POSTSCRIPT

Sir Frederick Gowland Hopkins in his 1929 Nobel lecture asked "Who was the 'discoverer' of vitamins? This question has no clear answer. So often in the development of science, a fundamental idea is foreshadowed in many quarters but has long to wait before it emerges as a basis of accepted knowledge". He continued, "…The work and words of true pioneers lay forgotten because published when average minds were not ready to appraise them at their right value" [23].

Winston Churchill, not a Hopkins "average mind", told us on the 7th December 1951[10] that he had in March 1946 fulfilled a boyhood ambition. He had deployed his B and O coach on the return to Washington, DC like George Brinton McClellan or Robert E Lee*. Churchill had looked for signs of Stonewall Jackson's extensive destruction: he had been told of the Garretts' heroic reconstruction efforts and their saving endowment of the Hopkins.

In the continuing focus of interest in Vitamin A and the dramatic public health improvements with its deployment by the World Health Organization[71,72], Johns Hopkins continues the path of Elmer V McCollum, Gowland Hopkins and JW Millen[73] (Fig. 9).

ACKNOWLEDGEMENT

Thanks are due to Mr James R Garrett, President, Evergreen House Foundation, Baltimore, MD, and to the staff of the US Library of Congress, Manuscript Division for permission to examine the *Robert Garrett Family Papers*. Container No. 1 has two communications dated 17th October and 8th November 1782, written and signed by Charles Carroll of Carrollton, who, on Independence Day 1828, aged 90, as the sole surviving signatory of the 1776 Declaration of Independence, laid the Cornerstone of the B & O Railroad. The authors have no conflict of interest.

* General McClellan, former President of the Ohio and Mississippi Railroad, was a life-long close friend of the Garretts, despite being fired after the September 1862 battle at Antietam, MD[65,66], by President Lincoln and John W Garrett. John W Garrett's son, Robert Garrett II, succeeded General Robert E Lee, on Lee's death in 1870, as President of the Valley Railroad, a B and O subsidiary. In 1863 Robert Garrett II had escaped through Union barricades to join Lee's Confederate Army of the North Potomac[65].

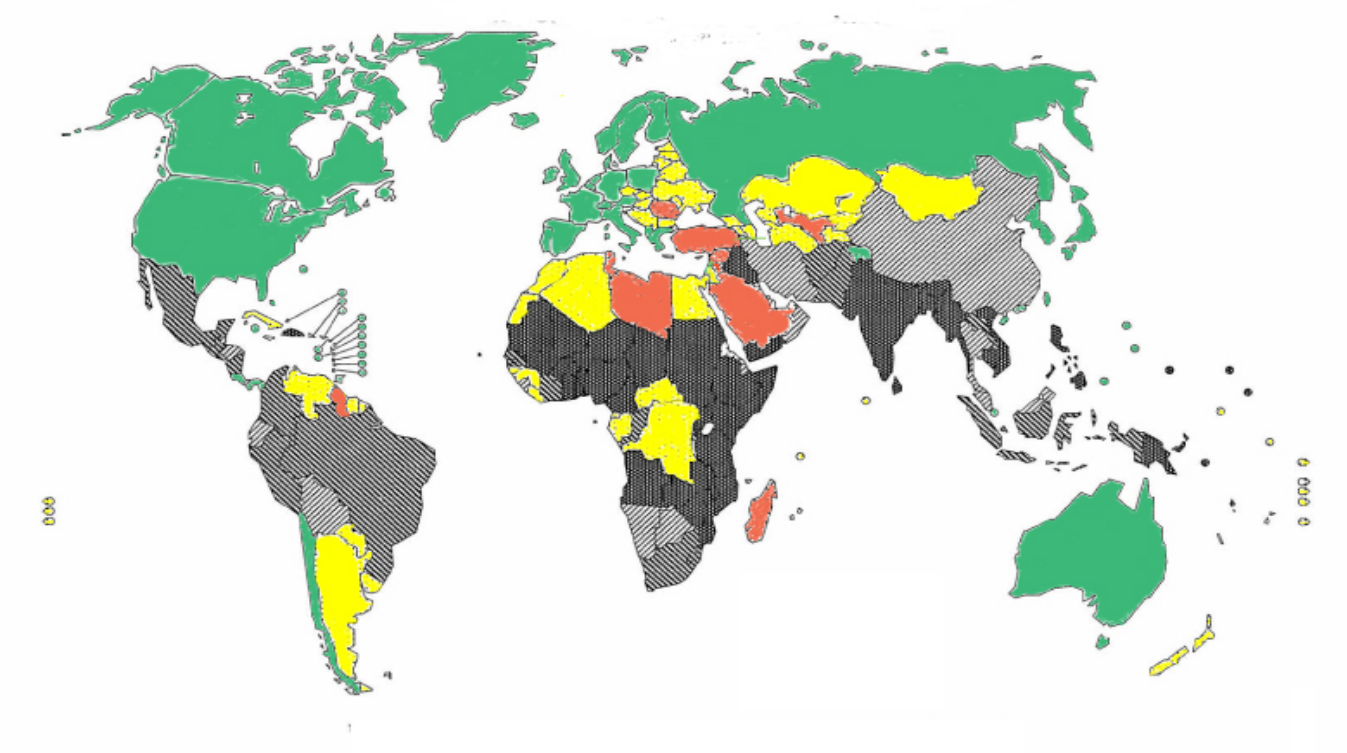

Fig 9. Countries categorized by degree of public health importance of vitamin A deficiency

Clinical
Severe; subclinical
Moderate; subclinical
Mild; sporadic or high-risk
No data; problem likely
Problem under control

This World Health Organization (WHO) map[74] does not purport to show current political boundaries, but does delineate the world-wide prevalence of Vitamin A deficiency. More current information is available from WHO[72] and from the recent review authored by the former Dean of the Michael R Bloomberg School of Public Health of Johns Hopkins University[73]. The underlying cause of the vitamin A deficiency is an inadequate diet, for example, the United States Armed Forces reliance on C and K rations during the years 1941-43[29].

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Medical History

Brice Clarke (1895-1975) and the control of tuberculosis in Northern Ireland.

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In acute cases consider the disease, in chronic cases consider the patient.

Hippocrates.

ABSTRACT

Among the problems facing Northern Ireland after its foundation in 1920, one of the most daunting was the prevalence of tuberculosis, a chronic communicable disease with highest mortality among young women and men in the prime of life. Over a quarter of a century, legislative changes tardily responded, and in spite of, or because of its magnitude, Brice Clarke (1895-1975) devoted himself to the challenge. After decorated service in the Great War of 1914-19 he returned to finish his medical studies in Queen's University Belfast and held hospital appointments until he became Chief Tuberculosis Officer for Belfast and soon afterwards Director of Tuberculosis Services in Northern Ireland.

For twenty years he was an enthusiastic proponent of collapse therapy, and even before the new chemotherapy hastened the natural decline in the tuberculosis epidemic he trumpeted the value of properly equipped chest clinics and generously funded welfare schemes. His garden at Hillsborough could not contain him in retirement; he set off on a slow boat to Japan in 1962, and returned to pen biographical sketches of famous consumptives until his death in 1975 at the age of 80.

Fig 1. Forster Green (1815-1903)

PROLOGUE

Before assessing Brice Clarke's contribution it behoves us to recall the social and legislative scene into which he entered with such good effect. By the close of the nineteenth century it was clear that phthisis was a communicable disease due to the tubercle bacillus and that infection was not only preventable but also increasingly the cause of morbidity and mortality throughout Ireland. Belfast responded by opening in 1880 a Hospital for Consumption and Diseases of the Chest whose nomadic existence in the city centre ended in 1897 through the munificence of Forster Green (1815-1903, Figure 1), a County Down Quaker, when he purchased Fortbreda House with its extensive grounds. In the Belfast Infirmary, patients were not segregated by diseases until 1899 when Robert Hall (1861-1941) persuaded the Board of Governors to provide separate wards for consumptives. When a mansion became available at Whiteabbey in 1904 it was purchased, pavilions were built, and Dr Hall (Figure 2) with 210 patients moved from the Infirmary. In 1913 the Corporation took over the administration of Whiteabbey sanatorium from the Board[1].

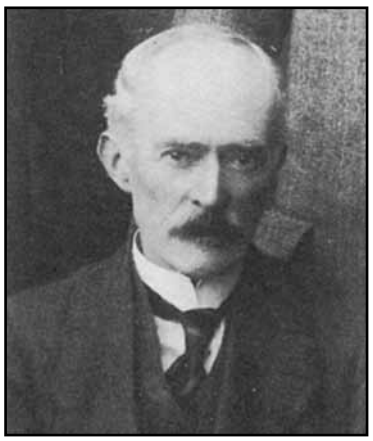

Fig 2. Robert Hall (1861-1941)

Lady Ishbel Aberdeen's (1857-1939, Figure 3) Tuberculosis Exhibition moved from Dublin to the Old Town Hall in Belfast on 7 December 1907, and evening lectures in her presence and that of the Viceroy continued for a week before the Exhibition moved to Lisburn on 18 December and Lurgan on 11 January. The crusade continued in the province in the shape of a horse-drawn caravan; "Phoenix" replaced "Eire" after it was destroyed by fire at Lifford in March 1909[2]. Unfortunately, the valuable provisions of the

Fig 3. Lady Aberdeen (1857-1939)

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Tuberculosis Prevention (Ireland) Act (1908) driven along by the ViceReine were neutered by the parliamentarians anxious not to offend the enfranchised rate-payers, and the permissive regulations were haphazardly applied if at all.

Table I.

Legislation in London and Belfast in the first half of the Twentieth Century

Year	NHI = National Health Insurance, NI = Northern Ireland
1908	Tuberculosis Prevention (Ireland) Act, (Lady Aberdeen's exertions)
1924	NHI (NI) Act sanatorium benefits for insured persons
1930	NHI (NI) Act sanatorium benefit from central funds
1934	LG (NI) Act compulsory notification by general practitioners
1936	NHI Medical Benefits (NI) Regulations
1944	NI Tuberculosis Authority Report treatment allowances
1946	Public Health (Tuberculosis NI) compulsory notification all forms
1947	National Health Service inauguration, Great Britain, 1 July.
1948	NH Assistance (NI) Act more generous allowances

The establishment of Northern Ireland under the Government of Ireland Act (1920) made no improvement and tardy legislation was piecemeal as is evident from Table I. Though anxiety about the inordinately high death rate from tuberculosis in Northern Ireland was continually expressed in Stormont, it was not until 1942 that a Select Committee on the Health Services was formed to consider all the health problems in the state[1].

Ruefully looking back over the tuberculosis service in 1955 Barr remarked:

> The most conspicuous feature of the development of the County Tuberculosis Schemes was their lack of uniformity and their haphazard growth. By 1927, schemes were in operation in all County and County Boroughs with the exception of Londonderry County and County Borough where there was only a scheme under the National Insurance Act of 1911. In Belfast, Tyrone and Armagh, the schemes were self-contained; each authority had control of a sanatorium and was able to provide comprehensive treatment for all patients living within its respective boundaries. The remaining counties of Antrim, Down, Fermanagh and Londonderry and Londonderry city had no sanatorium and thus were forced to make arrangements for patients to be cared for in private and voluntary institutions. There were, however, arrangements in Counties Down and Fermanagh whereby non-respiratory cases were dealt with in the County Infirmaries. Even with these *ad hoc* arrangements, the accommodation was in many instances inadequate, antiquated and unsuitable.

And he lamented that it was not until the end of 1945 that it was finally realised that a unified central scheme was necessary[3].

Tuberculosis ranked high among the problems faced by the 1942 Select Committee. From a summary of the Registrar General's Annual Reports for 1943, 1945 and 1947, it is clear from Table II that rural Fermanagh (69.64) had the lowest average annual death rate, and the highest (86.67) was seen in Antrim, where Belfast with a population of 438,086 (205,538 males, 232,548 females), reported 367 (184 m, 183 f) deaths from respiratory tuberculosis and 117 (61 m, 56 f) deaths from non-respiratory tuberculosis in 1943. In the city alone deaths from all forms of tuberculosis were 99.72 per 100,000 of population. Four years later there were 281 (116 m, 113 f) deaths from respiratory tuberculosis and 65 (37 m, 28 f) deaths from non-respiratory forms; the overall rate had fallen to 71.14 per 100,000 population - even though there had been no new developments in treatment[4].

When the Select Committee presented their Report in 1944 a Health Advisory Council was set up under surgeon Howard Stevenson (1875-1950) to advise the Minister of Health and Local Government. A Tuberculosis Committee of this Council reported in 1946. It stressed that a unified effort in a concentrated attack was needed, and that 500 additional beds should be provided, and that notification should be compulsory, after 'provisional intimation' of any suspected case, with additional power given to the Courts 'to order the removal to hospital of an infectious person'. To sweeten this pill, the Treatment Allowance Scheme was extended to all cases of pulmonary tuberculosis[1]. In 1946 the Public Health (Tuberculosis, Northern Ireland) Act became law, the Northern Ireland Tuberculosis Authority was set up, all forms of tuberculosis became compulsorily notifiable,[1,3] and the authorities had the good sense to appoint a man of wide experience and deep insight as Director of Tuberculosis Services.

BRICE RICHARD CLARKE

Brice Clarke was born on 12 May 1895, educated at

Table II.

Average annual deaths from all forms of tuberculosis in the years 1943, 1945 and 1947. Belfast is in included in the returns from Antrim. Population as of 1937[3].

County	Antrim	Armagh	Down	Fermanagh	L'derry	Tyrone
Population	635,352	108815	210,687	54,569	142,736	127,586
Tuber Deaths	1,652	273	521	114	350	309
Per 100,000	86.67	83.63	82.43	69.64	81.74	80.73

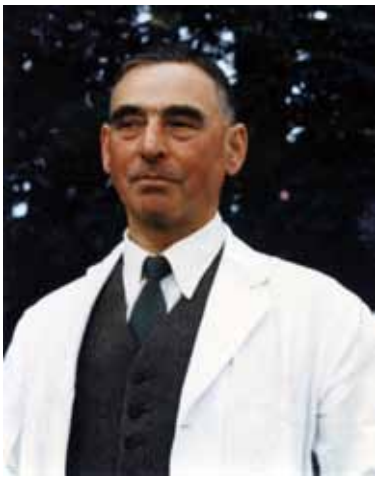

Fig 4. Brice Richard Clarke (1895-1975)

Campbell College, Belfast, and went on to study medicine at Queen's University where he was smitten by Helen Waddell (1889-1965), later the noted Latinist though more widely known for her historical novel *Peter Abelard* (1933). Unlike many a lovelorn young student he was inspired to work harder. He was fortunate in having a trusty go-between in his sister Maude, a classmate who informed Helen "He thinks you are wonderful. 'Maude', he said suddenly, 'think of hundreds of clever men that must be in England who don't even know there's anybody like Helen in the world'". Dame Felicitas Corrigan, Helen's biographer, surmised that Brice was the lonely figure wandering about the quad in the ballad *Il Penserosa* composed under Helen's blotting paper to while away a boring lecture:

I was a naughty medical,
I did not love to work,
But since the night she danced with me
I never want to shirk.

Helen did not fall in love with him: 'I think he fell in love with me, but he had done it several times before and was to do it several times after'. Nonetheless, they corresponded regularly while he was away at war and 'trysted' when he resumed his studies in January 1920. They remained friends right up to the time of her death in March 1965, fifteen years after the total eclipse of her dazzling gifts of intellect and charm[5].

After passing his second medical examination in 1914, Brice volunteered to serve as a dispatch rider in France and was later commissioned lieutenant in the Royal Dublin Fusiliers before becoming a tank commander in World War I. For his service as one of the first tank commanders he was awarded the Military Cross and was presented to the King and Queen of the Belgians. After a gas attack he was found to have 'incipient' phthisis - a diagnosis that shaped his future career. He returned to his studies (and fruitless pursuit of Helen) in 1920 and graduated with honours in 1921[6].

He was appointed Medical Superintendent of Forster Green Hospital in 1925. Meanwhile, the municipal Whiteabbey Hospital had fallen on evil days, and a commission of inquiry reported within six months in June 1941 that the Corporation had failed miserably in its duties. The exceptionally high casualty rates when the city was blitzed in April and May 1941 added to the embarrassment of the government as well as the councillors, and a Commission replaced the tuberculosis committee of the Corporation[7]. In 1943 Clarke was transferred to Whiteabbey Chest Hospital and the Greenisland Hospital for Children. Shortly afterwards in 1944 he became Chief Tuberculosis Officer for Belfast, and two years later Director of Tuberculosis Services when the Public Health (Tuberculosis) Act (Northern Ireland) 1946 established the Northern Ireland Tuberculosis Authority. (Figure 4)[1].

COLLAPSE THERAPY

Collapse therapy was in the ascendant at this juncture and, in the first volume of the *Ulster Medical Journal,* Clarke surveyed the methods in use[8]. Before discussing therapy he reminded readers of the results of conservative treatment in 688 patients discharged from Forster Green Hospital between 1919 and 1924 surveyed in 1928; the dire prognosis in patients whose sputum contained tubercle bacilli on admission is evident in Figure 5. Clarke was aware that some cases of pulmonary tuberculosis recover without any special treatment, that a group of patients in which the disease is early would benefit from rest and sanocrysin, but that a large group require some form of collapse therapy when conservative methods have failed.

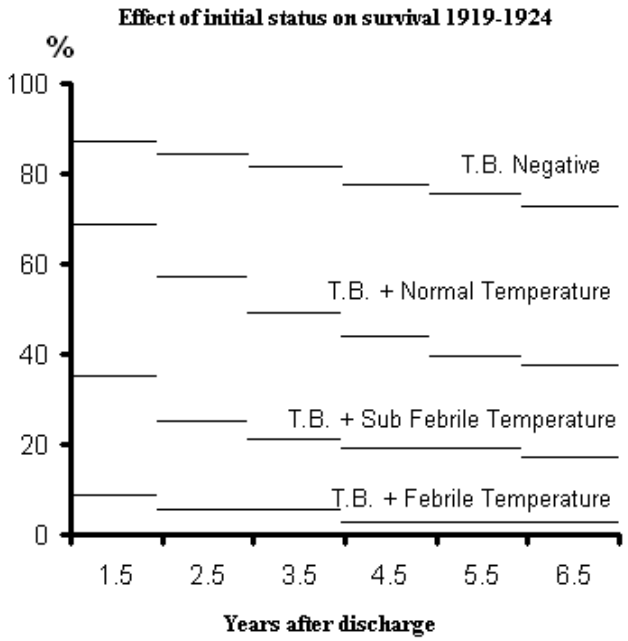

Fig 5. Results of conservative treatment of 688 patients discharged from Forster Green Hospital 1919-1924, showing the effect of + presence or –absence of tubercle bacilli in sputum, and of temperature, at time of admission.

'It is a mistake to collapse the lung too early . … When it is clear that cavity formation has commenced, the lung should be collapsed by artificial pneumothorax (APT) or, failing this, by phrenic evulsion or crush. Thoracoplasty is indicated in a group of cases where APT and phrenic crush have failed to arrest disease, especially where there is a large cavity or repeated haemoptysis.'

The dangers and complications of all these procedures were examined minutely in the paper[8].

With his colleague SLW Erskine, he examined the late results of artificial pneumothorax in 1940 in 400 patients[9]. Urban and rural workers, and men and women,were approximately equal in number, the majority of them belonging to the working classes (elaborate statistical analysis was eschewed). In the small community of Ulster it was possible to trace the

history of 99 per cent of the Forster Green Hospital patients for at least five years from the date when collapse of the lung was effected or attempted. Good relaxation of lung and disappearance of cavities in 131 patients was termed Satisfactory Collapse (SC). Failure of cavities to close or poor relaxation in 184 was deemed Not Satisfactory Collapse (NSC), and where no pleural space was found in 85 patients the group was identified as No Collapse (NC). After five years the patients with Satisfactory Collapse had a low mortality and the great majority (89) were alive and well. Mortality was higher among those with Not Satisfactory Collapse than in those in which the procedure had failed *ab initio* (NC). Phrenic evulsion improved the results as Purce and Clarke noted in 1936[10], but induction of the pneumothorax early in the disease was the factor most likely to produce a successful outcome: the success rate with induction within six months was 55 percent; induced within 6 to 12 months it was 28 percent; attempted thereafter the successes fell to 20 per cent. A slight shift from his position in 1932 – 'it is a mistake to collapse the lung too early'[9].

Of the 131 patients with successful collapse lasting between one and four years approximately, 96 were examined and X-rayed after expansion of the lung. In two cases only was the 'pneumothorax' lung normal, in nine, active disease was present, 50 showed fibrosis and 35 showed extensive fibrosis. The mediastinum was not displaced in 34 patients, it was detectably so in 35, and markedly so in 27. This pulmonary fibrosis is not counted among the complications of artificial pneumothorax listed at the close of the paper[9], although it was subsequently realised that impairment of pulmonary function inevitably followed 'resting' the lung.

At the annual conference of the British Tuberculosis Association in Edinburgh in July 1947 he read a paper on the causes of relapse in quiescent cases of pulmonary tuberculosis[11]. The paper was what would now be called a meta-analysis of results of collapse therapy, and was openly polemical in nature. The statisticians had begun to doubt its effectiveness even though the 'curative effect was self-evident' to medical and surgical teams who employed it 'systematically and scientifically':

'Failure to cure a substantial percentage of patients by collapse therapy suggests that the selection of cases or the technique (including the after-care technique) is faulty and in need of revision. … It is a pity that some of the energy which has been expended in demanding statistical proof of the value of AP and other collapse measures has not been devoted to improving the equipment of small sanatoria and chest clinics. … the apparent relapse of many patients is the result of faulty classification on discharge, due to errors of judgement or, more frequently, to failure to carry out a proper radiological and bacteriological control. But even after the most conscientious investigations there will be a high rate of relapse'[11].

He moved on to surer and safer ground:

Another factor with an obvious bearing on relapse is that of after-care, and particularly that of financial assistance for the patient who has recently suffered from active disease. If it is impossible to prove the value of sanatorium treatment statistically, it is not difficult to prove the effect of poverty on the prognosis of pulmonary tuberculosis.

And then he blithely undermines his defence of sanatorium and collapse therapy:

It is a remarkable fact that many of the soldiers who contracted tuberculosis in the 1914-19 war, including the TB positive cases, have made good recoveries and are alive at the present time. These men had comparatively little sanatorium treatment and very little collapse therapy. What they did get was a measure of financial security through their disability pensions and this has been sufficient to bring about the recovery of a remarkable degree of health in many of the men[11]. (Himself among them!)

As had happened in World War I shortages of foodstuffs and fuel between 1940 and 1942 increased the tuberculosis morbidity and mortality rates aggravating the demand for sanatorium and hospital accommodation. The rise in death rate was apparent all over Ireland, but because tuberculosis was not not classified as an infectious disease, notifiable only in the advanced stage the Republic laboured under an additional disadvantage[12] (Figure 6).

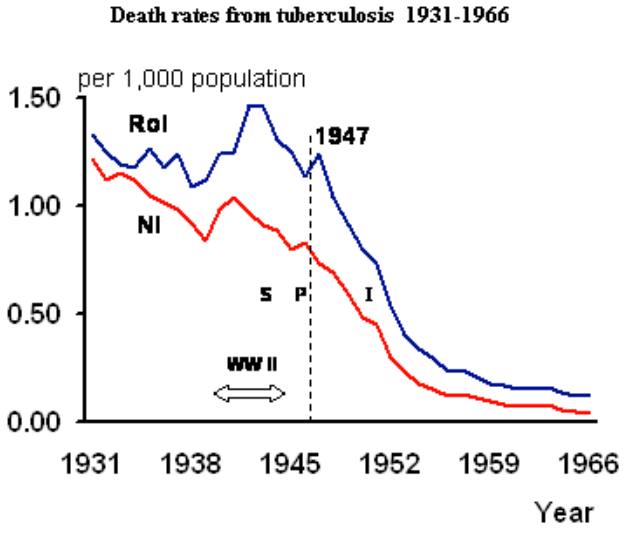

Fig 6. Death rates from tuberculosis in Northern Ireland and Republic of Ireland 1931-1966. Data provided by the Departments of Health in Belfast and Dublin from Annual Reports. S streptomycin introduced in 1944, P para-aminosalicylic acid in 1947, and I isonicotinic acid hydrazine in 1952. WW II - duration of World War II 1939-45.

The financial world for tuberculosis patients was slowly changing. In November 1942 Sir William Beveridge (1879-1963) published his report *Social Insurance and Allied Services*. He recommended a 'health service providing full preventive and curative treatment of every kind to every citizen without exceptions, without remuneration limit, and without an economic barrier at any point to delay recourse to it'[13]. In a Labour administration at Westminster, Aneurin Bevan (1897-1960) inaugurated a National Health Service, based on Beveridge's report, for Great Britain on 1 July 1947. At Stormont a Health Services Act (1947) extended the measure to Northern Ireland. Under the National Assistance (Northern Ireland) Act (1948) outdoor relief was abolished, and financial allowances were paid to all persons

in need; patients with respiratory (but not non-respiratory) tuberculosis received a more generous allowance than the ordinary rate[3]. Individual patients or doctors and institutions could opt out, but in effect health care in all its aspects had become a surprisingly well-funded nationalised industry. [Why the Republic did not copy the Beveridge template is easily answered: want of cash for either current or capital expenditure. For example, when a hospital and sanatorium building programme did begin in mid-century it was funded from the accumulated Sweepstakes Fund that had fallen into the hands of the Minister of Health because the hospital consultants who had initiated the lottery squabbled over its distribution[12]].

By 1947 a therapeutic revolution was under way: streptomycin was discovered in 1944, para-amino salicylic acid in 1947 and isonicotinic acid hydrazine (isoniazid) in 1952 (Figure 6).

AIDS TO DIAGNOSIS AND CONTROL

The doctor's dilemma of masterly inactivity was addressed in a paper on diagnosis and treatment. Clarke expressed 'utmost faith' in rest treatment at home or in a sanatorium. He acknowledged that 'the average patient endures rest treatment more cheerfully if it is combined with some specific and systematic medical treatment which convinces him (sometimes without reason) that the doctor can influence radically the course of disease'. Before sending a patient to a hospital or sanatorium, the Hippocratic maxim 'in acute cases consider the disease, in chronic cases consider the patient' should be kept in mind[14].

Early diagnosis can never be easy, even with the best laboratory and radiological aids, for if the diagnosis is obvious the disease is no longer early. Missing an early case of active phthisis is a most annoying experience, but labelling a patient tubercular without sufficient cause is more grievous. A full investigation of every suspected case is necessary in order to reduce the number of errors and avoid gross mistakes[15]. Clarke therefore gave a warm welcome to Mass Miniature Radiography (MMR) introduced by a Brazilian worker, de Alreu, because early detection is frustrated by a variety of factors: the patient rarely feels ill and symptoms are not specific; the stigma attaching to the disease makes the relatives or parents resentful and the persistent doctor makes himself unpopular; furthermore 'a poor man cannot afford to have early phthisis'[16].

PREVENTION

His monograph on *Causes and prevention of tuberculosis* was published in 1952[17] and he described 'the development and function of the chest clinic' in a symposium on tuberculosis in the *British Medical Bulletin* in 1954. Therein he pointed out that common sense dictates that such a clinic must first meet the urgent needs of the community, and where resources are limited the routine use of tuberculin testing, chest radiography, and standard bacteriological tests should permit large numbers to be examined and assessed quickly[18].

He argued that prevention is the true aim of the clinic service, and to be effective must go beyond the medical and nursing care of the patient. Good organisation should spot gaps in notification, patients not recalled at the proper time, patients lost sight of, and insufficient number of contacts examined. The search for tuberculosis in contacts should be followed by measures to protect the tuberculin-negative contact from infection, including BCG vaccination. Separation of facilities for children from the adult service was imperative. For control of infection in the home, the minimum standard of housing to be tolerated should provide a separate room for the person with active phthisis who has to be nursed at home, and the patient's attendants and contacts should be protected in the same way and to the same high standard as the tuberculosis nurse. In conclusion he stressed:

'The control of tuberculosis depends on many factors, not all of which are within the sphere of the clinic service. Maintenance of a good standard of life and the provision of more beds, particularly for the older patients who are carriers of infection, are important aims. It is for the chest clinic to direct and execute every measure of prevention that promises to reduce the number of new cases of tuberculosis'[18].

The success of the tuberculosis clinic is to be judged by the control of morbidity from tuberculosis (Figure 7); a major theme in his 1952 monograph *Causes and Prevention of Tuberculosis*, which predicted the end of the epidemic within ten years[17]. Perhaps the most important feature of Clarke's prescription for an effective clinic is that it appeared after the introduction of successful chemotherapy and before multiple drug resistance had emerged as a major problem.

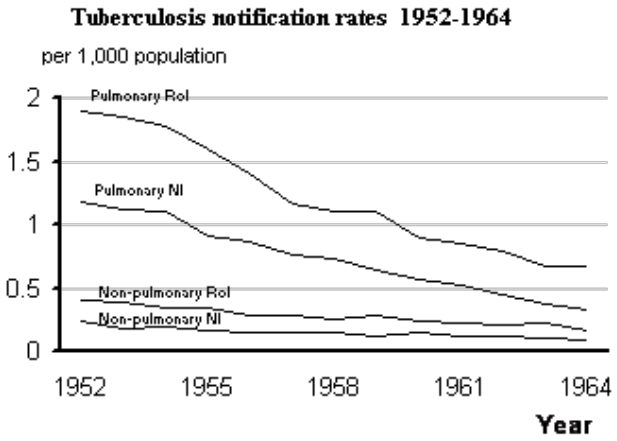

Fig 7. Notification rates of pulmonary and non-pulmonary tuberculosis in Northern Ireland and Republic of Ireland (where contacts on chemoprophylaxis are notified unlike the rational NI). Data provided by Departments of Health in Belfast and Dublin from Annual Reports.

From 1946 the Director ensured the provision of a domiciliary service, and by 1955 there were 29 Chest Clinics, all of them adequately equipped with radiological and ancillary necessities, supported by a comprehensive welfare scheme for all patients[3].

RETIREMENT

Retirement saw him tending his garden quietly at Hillsborough until in 1962 he succumbed to an attack of wanderlust[1]. With his wife he made a slow trip to Japan by cargo boat and kept a journal of his experiences[6]. He wrote accounts of authors who had suffered from tuberculosis, best exemplified by his account of Katherine Mansfield's illness[19]. In this avocation

he was influenced perhaps by a previous Chief Tuberculosis Officer in Belfast: in April 1919 Andrew Trimble entertained the members of the Belfast Natural History and Philosophical Society with an address on 'The Romance of Tuberculosis'[20], at a juncture when it was the primary cause of death in the Western world and the most dreaded chronic communicable disease[21]. Brice died on 15 June 1975 at the age of 80, survived by his wife and two sons, both of whom followed in his footsteps into medicine[6].

Acknowledgements: Figures 1, 2 and 4 are reproduced by kind permission of the Ulster Medical Society[1], and Figure 3 permission of the MultiText Project, University College Cork. We are grateful to Dr Margaret Boyle, Senior Medical Officer, Department of Health, Dundonald House, Belfast, and Mr Aidan Beatty, Librarian, Department of Health, Hawkins House, Dublin, for providing the data in Figures 6 and 7 abstracted from Annual Reports.

The authors have no conflict of interest.

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REQUEST FOR INFORMATION ON WOMEN MEDICAL STUDENTS.

Dear Editor,

I am a second-year history of medicine PhD student at the National University of Ireland, Galway, studying early women medical students and doctors in Ireland in the period 1877-1922. My PhD thesis examines attitudes towards women in medicine in Ireland in the late 19th and early 20th century. In addition, a major part of my project involves the creation of a collective biography of the social backgrounds, experiences and subsequent careers of early women medical graduates of Irish institutions. I would like to hear from any *Ulster Medical Journal* readers who might have a relative who was an early Irish woman doctor who trained at one of the Irish universities in the period 1880-1930. These institutions include Queen's College Galway, Queen's College Cork, Queen's College Belfast, the Royal College of Physicians, the Royal College of Surgeons, the Catholic University (later University College Dublin) and Trinity College Dublin, although I am also interested in Irish women doctors who trained abroad.

If any readers happen to know of any historical sources such as the letters or diaries of Irish women doctors or information relating to Irish women in medicine, I would be interested to hear from them. I would be particularly interested in meeting descendants of early Irish women doctors so that I might be able to include their relatives' personal stories in my work All replies I receive will be responded to in complete confidentiality.

Contact details: Laura Kelly, (PhD student), Department of History, National University of Ireland, Galway, University Road, Galway, Ireland.

irishwomendoctors@googlemail.com

Ulster Med J 2009;**78(3):**185-186

Case Report

Pancreaticopleural fistula: a rare complication of ERCP - induced pancreatitis

Michal Sut, Ronan Gray, Moncompu Ramachandran, Tom Diamond

Accepted 26 June 2009

INTRODUCTION

Pancreaticopleural fistula is a rare complication of acute and chronic pancreatitis caused by an inflammatory or traumatic injury to the pancreatic duct. The ensuing thoracic collections may be in the form of pleural effusions, pleural pseudocysts or mediastinal pseudocysts. Treatment options may be conservative or surgical. We present a case of post endoscopic retrograde cholangio-pancreatography (ERCP) acute pancreatitis with a pancreaticopleural fistula where conservative management failed.

CASE REPORT

A 51 year old lady presented with dyspnoea, cough, chest pain and a pleural effusion two months after recovering from an episode of ERCP- induced pancreatitis. A CT scan revealed pancreatic necrosis and bilateral pleural effusions. Bilateral chest drains were inserted and the amylase content of the pleural fluid was elevated at 5488 IU. The presence of a pancreaticopleural fistula was considered as a differential diagnosis. She developed multiorgan failure requiring ventilation, inotropic support and renal dialysis. A repeat CT scan (fig.1) revealed a pancreatic pseudocyst (7 x 2 cm), a mediastinal fluid collection, partial collapse of the left lung and bilateral pleural effusions (fig.2). Magnetic resonance cholangio-pancreatography (MRCP) suggested a fluid containing tract extending from the pancreas into the chest, associated with a collection in the left pleural cavity.

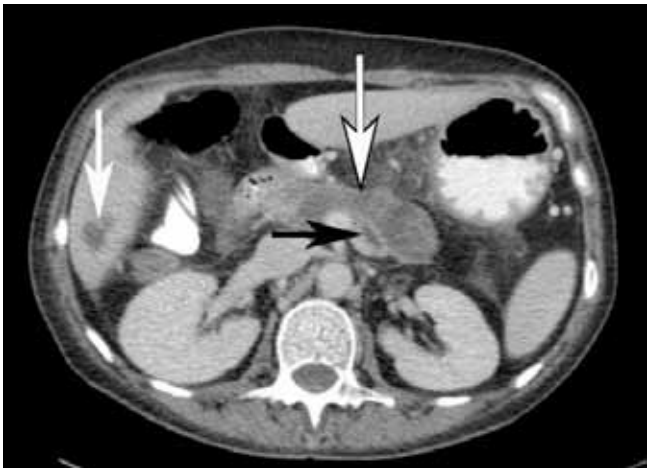

Fig 1. CT of abdomen demonstrating 7x2cm pancreatic pseudocyst (outlined arrow) and dilated pancreatic duct (black arrow). Incidental finding of cyst in VI liver lobe (white arrow) is noted.

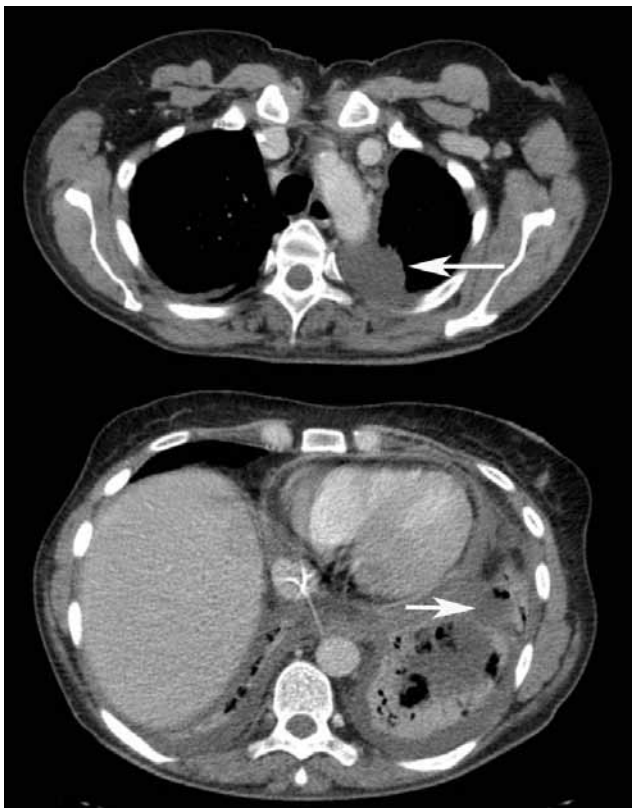

Fig 2. CT scan of chest demonstrating collapse of the left lung and effusions in the left pleural cavity (arrows).

She initially improved clinically with supportive and conservative measures but deteriorated again and surgical drainage of the pseudocyst was undertaken via a cystgastrostomy. At operation a communicating tract leading superiorly through the oesophageal hiatus was identified. The wall of the cavity was sutured to the posterior wall of the stomach and a nasogastric tube was placed into the pseudocyst cavity to allow it to collapse and fibrose. Parenteral nutrition was commenced post-operatively. The pseudocyst and pleural effusions resolved. She was discharged on day 12 and remains asymptomatic with no evidence of recurrence after four years.

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DISCUSSION

Pancreaticopleural fistula is an uncommon complication of both acute and chronic pancreatitis and pancreatic trauma with duct disruption. The majority of cases (80%) are associated with alcohol induced chronic pancreatitis[1-3]. There is an incidence of 0.4% in patients presenting with pancreatitis and 4.5% in those presenting with a pancreatic pseudocyst[3]. The pathogenesis involves recurrent, chronic inflammation of the gland eventually leading to ductal disruption. If this occurs posteriorly pancreatic secretions will tract through the retroperitoneal space via the path of least resistance to the pleural cavity[4,5]. Fistulization through the oesophageal or aortic hiatus is most frequent, although extension directly through diaphragmatic muscle has been reported[6]. Conversely, anterior ductal disruption is responsible for pancreatic ascites.

Clinical presentation is often misleading, as symptoms are usually associated with a significant pleural effusion, and consist of dyspnoea, cough and chest pain. Rarely do patients complain of abdominal pains typical of pancreatitis[3,7]. In one study only 52% of patients had a prior history of pancreatitis highlighting that a pancreaticopleural fistula may be the first presentation of significant pancreatic disease[3]. Pleural effusions of this nature tend to be large and recurrent despite repeated thoracocentesis. Frequently, the diagnosis is delayed and it is therefore of vital importance to have a high index of suspicion, enquire about excess alcohol consumption, assess nutritional status, and examine for the presence of ascites.

Pleural effusions associated with pancreaticopleural fistulae should be distinguished from the small, reactive, self-limiting left-sided effusions that commonly occur in 3-17% of patients with acute pancreatitis[8]. A pancreaticopleural fistula may be suspected on the basis of the clinical picture and an extremely elevated pleural fluid amylase level (normal range <150 IU/L) following thoracocentesis. Importantly, however, pleural fluid amylase may also be elevated in acute pancreatitis (<4000 IU/L), oesophageal perforation and certain neoplastic processes including lung adenocarcinoma, lymphoma and ovarian, rectal, cervical, breast and pancreatic carcinoma[2].

The pleural effusions are predominantly left sided, however right sided and bilateral effusions occur in 19% and 14% of patients respectively. Simple chest radiography is the first line investigation but this provides only limited information about the fluid collection in pleural cavity. Currently, the gold standard for investigating pleural effusions is CT. It is very useful in determining the site and size of the effusion but overall ability to provide accurate delineation of the fistula is disputable[2,8]. MCRP and ERCP are also available to visualise the biliary tree and pancreatic duct. The latter is less sensitive but offers the therapeutic option of stent insertion[1,2].

Currently there are no systematic studies evaluating the optimal management of pancreaticopleural fistulae and current methods derive from case reports and small case series[1]. Initial management should be directed at achieving symptomatic control of the pleural effusion, with thoracocentesis and chest drain insertion if required. Suppression of pancreatic exocrine secretions by somatostatin or its analogue octreotide should then be considered. In one study a combination of thoracocentesis, octreotide analogues and TPN resulted in a 48% closure rate after three weeks[9]. Surgical treatment, however, is safe and effective and is appropriate either when medical management fails or where the underlying condition requires surgical intervention. Cystgastrostomy, cystjejenostomy, and distal or middle segment pancreatectomy are appropriate options in the setting of symptomatic pancreatic pseudocysts or pancreatic duct obstruction. Finally, ERCP and pancreatic duct stenting is a less invasive alternative to surgery. Fistulae are unlikely to heal with medical measures alone if drainage is impaired by a pseudocyst or stricture. A pancreatic stent that bridges the ductal disruption facilitates closure of the fistula by decreasing ductal pressure and occluding the luminal defect[1]. Sphincterotomy and non-bridging stents have also been reported as being successful but overall a significant proportion of patients undergoing ERCP still ultimately require surgical intervention[1]. In one study, 7 of 18 cases managed endoscopically eventually required surgical intervention and even advocates of ERCP acknowledge that the issue of how long to persist with this form of treatment is, as yet, unresolved[1,10].

CONCLUSION

Pancreaticopleural fistulae are difficult to diagnose and require a high index of suspicion, particularly in the setting of recurrent pleural effusions with a coexisting history of pancreatitis or alcohol abuse. Early pleural fluid amylase testing will avoid a delayed diagnosis. First line treatment includes drainage of the effusion, inhibition of pancreatic secretions with octreotide and possibly ERCP plus stenting of the pancreatic duct. As demonstrated by this case, surgery is appropriate when medical measures fail or if there is an associated symptomatic or complicated pseudocyst.

The authors have no conflict of interest.

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Letters

LOBAR PNEUMONIA TREATED BY MUSGRAVE PARK PHYSICIANS.

Editor,

In the excellent historical article by John Hedley-Whyte[1], I saw the photograph of Sir Alexander Fleming with Professor William Thomson on the doorsteps of Number 25 University Square and I remembered that in my grandfathers visitors book there were the signatures of Sir Alexander and Lady Fleming not only at number 12 University square (figure 1), but also at Greenlawn in Donaghadee (figure 2). The exact date is not clear but I suspect about April 1942.

Fig 1. Visitors book from 12 University Square.

Professor CG Lowry (known as CG) and Professor Thomson (known as WWD) were close friends, colleagues and neighbours both in University Square, CG at number 12, and WWD at Number 25, and also next door at Donaghadee, and hence this accounts for the above records of those events.

Alastair L Macafee, *(Retired Consultant Orthopaedic Surgeon).*

Stramore Lodge, 142 Warren Road, Donaghadee, Co Down. United Kingdom

REFERENCE:

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CORONARY ARTERY DISEASE: ANATOMY AND PRESENTATION IN IDENTICAL TWINS

Editor,

A 47 year old man (twin 1) was admitted electively for coronary angiography following an acute myocardial infarction (MI) one month previously. His risk factor profile included smoking, a positive family history, hypertension and hypercholesterolaemia. On the day of admission, it was discovered that his identical twin brother (twin 2) was an elective inpatient for coronary angiography. His history included acute MI aged 42 years, with subsequent percutaneous coronary intervention to the circumflex. His risk factor profile included previous MI, a positive family history, hypertension and hypercholesterolaemia.

Fig 2. Visitors book from Greenlawn, Donaghadee

Coronary angiograms were performed on consecutive days. Coronary arterial anatomy was discordant between the twins. Angiographic images from twin 1 are shown in figure 1 (panels 1a-1c), beside matched images from twin 2 (panels 2a-2c). In twin 1 the left main stem bifurcates into left anterior descending (LAD) and circumflex (CX) branches (panel 1a), while in twin 2 it trifurcates into an LAD, CX and ramus intermedius branch (panel 2a). The first obtuse marginal branch (OM1) arises and bifurcates proximally in twin 1 (panels 1a and 1b) but arises and bifurcates more distally in twin 2 (panels 2a and 2b). The right coronary artery supplies a prominent sinus node branch in twin 1 (SA node, panel 1c) which is not apparent in twin 2 (panel 2c).

Coronary artery disease distribution was also discordant between the twins. Twin 1 was found to have a normal left main stem, with a long area of moderate to severe disease in the mid part of the LAD. A large diagonal branch had a 90% ostial lesion. There was a 50% lesion in the main CX and a 90% lesion in its first marginal branch. The right coronary artery was diffusely diseased. Twin 2 had a normal left main stem, with an angiographically near-normal LAD. The CX was diffusely diseased. The right coronary artery was diffusely diseased but with no significant stenosis.

Our observation of discordant coronary artery distribution and coronary atherosclerosis in identical twins supports the findings of previous observational studies[1,2]. Furthermore age at first cardiac event, type of cardiac event and risk factor profile show concordance in this pair of identical twins, also consistent with previous observations[2].

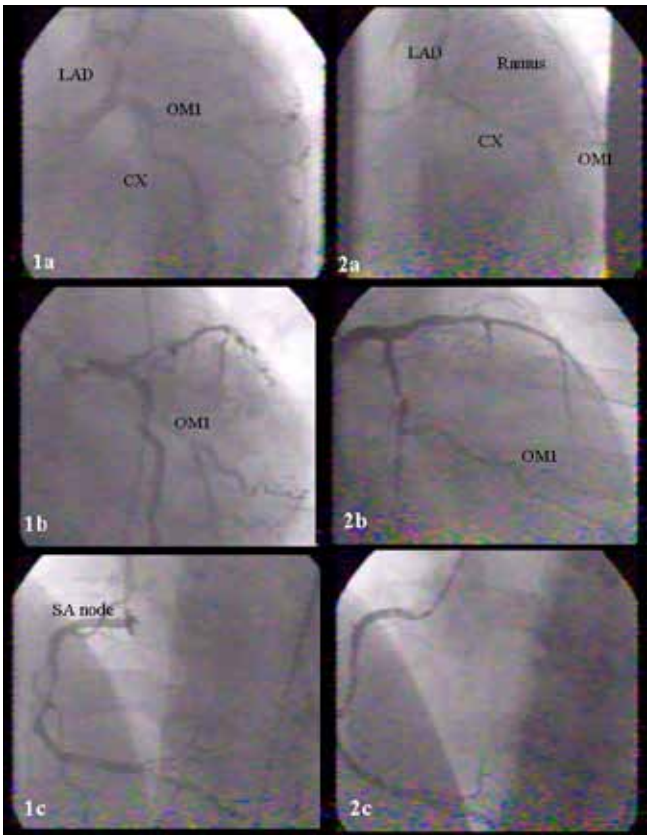

Fig 1. Coronary angiograms from twin I (left panel, 1a-c) and twin 2 (Right panel, 2a-c)

We conclude that coronary anatomy is independent of the human genome. Disease lesion sites are at least partly independent of the human genome. In contrast, age at first cardiac event, type of cardiac event and risk factor profile appear to be more closely related to genetic profile. We suggest that when one twin presents with IHD, the second should be subject to increased medical surveillance

The authors have no conflict of interest

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DRUGS, ELECTROLYTES AND TAKO-TSUBO CARDIOMYOPATHY: TRIPLE AETIOLOGY OF ACQUIRED LONG QT SYNDROME AND TORSADES DE POINTES.

Editor,

Physical or emotional stress can have unforeseen consequences. We document a 67 year-old female admitted with syncope following emotional stress. She had a history of depression and had been "crying and crying all day". In addition, she had a history of ileostomy following severe diverticular disease. Her daily medication included ondansetron 4mg b.d. for nausea and fluoxetine 60mg for depression.

On admission, serum magnesium was low at 0.73mmol/l (0.75 – 1.25) and serum potassium was 3.9mmol/l (3.5 – 5.1). Troponin I was mildly elevated at 0.17u/l (0 – 0.04). B-type natriuretic peptide (BNP, Abbott) was grossly elevated at 2569pg/ml (normal < 100). Initial ECG (fig 1) showed new T wave inversion in ECG leads; II, III, aVf and V1 through to V6 with a prolonged corrected QT interval (QTc) of 524ms (upper limit of normal for females = 450ms). An ECG dated June 2007 was normal apart from a QTc of 509ms. She was initially treated as an anterior non-ST segment elevation myocardial infarction. Shortly after admission, she developed polymorphic ventricular tachycardia (torsades de pointes, figure 2). The risk of torsades de pointes increases substantially once QTc is > 500 ms. This was treated with a 200J DC shock, 4mmol of intravenous magnesium with oral beta-blocker, and potassium therapy. Further self-terminating runs of torsades de pointes occurred when her potassium levels dipped below 4mmol/l.

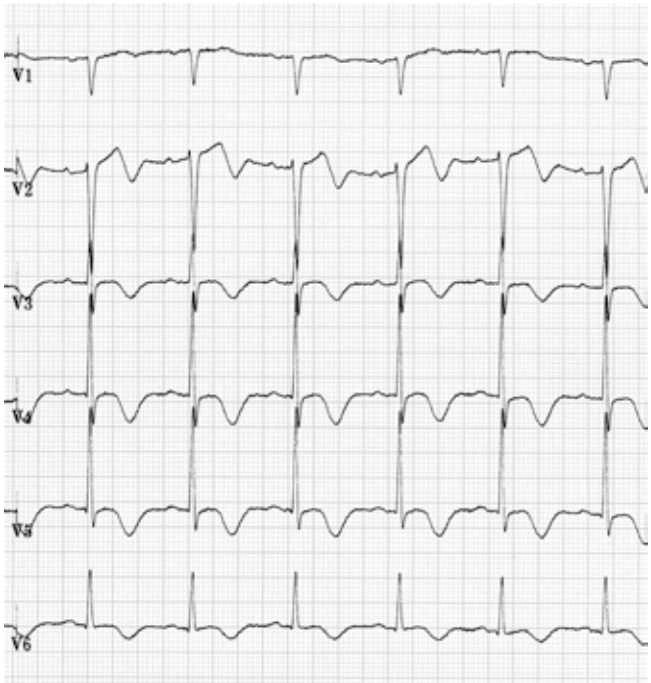

Fig 1. Leads V1 – V6 of admission 12-lead ECG showing T wave inversion resembling non-ST segment elevation MI. QTc is greatly prolonged at 524ms.

On day two, she underwent cardiac catheterisation, which showed normal coronary arteries but marked impairment of systolic function in the apical half of the left ventricle with a characteristic "ballooning" appearance (figure 3). These findings, in association with physical or emotional strain, are diagnostic of tako-tsubo cardiomyopathy. Oral magnesium supplements and bisoprolol 5mg were added in to her medication. Ondansetron and fluoxetine both prolong the QT interval and were stopped. A cardio-defibrillator device was

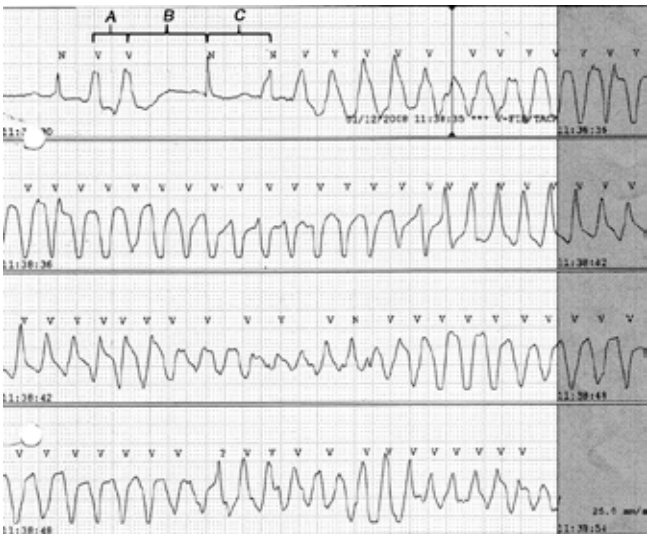

Fig 2. ECG monitor tracing shows a characteristic short (A), long (B), short (C) sequence of ventricular activity initiating polymorphic ventricular tachycardia also known as "torsades de pointes" for its twisting QRS axis about the iso-electric line.

implanted due to continued risk of arrhythmia from electrolyte loss from the ileostomy. The QTc came down to 454ms and BNP fell to 179pg/ml at discharge.

QT prolongation is the surface ECG manifestation of abnormal repolarisation of myocardial cells due to problems with cellular ion channels. The disorder is classified as either congenital or acquired. Acquired QT prolongation may be due to:

1. Electrolyte depletion, particularly potassium or magnesium,

2. Drugs that affect myocardial ion channels

3. A feature of tako-tsubo cardiomyopathy, a catecholamine induced metabolic disorder of myocardial cells caused by physical or emotional stress, especially seen in older females[1,2].

A reference list of drugs causing QT prolongation is available from the University of Arizona (http://www.azcert.org) or the British National Formulary.

Initial presentation and ECGs in tako-tsubo cardiomyopathy are similar to an anterior ST or non-ST segment myocardial infarction but often with QT prolongation. A small troponin rise may be seen but coronary arteries are normal with a characteristic "apical ballooning" or Japanese octopus pot ("tako-tsubo") pattern seen on ventriculography. Beta-blockade is a key element of treatment. The ventricular changes are mostly reversible if the patient survives the acute phase[3].

Our patient had all three causes of an acquired QT prolongation - excessive secretion from her ileostomy producing hypomagnesaemia, daily ondansetron and fluoxetine therapy, and acute tako-tsubo cardiomyopathy. We believe the development of tako-tsubo cardiomyopathy exacerbated our patient's pre-existing QT prolongation to a degree where potentially fatal arrhythmias occurred.

A case of congenital long QT syndrome and tako-tsubo cardiomyopathy with torsades de pointes has been described[4] but MEDLINE and PubMed searching (keywords: long QT and cardiomyopathy) revealed no acquired cases. Tako-tsubo cardiomyopathy induced by physical or emotional stress may exacerbate an underlying long QT syndrome with risk of sudden cardiac death.

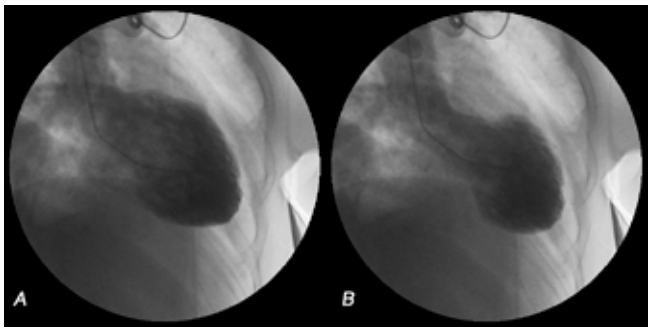

Fig 3. Left ventriculography during diastole (A) and systole (B) demonstrate typical left ventricular apical ballooning and hyper-contractile base of tako-tsubo cardiomyopathy.

The authors have no conflict of interest

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PSEUDOMYXOMA PERITONEI PRESENTING AS INGUINAL HERNIA.

Editor,

Pseudomyxoma peritonei (PMP) is an uncommon disease with varied presentations. We present two cases presenting at inguinal hernia repair.

Case 1: A 41 year-old man presented for right inguinal hernia repair. An encysted swelling was discovered at surgery. Histopathology of the sac showed chronic inflammatory tissue containing lakes of mucin but no neoplastic epithelial cells. Postoperative CT scan showed thickening around the caecum with a fluid collection and abnormality related to the appendix. Colonoscopy and biopsies were normal. The patient was referred to the National Specialist Commissioning Advisory Group Pseudomyxoma Peritonei Centre (Basingstoke) where a laparotomy revealed a

perforated appendiceal tumour and widespread peritoneal disease. A radical greater omentectomy, right hemicolectomy, cholecystectomy and removal of peritoneal disease was performed. Intraperitoneal chemotherapy was administered and the patient made a satisfactory recovery.

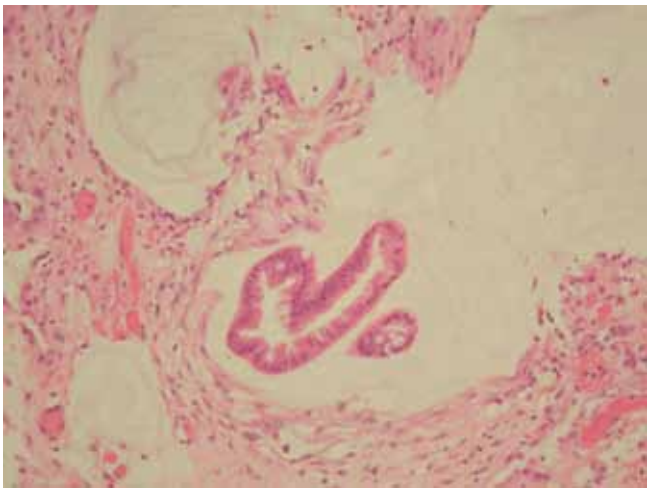

Fig 1. H&E stain (x200)

Case 2: A 73 year-old man presented for right inguinal hernia repair. At surgery the hernial sac appeared thickened. Histopathology (fig 1) showed a thick inner wall composed of chronic inflammatory tissue containing lakes of mucin and well-differentiated enteric type glandular epithelium with minimal cytonuclear atypia. This was considered diagnostic of PMP. Immunohistochemistry showed cytokeratin 7-/20+ staining, characteristic of pseudomyxoma peritonei of large bowel, especially appendiceal origin (fig 2). Post-operative CT scan showed omental cake and ascites. The appendix appeared normal. CEA was raised at 45ng/ml; Ca19-9 was normal. Due to the extent of disease the patient was managed conservatively with follow up imaging and monitoring of tumour markers.

Discussion: PMP is characterised by the build up of mucoid material and fluid within the abdomen and pelvis. The diagnosis is challenging due to the range of presenting features. Patients typically present with abdominal pain, increased abdominal girth or an abdominal mass. A recent review of the clinical presentation of PMP found new onset hernia to be the fourth commonest presentation (14% of cases)[1].

It is well established that the majority of cases are of appendiceal origin[2]. The ovary is rarely the origin of PMP except for the rare case of an intestinal type mucinous neoplasm arising in a teratoma[3]. The ovary may however be a site of secondary spread from the appendix. There are two variants of PMP; Disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA). DPAM arises from an appendiceal mucinous adenoma and peritoneal mucinous carcinomatosis (PMCA) is associated with mucinous gastrointestinal adenocarcinomas[4]. The CK7-/CK20+ immunohistochemical staining pattern is characteristic of pseudomyxoma peritonei of gastrointestinal, especially appendiceal origin (Case 2). Primary ovarian mucinous tumours are characteristically CK7+/CK20- [3].

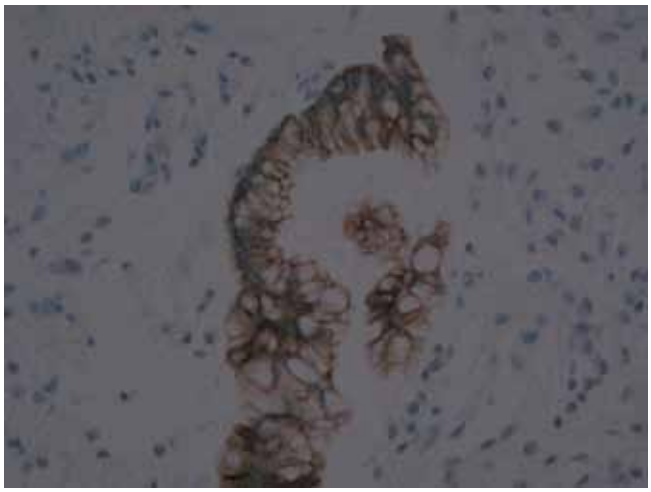

Fig 2. Cytokeratin 20 (x400)

If mucoid material or fluid is found at the time of hernia repair it should be sent to histopathology and the hernia repaired without mesh, thus avoiding trapping tumour cells. Tumour markers should be sent, a CT scan arranged, and the patient referred to a specialist treatment centre once the diagnosis is confirmed[5]. Treatment consists of a combination of peritonectomy procedures and intraperitoneal chemotherapy. This approach has reported 5-year survival rates in excess of 80%[5].

Conclusion: These cases emphasise the importance of considering PMP if a thickened sac or mucinous material is encountered at hernia repair.

The authors have no conflict of interest.

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Ulster Med J 2009;**78(3):**191-193

Abstracts

81st (Spring) Meeting of Ulster Society of Internal Medicine, Friday 15th May 2009

Medical Education Centre, Craigavon Hospital, Portadown

PROGRAMME:

2.00pm Papers I

3.00pm Invited Abstract: 'Thrombolysis for acute ischaemic stroke' Dr Ivan Wiggam, Consultant in Care of the Elderly Medicine, Belfast City Hospital.

3.30pm Afternoon Tea

3.50pm Papers II

4.15pm Presentation of prize for best abstract

4:50pm Guest lecture: 'Modern Management of Inflammatory Bowel Diseases'. Dr John Collins, Consultant Gastroenterologist, Royal Victoria Hospital, Belfast

PAPERS

S1. Trends in clinical outcome of patients admitted with ST elevation myocardial infarction. Insights from The Heart Centre, Royal Victoria Hospital, Belfast.

NA McKeag, VN Kodoth, AJ Tomlin, SL Fairley, MJ Daly, AAJ Adgey.

The Heart Centre, Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast, UK.

Background: A decrease in incidence and major complication rate of ST elevation myocardial infarction (STEMI) has been observed across several population groups.

Methods and Results: Information on patients admitted to our centre with STEMI is entered into a computerised database. Data entered between January 2001 and December 2007 were analysed; 945 patients were admitted over this time, 654 (69%) were male with an average age of 63, 291 (31%) were female with an average age of 71. Admissions reduced from 239 in 2001 to 76 in 2007. Thrombolysis was administered to 611 (65%) patients. Inpatient coronary angiography was performed in 878 patients (93%) and 817 patients (86%) underwent percutaneous coronary intervention (PCI). The proportion of patients undergoing coronary angiography and PCI increased from 79% and 61% respectively in 2001 to 99% and 95% in 2007. The overall in-patient mortality rate was 10%, decreasing from 11% in 2001 to 3% in 2007. In total, 102 (11%) patients suffered cardiac arrest, decreasing from 9% in 2001 to 5% in 2007. Heart failure was noted in 284 (30%) patients, decreasing from 39% in 2001 to 11% in 2007. Major haemorrhage was noted in 41 (4%) patients, decreasing from 4% in 2001 to 0% in 2007. In total, 7 (1%) patients suffered from a stroke. The average hospital stay decreased from 12.4 days in 2001 to 8.8 days in 2007.

Conclusions: This study demonstrates decreasing trends in STEMI admissions and major complications in our centre. Recent in-patient mortality rates are low compared to those reported in major registries. This may reflect more aggressive primary and secondary prevention and increased implementation of invasive management strategies.

S2. 'All in the eyes': basilar tip occlusion, paroxysmal atrial fibrillation and mechanical clot retrieval.

JJ McKinley[1], E Mawhinney[2], M Watt[2], I Rennie[3], MT McCormick[1]

Department of Medicine, Daisy Hill Hospital, Southern Trust, Newry, UK[1]. Departments of Neurology[2] and Neuroradiology[3], Belfast HSC Trust, Belfast, UK.

A 73-year-old lady presented with unsteadiness to her local A&E department. She had been well the night before, gone to bed and awoke on two occasions with difficulty on mobilising to the bathroom. Medical attention was sought later that morning. Initial examination in A&E demonstrated a left sided internuclear opthalmoplegia and controlled atrial fibrillation (AF). She had a recent diagnosis of paroxysmal AF treated with aspirin and beta-blocker. Urgent CT Brain was reported as normal. Her condition fluctuated within hours of admission. She developed an intermittent dense right-sided hemiparesis, one and a half syndrome, dysarthria and fluctuating conscious level. Repeat CT Brain with limited CT angiogram suggested a patent basilar artery with no obvious acute ischaemic changes. The clinical diagnosis was consistent with basilar artery occlusion. In view of the fluctuating course and time to presentation she was not suitable for intravenous thrombolysis. Her case was discussed with the regional neurosciences centre and she was transferred. Multi-slice CT angiography confirmed thrombus in the upper basilar artery and she underwent formal cerebral angiography, mechanical clot retrieval and resultant recanalisation. She made an excellent clinical recovery, remained in hospital for formal anticoagulation and discharged home later that week.

The prognosis of basilar artery occlusion is generally poor. This case demonstrates the potential devastating sequelae of atrial fibrillation, the need for prompt consideration of anticoagulation, limitations in single slice CT imaging, the importance of clinical acumen and the urgency in escalating therapy given the potential to restore circulation by means of novel therapies.

S3. Outcome of 64-slice multi-detector coronary CT angiogram when exercise stress test is equivocal or not possible.

JA Purvis, SM Hughes.

Department of Cardiology, Altnagelvin Hospital, Western HSC Trust, Londonderry, UK.

64-slice coronary CT angiography (64-CCTA) is currently being evaluated for patients at intermediate risk of coronary artery disease (CAD). We analysed data on patients referred to us because of equivocal EST result or technical problem.

Pre-treatment with oral beta-blockade was used to achieve HR<64bpm. Intravenous beta-blocker was given pre-test if required. Sublingual GTN was given to all. A calcium scan was performed then contrast study.

89 patients were referred over 15 months. 53(60%) had an equivocal EST result, 6(7%) had inadequate exercise duration, 15(17%) had mobility problems, 8(9%) had LBBB, 3(3%) had COPD, 2(2%) had hypertension or LVF, 2(2%) didn't want to EST.

All calcium scans were evaluable. 65(74%) patients had mild calcification (Agatston score = 0 – 100), [41(46%) had a score of 0]. 12 had moderate (13%) calcification (Agatston score = 101 – 300) and 12(13%) had severe calcification (Agatston score >300).

In 5 cases, calcium score was too high for contrast study. 84 contrast studies were performed, all were evaluable, 47(56%) patients had normal studies. 23(27%) patients had mild coronary plaque not requiring catheter study. 13(15%) patients had severe coronary plaque and underwent catheter study. Cath agreed with 64-CCTA in 10(77%), 64-CCTA over-called 2(15%) cases and under-called 1(8%).

In conclusion, 64-CCTA can exclude CAD in 56% of this category of patients. In a further 27% non-obstructive plaque is seen. 64-CCTA shows a high correlation with cath findings for severe plaque.

S4. The outcome of fixed dose radioiodine (550MBq) in the treatment of relapsed hyperthyroidism

AS Lewis, T Rea, AB Atkinson, PM Bell, CH Courtney, DR McCance, K Mullan, SJ Hunter.

The Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, UK.

Radioiodine is the treatment of choice for relapsed hyperthyroidism although the optimum protocol is uncertain. We assessed the outcome of therapy with radioiodine in relapsed hyperthyroidism using a fixed dose regimen.

We retrospectively studied 449 patients (M: F 82:367; age range 13-89y, median 42y) treated between 2003 and 2007 with a fixed dose of 550MBq radioiodine for relapsed hyperthyroidism. Patients were classified as Graves' disease, toxic multinodular goitre or indeterminate aetiology. Where patients were on antithyroid drugs these were stopped at least 1 week prior to radioiodine.

One year following radioiodine 334 patients (74%) were hypothyroid, 85 (19%) were euthyroid and 30 (7%) had required a further dose of radioiodine. Patients with Graves' disease were more likely to become hypothyroid than those with toxic multinodular goitre (78% v 37%, p<0.001) whereas the latter were more likely to become euthyroid (55% v 11%, p<0.001). Free thyroxine >80pmol/L at presentation was associated with an increased failure rate (17% compared with 5% and 3% for 40-79pmol/L and <40pmol/L respectively; p = 0.01). Patients with a small / no goitre were more likely to be successfully treated by a single dose of radioiodine (96%) than those with a medium/large goitre (85%, p<0.001). Anti-thyroid medication was taken by 345 patients (77%) (carbimazole n = 319) and was associated with an increased failure rate (8% v 2%, p = 0.027).

In conclusion, a single fixed dose of 550MBq radioiodine is highly effective in treating relapsed hyperthyroidism. The aetiology, severity of hyperthyroidism, goitre size and prior anti-thyroid medication have a significant effect on outcome.

S5. PSD502, a novel metered-dose, aerosol formulation of lidocaine and prilocaine, is a safe and effective treatment for premature ejaculation (PE); results of a phase III, randomized, double blind, placebo-controlled study.

Wallace Dinsmore, Michael G Wyllie, Patricia Heath

Royal Victoria Hospital, Belfast, UK.

Introduction and Objective: Reducing the sensitivity of the glans penis with topical desensitizing agents in men with premature ejaculation may represent a way of improving intravaginal ejaculatory latency time (IELT) without adversely affecting the sensation of ejaculation. PSD502 is a novel aerosol formulation of lidocaine and prilocaine, which selectively desensitizes non-keratinized skin. The objectives of this study were to assess the clinical benefit and safety of PSD502 or placebo in men with PE when applied to the glans penis on an 'as needed' basis. **Methods:** A total of 300 men with primary PE diagnosed according to the recently published ISSM definition (including an IELT of 1 minute), were randomized from 32 centres in UK, Czech Republic, Hungary and Poland to apply 3 sprays of PSD502 or placebo (double-blind) to the glans penis 5 min before intercourse. Efficacy was assessed by changes in IELT, Index of Premature Ejaculation (IPE; a patient-rated scale of improvement in ejaculatory control, sexual satisfaction, and distress), and Premature Ejaculation Profile (PEP; patient and partner-rated scales of improvement in PE symptoms). Subjects were followed up at intervals for 3 months and offered open label treatment with PSD502 for a further 9 months. **Results:** Preliminary analyses show that PSD502 produced a highly clinically and statistically significant increase from baseline in all three co-primary endpoints. Both groups had a geometric mean baseline IELT of 0.6 min, which increased to 4 min in the PSD502 group compared to 1

min in the placebo group (p<0.0001). There was a 7-point difference between PSD502 and placebo in the IPE domain for ejaculatory control (p<0.0001) and a 6-point difference in the IPE domain for sexual satisfaction (p<0.0001). These positive results were supported by similar improvements in secondary endpoints. There were no serious adverse events and only 2.6% of patients reported treatment-related adverse events in the PSD502 group compared with 1% in the placebo group. PSD502 was well tolerated by both patients and partners, and with no systemic adverse events reported. **Conclusions:** This large placebo-controlled study indicates that PSD502 is a safe and effective treatment for primary PE, when applied 5 min before intercourse, demonstrating highly significant improvements in IELT and patient-rated improvement scales and a good safety profile in both patients and their partners.

S6. Takotsubo cardiomyopathy in preoperative patients with pain: a report of two cases

MJ Daly, LJ Dixon

Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, UK

Reversible stress-induced cardiomyopathy, i.e. Takotsubo cardiomyopathy, rarely presents in preoperative patients. We provide the case reports of two patients who presented to hospital with uncontrolled pain from an acutely ischaemic limb and femoral neck fracture, with an absence of chest pain. Electrocardiogram revealed dynamic T-wave inversion, with peak Troponin-T elevation in each case, i.e. 0.66ug/L and 0.14ug/L (NR <0.03ug/L). Despite these findings consistent with acute myocardial infarction, neither patient had obstructive coronary disease at angiography. Left ventriculography at this time showed moderate systolic functional impairment with apical ballooning. This feature is pathognomonic of the Takotsubo syndrome, which we surmise was due to excess endogenous catecholamine production in response to acute pain in these patients. All features of ventricular dysfunction had resolved completely at repeat echocardiography two-weeks later, following definitive vascular/orthopaedic surgery to their lower limbs.

Patients with Takotsubo cardiomyopathy have been shown to possess higher catecholamine levels than patients with myocardial infarction in the same Killip class[1]. Apical myocardium is particularly receptive to sympathetic stimulation, resulting in characteristic ballooning as seen in our patients. Furthermore, catecholamine stress-injury is likely to be present in a number of disorders whose common phenotypic expression is that of regional wall motion abnormality, e.g. subarachnoid haemorrhage, phaeochromocytoma, acute asthma and Guillain-Barré syndrome.

Treatment of Takotsubo cardiomyopathy remains largely pragmatic, with standard supportive care and treatment of complications, e.g. pulmonary oedema. Recent reports attribute 12% of all cases to non-cardiac surgery/procedures and 4% to skeletal fractures[2]. Although this syndrome remains uncommon, it should be considered in any patient with symptoms suggestive of an acute coronary syndrome, when the electrocardiographic changes are disproportionate to the cardiac enzyme rise, and particularly those in acute pain.

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S7. Day Case Percutaneous Coronary Intervention in Selected Patients – A Pilot Study in Northern Ireland

EC Hodkinson, J Shand, DJ Flannery, DJ McEneaney, IBA Menown, AJ McClelland, SJ Walsh.

Cardiology Department, Craigavon Area Hospital, Craigavon, UK.

Further to the development of intracoronary stents post-procedural complications rates after percutaneous coronary intervention (PCI) are low. Acute complications post-PCI occur almost exclusively within six hours[1,2], therefore day case PCI is both feasible and safe.

Day case PCI has been performed in Craigavon since November 2008. Patients are discharged after 6 hours if there has been a successful PCI (TIMI 3 flow and <20% residual stenosis of the target lesion) and they meet criteria for same day discharge. Exclusion criteria include: unstable patients (ischaemia or loss of a side branch >1mm, instability during the PCI or LVF), any vascular complication or a sub-optimal technical result.

The first 100 cases are presented: 71% were male; mean age was 64 (range 42-84 yrs). LV function was severely impaired in 2% and moderately impaired in 16%. A total of 105 lesions were treated, 46% of which were high risk (AHA/ACC classification) and 36% moderate risk. A total of 129 stents were deployed, 78 (60%) of these were drug eluting. To date, 30-day follow-up is available for 70 patients. There have been no major adverse cardiac events (death, MI, CVA) or other adverse events (repeat angiography/PCI, contrast induced nephropathy, CK rise > 2x the upper limit of normal). Follow-up for all 100 cases will be presented at the meeting. The total cost saving from preventing a single overnight stay for each patient is £47,100.

Day Case PCI in selected cases is safe, feasible and offers substantial cost savings to the local health service.

[1]Small A, Klinke P, Della Siega A *et al.* Day Procedure intervention is safe and complication free in higher risk patients undergoing transradial angioplasty and stenting. The Discharge Study. *Catheter Cardiovasc Inter* 2007;**70:**907-12. [2]Koch KT, Piek JJ, Prins MH *et al.* Triage of Patients for short term observation after elective angioplasty. *Heart* 2000;**83:**556-563.

Ulster Med J 2009;**78(3):**194-199

Abstracts

Out of Town Meeting of the Ulster Paediatric Society, Friday 8th and Saturday 9th May 2009.

Shandon Hotel, Dunfanaghy, Ireland

PROGRAMME:

Friday 8th May

6.30pm - Welcome – President: Dr Denis Carson

6.35pm - 7.00pm Presented Abstract 1

7.00pm - 8.00pm Guest speaker: Recent advances in the diagnosis and management of hyperinsulaemic, hypoglycaemia. Dr K Hussain, Institute of Child Health, University College Hospital, London.

8.30pm - Dinner

Saturday 9th May

9.30am - 10.00am Annual General Meeting

10.00am - 11.15am Presented Abstracts 2-6

11.15am - 11.30am Tea -Coffee

11.30am - 13.00pm Guest Lecturers: Assessment and treatment of breathing disorders during sleep. Prof. M Shields, Mr K Trimble

13.00pm – Lunch

18.00pm - Dinner

PRESENTED ABSTRACTS

A1. Aetiology of acute hypoglycaemia: Re-audit of procedures for diagnosis

TF Lang[1], D Cardy[1], H Leslie[1], B Sheridan[1], D Carson[2], CM Loughrey[1]. [1]Department of Clinical Biochemistry, and [2]Department of Paediatrics, Belfast Health and Social Care Trust, Belfast, UK.

Introduction: A protocol exists for the collection of samples to investigate non-diabetic hypoglycaemia, termed the "hypopack". These packs are kept in A&E departments, most children wards and neonatal SCBUs throughout the region. A retrospective audit of 107 hypopacks received between July 2001 and Dec 2003 highlighted a numbers of problems: samples collected when patient was receiving dextrose, incomplete clinical history, insufficient and haemolysed samples and filing of reports in charts. These were addressed by redesigning the request form, updating the protocol and introducing a summative report. The new protocol was introduced in April 2006 and was supported by presentations to regional centres.

Methodology: A retrospective audit of 100 Hypopacks received between April 2006 and May 2007 was performed to assess whether all samples were analysed and reported, and were taken when the patient was hypoglycaemic. Charts were reviewed to determine the cause of hypoglycaemia and to check reports were filed appropriately.

Results: 49% of patient were hypoglycaemic (<2.6mmol/L) compared to 35% in the original audit. 64% of patients had samples taken before dextrose compared to 54% previously. Haemolysed insulin samples remained a problem with 21% of samples being rejected. In both audits 35% of laboratory reports were missing from patients charts. Intrauterine growth retardation was the most common problem in neonates and fasting due to gastroenteritis the most common in children. In the re-audit period, 1 case of isolated ACTH deficiency, 3 cases of hyperinsulinism of infancy (of which two were transient), 1 case of MCADD and 1 patient with a previous diagnosis of Morquio Disease were identified.

Conclusions: The new hypopack protocol has increased the number of appropriately performed investigations but there is still scope for improvement. Provision of clinical history and information concerning dextrose infusion has assisted with the interpretation of the hypopack results.

A2. Congenital Hyperinsulinism of Infancy in Northern Ireland: 1980-2009

NM Flanagan, DJ Carson. Royal Belfast Hospital for Sick Children, Belfast Health and Social Care Trust, Belfast, UK.

Background: Congenital Hyperinsulinism of Infancy (CHI) is the most common cause of persistent or recurrent episodes of hypoglycaemia in infancy. It is a complex genetic condition caused by activating mutations in a number of different genes resulting in continuous depolarisation of potassium gated channels in pancreatic beta cells, leading to dysregulated insulin release. Clinical manifestations range from life-threatening hypoglycaemia in the newborn to a milder degree of hypoglycaemia in older babies. All patients known to the Royal Belfast Hospital for Sick Children (RBHSC) from 1980 – 2009 have been reviewed.

Objective: To evaluate the clinical presentation, diagnosis, medical or surgical treatment required and long-term complications of CHI over a 29 year period in the RBHSC.

Results: Case notes were retrieved for 12 patients: 6 females and 6 males, 4 presenting in the 1980s, 8 since 2001. 7

presented within the first 4 days of life, the others up to age 12 months. 8 had hypoglycaemic seizures, all were symptomatic at presentation. Minimal glucose requirements were recorded between 8-20mg/kg/min prior to treatment. All had inappropriately raised insulin levels (5-39mU/l) with recorded plasma glucose levels below 2.6mmol/l. Genetic studies have been positive in 5 of 7 patients investigated, including a mother and son, and brother and sister. All patients were initially commenced on diazoxide (a potassium channel agonist in beta cells) and chlorothiazide (to reduce fluid retention) with dietary advice and a carbohydrate–enriched diet, but medical treatment failed in 7. Subtotal pancreatectomy (over 90% of the pancreas removed) was required for 4 patients with diffuse disease and 1 with histologically focal disease when symptoms recurred after the focal lesion was resected. Another patient had a 50% pancreatectomy with removal of a focal lesion. Long-term complications include 2 of the 5 medically treated patients with developmental delay -1 with autism, 1 with epilepsy. In the surgically treated group 4 have developmental delay, 1 with infantile spasms, 2 have insulin dependent diabetes, 2 have exocrine pancreatic insufficiency and 1 developed a stricture in his common bile duct. Of the 7 patients on long-term diazoxide 5 developed hirsutism. To date 3 of the 5 medically treated patients have successfully stopped diazoxide at age 3 years, 4 years and 5 years. The 2 patients on diazoxide post-operatively successfully discontinued the diazoxide at age 1 year and age 15 years.

Conclusions: Early recognition, appropriate investigation and medical management of CHI often fails to preserve neurological function. In severe CHI unresponsive to medical management pancreatic resection can be undertaken. Medical and surgical therapies have associated long-term risks, although recent genetic advances and the introduction of 18F-DOPA PET-CT imaging allows differentiation between focal and diffuse disease pre-operatively which permits limited resection and lowers post-operative complications.

A3. Impact of Congenital Heart Disease on Perinatal Services

S Millar, F Casey, D Sweet. Royal Maternity Jubilee Hospital, Belfast Health and Social Care Trust, Belfast, UK.

Aim: To determine numbers, time of diagnosis, delivery and management of babies with congenital heart disease in Regional Neonatal Intensive Care Unit (NICU).

Standard:

- All major congenital cardiac conditions antenatally diagnosed.
- All planned deliveries occur when planned.
- All planned deliveries take place during working hours i.e. 09:00-17:00.
- Minimum time in NICU post-discharge of mother.

Methods: Coding system in RMJH and Heartsuite (Paediatric cardiology coding) used to identify babies with major Congenital Heart Disease, Dysrhythmias, Trisomy-21, -18 and -13 over 5 years.

216 patients identified, of these 204 charts were available for retrospective review. 179 had a congenital cardiac condition. The remaining 25 had no cardiac diagnosis or had Trisomy-21, -18 or -13 with no documented cardiac defect.

Charts were reviewed for date of birth, gestation, birth-weight, sex, time of diagnosis, delivery details including time of induction and delivery, whether antenatally or postnatally transferred from District General Hospital, investigations and management relevant to the cardiac condition, associated anomalies and time spent in Regional NICU.

Results:

- 64% of congenital cardiac conditions diagnosed postnatally, at least 35% of these with significant congenital heart disease.
- 44% of planned deliveries were due to cardiac condition.
- 8% delivered later than planned
- 6% due to lack of neonatal cots.
- 17% IOL of planned deliveries occurred between 12:01 and 00:00.
- 36% planned deliveries delivered between 17:01 and 08:59.
- 539 days taken in NICU due to cardiac conditions over the five-year period, i.e. 108 days/year.

Conclusions: Congenital Heart Disease has a significant impact on Regional Perinatal Services. Increasing antenatal detection rates will lead to more neonates with severe congenital heart disease being delivered in tertiary centres. This increased demand needs to factored into resource planning for such centres.

A4. Hartmann's with glucose, saline with glucose and half normal saline with glucose; an audit of electrolytes children following appendicectomy

PC Stewart, KL McGrath. United Kingdom.

We audited electrolyte data in children undergoing unscheduled appendicectomy in a non specialist unit over a period of three years. Children received maintenance hydration as part of a strict protocol using one of three solutions; 25% of children maintained on 0.45% sodium chloride (n=53) were hyponatraemic throughout and more of them required fluids for longer, over 50% of children maintained on 0.9%sodium chloride and 5% glucose (n=57) were hyperchloraemic with a high incidence of hyperglycaemia. Those maintained on Hartmann's solution and 3% (n=62) glucose exhibited the best biochemistry with regard to major ions and glucose. We feel that this highlights the value of audit in better prescribing and advocate using a similar approach regionally.

A5. Peer Assessment of Foundation Doctors Ability to Record Injuries: An analysis of Results During Children Protection Training.

JM O'Donohoe, Erne Hospital, Enniskillen, United Kingdom.

Background: Recording of medical activity is widely accepted as being important. Because of the long term social services and legal relevance of child protection examination high quality of recording is likely to be particularly important,

The Northern Ireland Medical and Dental Training Agency

Question 1 **Size**	At least two dimensions:, internal sizes where appropriate	Recorded for All	Recorded for Most	Recorded for Some	Recorded for few	Recorded for None
		6/36 16.7 %	7/36 19.4%	10/36 27.8%	4/36 511.1%	9/36 25%
Question 2 **Colour**	A reasonable representation of the colour recorded	Recorded for All	Recorded for Most	Recorded for Some	Recorded for few	Recorded for None
		1036 27.8%	7/36 19.4%	7/36 8.3%	5/36 13.9%	11/36 30.6%
Question 3: **Shape**	A reasonable representation of the outline	Recorded for All	Recorded for Most	Recorded for Some	Recorded for few	Recorded for None
		22/36 61.1%	8/36 22.2%	3/36 8.3%	3/36 8.35	0/36 0%
Question 5 **Number**		All marks of relevance recorded	Most marks of relevance recorded	Some marks of relevance recorded	Few marks of relevance recorded	No marks of relevance recorded
		24/34 70.6%	6/34 17.7%	2/34 5.9%	1/34 2.9%	1/34 2.9%

(NIMDTA) has opted to make a days training in child protection mandatory for Foundation Doctors in their second year after qualification (FY1).

Results are presented from a training activity undertaken during such a training session designed to look at the ability of a group of FY1 doctors to record injuries.

Methods: NIMDTA has acquired a keypad system for real time analysis of questions asked to learners (Turning Point 2006, Turning Technologies, Ohio, USA). This allows questions to be asked of an audience and the results presented to them within a few seconds of the data being recorded. a training exercise was devised based on a picture of multiple injuries due to non-accidental injury which is in the public domain (fig 2 in Evaluation of Physical Abuse in Children, Presse DM. 2000 American Family Physician p 3075). The results from this exercise are reported here. A fictitious name was added and a date of attendance. A scale was superimposed on the picture to allow sizes to be identified.

Attendees at the training session were asked to make a record of the injuries in the figure above which was projected on a screen in the training room. When each trainee passed their record to another trainee to be scored.

Since there is no validated scale for assessing recording of injuries questions were devised to assess the recordings on a 1 to 5 point scale under the following headings: identifying information (name of recorder etc.), orienting information (right / left, front/back etc.); number of injuries recorded, shape of injuries recorded, colour of injuries recorded and localizing information (to describe where the injuries were situated). Scores were recorded via Turing Point, shared with the group as a whole and the diagrams returned to the original recorder.

Three summary questions were asked at the end about the scorers' opinion as to whether the diagram was good enough to allow an expert to review the situation later, if the scorer would be happy to rely on the record for court purposes and how well the record resembled the original photograph.

Results: 6 training days on child protection were held over the period October 2008 – April 2009. There were a total of 214 trainees for whom this training was mandatory. 41 trainees attended the last of a series of these 6 training days which was the first time the above exercise was undertaken. The number of responses was less than 41 to all questions. It is not possible to identify if this shortfall was due to technical difficulties or trainees who didn't wish to participate.

Question: Site of injuries was scored as follows: for each of the following pieces of information one point was scored when the information was recorded and 0 when it was absent: top/ bottom, left/right, anterior/ posterior, some localizing anatomical features, all anatomical features necessary to locate.

Question 3: **Site of Injuries**	5	4	3	2	1
	15/36 41.7%	8/36 22.2%	10/36 27.8%	1/36 2.78%	2/36 5.6%

Question 6: Identifying information was scored as follows: for each of the following pieces of information present one point was scored when the information was recorded and 0 when it was absent : Patients Name, Patient DOB, Date of Recording, Name of Recorder, Signature of recorder.

Question 6: **Identifying Information**	5	4	3	2	1
	2/34 5.9%	1/34 2.9%	7 20.6%	12/34 35.3%	12/34 35.3%

Total Scores (out of 30)	26-30	21-25	16-20	11-15	6-10	0-5
	1/36 2.78%	19/36 52.78%	11/36 30.56%	5/36 13.89%	0/36 0%	0/36 0%

The answers to the summary questions are as follows:

Overall what is your opinion: This recording is good enough to allow the situation to be reviewed by an expert later?

Strongly Agree	4 /36 (11.1%)
Agree	1/36 (41.7%)
Neutral	6/36 (16.7%)
Disagree	9/36 (25%)
Strongly Disagree	2/36 (5.6%)

What is your opinion? I would be happy to rely on this diagram for court purposes.

Strongly Agree	2/36 (5.6%)
Agree	11/36 (30.6 %)
Neutral	5/36 (13.9%)
Disagree	12/36 (33.3%)
Strongly Disagree	6/36 (16.7%)

How Closely Does the Report represent the original picture?

Close to identical to it.	3/36 8.33%
A lot of similarity to it	9/36 25%
Similar to it	13/36 36.11%
Some points of similarity	8/36 22.22%
Little if any similarity	3/36 8.33%

Discussion: The doctors who took part in this exercise were 3 quarters way through their second year after qualification at the time of the exercise. Some will have had attachments where there is likely to have been particular emphasis on recording of injures (e.g. casualty) whereas others may not have had such rotations.

Despite this limitation it is still disappointing to see that in 25% of cases no sizes for the injuries were recorded. In a similar vein colour was not recorded at all in 30.6% of records. This is echoed by the fact that in just over 30% of cases the scorer disagreed or strongly disagreed with the idea that the recording was good enough to allow a review of the situation by an expert later on. Similarly just over 30% of scorers felt that the report either bore little if any similarity to the original or only had some points of similarity. In only just over 35% of cases the scorers were agreed or strongly agreed they would be happy to rely on the diagram for court purposes.

No effort was made to identify to what extent attendees had formal training or supervision in the production of such reports or diagrams and it may be that the relatively low score may be a reflection of limitations in this regard.

The generalisability of the results is limited by the nature of the sample. However it is unlikely that results for those attending this training day earlier in year would have been better. This is partly on the basis that they would have had less clinical experience and is supported by the authors' observations of similar exercises undertaken on a pencil and paper basis with previous groups of trainees.

There is also a limitation in the sense that the tool used to examine this issue has not been subject to formal analysis in terms of reliability and validity. It would seem likely to have high face validity and there doesn't seem to be a gold standard with which to compare it. In the absence of any other technique for formally assessing such recording this tool may be of value in audit, assessment or in comparing the impact of different approaches to encouraging improved recording but each of these situations will need to be studied in its own right. Original records were returned to the recorder. It was not possible to examine the recorders attitude to the scores returned to him or her.

A6. Attitudes of Foundation Doctors To Mandatory Training in Child Protection

JM O'Donohoe, Erne Hospital Enniskillen, United Kingdom.

Background: Recent high profile cases have made it clear that no medical practitioner is immune from contact with child protection issues, either directly or indirectly. The Northern Ireland Medical and Dental Training Agency (NIMDTA) has decided to make a days training in child protection mandatory for Foundation Doctors in their second year after qualification (FY1). This extent of child protection is still relatively unusual within the NHS. When designing this training day there were various issues about which there was no background information for guidance. For example what would the attitude of Foundation Doctors, many of whom would not be intending to work in paediatrics feel about such training being mandatory? During the course of one such day an audience response system was used to address some of these ideas.

Methods: NIMDTA has acquired a keypad system for real time analysis of questions asked to learners (Turning Point 2006, Turning Technologies, Ohio, USA). This allows questions to be asked of an audience and the results presented to them within a few seconds of the data being recorded.

Attendees at one training session were asked to respond to a number of questions during the course of the day. These questions were originally designed to allow those teaching the day to identify where the trainees were starting from as trainees.

6 training days on child protection were held over the period October 2008 – April 2009. There were a total of 214 trainees for whom this training was mandatory. 41 trainees attended the last of a series of these 6 training days which was the first time the above exercise was undertaken. The number of responses was less than 41 to all questions. It is not possible to identify if this shortfall was due to technical difficulties or trainees who didn't wish to participate

Results: The first question asked, during an introductory session, was about whether this child protection training was considered to be relevant to them. 36 of 40 response said it was. Of the remaining 2 (2.5%) answered no and 2 didn't know.

The trainees were then asked to rate their ability to recognise a child protection concern by responding to the question: "**I would recognize a child protection concern?"** 22/39 56% believed they would be able to recognize a child protection concern, 3/39 (8%) thought not and 36% didn't know.

The extent to which they knew who to talk to if concerned was assessed with the question" **If I am concerned about a child's welfare I know who to talk to:"** 20/38 (57%) believed they did and the remaining 18 (47%) did not. When it came to know what to do (in response to "**If I need to refer a child with a child protection concern, I know how to do so"** 11/39 (28%) said they knew, 25/39 (64%) said they did not and 3/39 (8%) said this didn't apply to them since they didn't anticipate coming across such an issue during their professional life.

Self perceived ability to record child protection issues was measured with the responses to the question "**I know how to record my involvement in child protection issues".** 5 (13%) said they 33 (85%) said they did not know how to do so and 2/40 (5%) didn't know.

During a subsequent session on background issues the trainees were asked to rate their ability to work in a child protection situation with the question with the prompt: "**Your ability to work in a situation where there may be a child protection element"** by choosing between the categories in table I, which also includes the responses. The categories were based on Millars pyramid of competence[1].

I know nothing about this topic	4/39 10.3%
I know something about this topic but not enough to work with a case even with direct supervision	12/39 30.8%
I could work with a case if there is direct supervision.	20/39 51.3%
I could work with a child protection case with some supervision.	3/39 7.7%
I can work independently in child protection ...	0/39 0%

TABLE I:

Self-assessed ability to work in child protection.

During a session run by police questions were asked about a number of other areas related to child protection and summarised in Tables II-IV.

Certain	4 11.11%
Very Likely	9 25%
Likely	9 25%
Unlikely	14 38.89%

TABLE II:

Responses to the question: Domestic Violence – How likely are you to ask about it when dealing with injuries?

Agree	2/38 5.3%
Disagree	26/38 68.4%
Neutral	10/38 26.3%

TABLE III:

Responses to the question: Domestic Violence - I feel familiar with this issue and I am sufficiently skilled to launch direct questions regarding partner abuse

Yes	11/38 29%
No	27/38 71%

TABLE IV:

Responses to the question:" I was aware before today of my legal obligation to report to police any crime carrying a sentence of 5 years are more that I become aware of".

To assess the degree of discomfort associated with Child Protection Matters they were asked to score their degree of discomfort with various activities they might become involved with. They were asked to score in categor1es ranging from 1 to 10. Each category was described as being a sub-category of a scale of 1 to 100. Anchor points on the scale of 1 to 100 were given as follows: 1: Everything more uncomfortable, 25: Many things more uncomfortable, 50: Some things more uncomfortable, 75: Few things more uncomfortable and 100: Nothing more uncomfortable.

Two of the situations clustered at the lower end of the scale (doing a lumbar puncture and being called to a cardiac arrest) as in Fig 1 for the Degree of Discomfort at the Prospect of Doing a Lumbar Puncture.

In increasing order of discomfort were inserting an IV cannula into a HIV positive patient, relaying a diagnosis of carcinoma both of which were around the middle of the scale (fig 2 for example). Discussion with a patient about a medical intervention that has caused a serious, unexpected damage was towards the upper end of the discomfort scale (Fig 3).

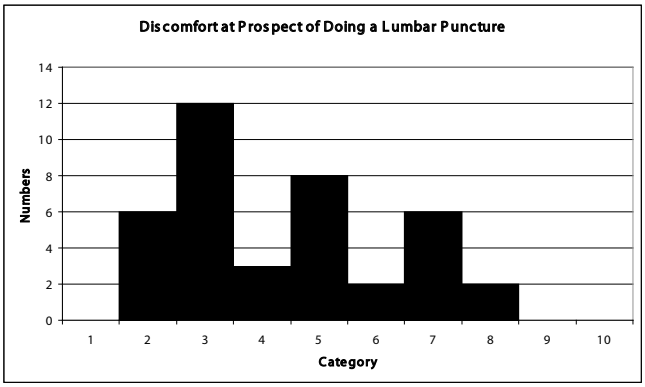


Fig 1. Discomfort at the Prospect of Doing a Lumbar Puncture.

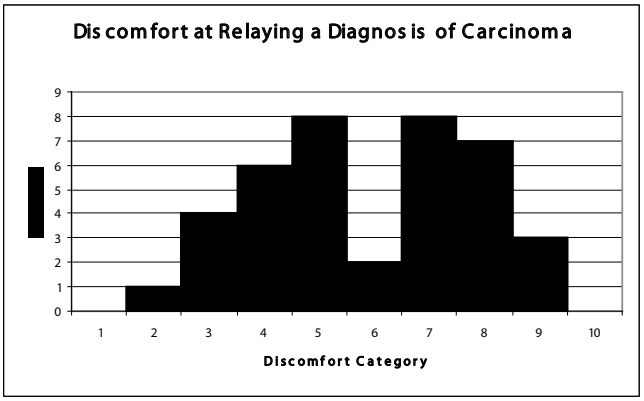


Fig 2. Discomfort at relaying a Diagnosis of Carcinoma.

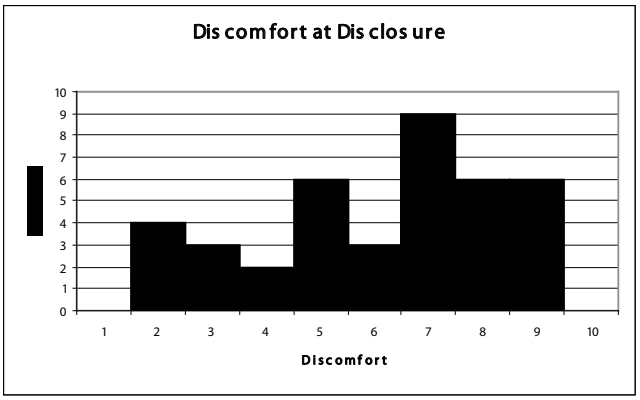


Fig 3. Discomfort at having to discuss with a patient about a medical intervention that has caused a serious, unexpected damage.

Fig 4. Discomfort at the prospect of being involved in an unanticipated Child Protection issue.

Discussion: One of the difficulties practitioners may experience when starting to become involved in teaching is to forget that what seems normal and would be anticipated to be widely known may not be so. Some areas of learning may be particularly susceptible to this effect and in some cases this may relate to the need for medical students to choose what to study. Sometimes areas may be chosen on the basis of their likelihood of not being examined or on the basis that there is little direct exposure to relevant clinical material as a student. Both of these may apply to child protection issues. The number of FY1 doctors (three quarters way through their second year after qualifying) who rated themselves as able to recognise child protection matters and to know who to talk to about such matters was only a little over a half.

Over 90% believed that at most they were capable of only dealing with child protection matters with direct supervision.

The degree of discomfort at the prospect of having to deal with child protection suggests that whatever knowledge had been acquired in the past it has not prepared doctors well for the task of dealing with such matters. It may be that different forms of training, possibly based on more real life types of training e.g. scenario based training may be more useful than traditional didactic teaching.

It may be possible to evaluate the training being offered by using a before and after approach using some of the methods described above.

The frequency of child protection issues in the population may contribute to the degree of discomfort that Foundation doctors feel about the prospect of being involved in such issues in the sense that it is likely that some of those attending have been affected either directly or indirectly by such matters. With further development it may be possible to identify if there is a valid "discomfort" scale such as is mentioned above. Such a scale may allow an open recognition of the intensity of the discomfort involved in some areas. This may promote a pedagogically safer learning environment within which learning may be more easily encourage.

Reference: 1: Norcini J. ABC of learning and teaching in Medicine: Work Based Assessment. *BMJ* 2003;**326:**753-755.

Ulster Med J 2009;**78(3):**200-202

Abstracts

Spring Meeting of the Irish Association of Dermatologists. Friday 24th April 2009

Inishowen Gateway Hotel, Buncrana, Ireland

S1. The Effects Of Obesity And Smoking On The Function Of Natural Killer Cells In Psoriasis

AM Tobin, L Lynch, A Kwasnik, S Rogers, P Collins, D O'Shea, B Kirby.

Department of Dermatology and Obesity Research Group, St Vincent's Hospital, Dublin.

Obesity has emerged as a major co-morbidity in patients with psoriasis. In a case control study we found that patients with psoriasis had significantly higher body mass indices (BMI) compared to controls ($p = 0.004$). Increased adiposity and weight gain were strong risk factors for the development of psoriasis in the Nurses Health study[1]. Multivariate analysis demonstrated a clear, graded association between BMI and the risk of having psoriasis[1].

Adipose tissue actively secretes cytokines such as TNF-alpha and interleukin-6 and pro-inflammatory adipokines such as leptin and resistin along with adiponectin which has anti-inflammatory effects. Patients with psoriasis had raised levels of serum resistin compared to controls[2]. Serum levels were also correlated with psoriasis disease activity and were unrelated to BMI suggesting a link between psoriasis and adipokines. A second study of 39 patients found disease severity was correlated with insulin resistance and serum resistin.

Recent studies have shown that patients who are obese have lower levels of natural killer (NK) cells when compared to controls. Natural killer cells from obese patients also had decreased levels of in-vitro activity compared to lean controls. Natural killer cells are thought to be involved in the pathogenesis of psoriasis and patients have lower levels of circulating NK cells than controls.

We have investigated levels of circulating NK cells in obese and lean patients with psoriasis, their in vitro cytotoxcicity and also the effect of the adipokines leptin, adiponectin, resistin and cigarette smoke extract on the cytotoxcicity of circulating NK cells.

CD 56; a marker of NK and NK-T cells; cells have been extracted from peripheral blood monocytes (PBMCs) of patients with psoriasis with magnetic beads. Using ethidium bromide and UV microscopy these CD 56 cells were counted. Psoriasis patients who are obese, defined as BMI > 30 ($N = 6$) have on average 3.84% CD 56 of total PBMCs cells versus patients who are lean defined as BMI < 25 ($N = 7$) have on average 8.9% CD56 cells ($p = 0.02$).

CD 56 cells isolated above from PBMCs of patients with psoriasis and also controls were incubated with the myelogenous tumour line K562 in the presence of the adipokines resistin, leptin and adiponectin and also cigarette smoke extract for four hours. Using 7-AAD staining, the numbers of killed tumour cells were counted by flow cytometry and gating on the tumour cells.

In the presence of resistin tumour killing by CD 56 cells was increased by on average 28% when compared to CD 56 cells alone in six patients with psoriasis ($p = 0.08$). In the presence of cigarette smoke extract the killing of CD 56 cells was decreased by on average 38 % in eleven patients with psoriasis ($p = 0.001$).

These results indicate a possible mechanism whereby obesity affects psoriasis by further lowering NK cells. They also indicate that resistin and smoking may exacerbate this NK defect. By stimulating NK cells resistin may be hastening their apoptosis and cigarette smoke appears to be having a directly toxic effect.

1. Arathi RS, Curhan G, Hyon CK. *Arch Intern Med* 2007;**176:**13-27. 2. Johnston A, Arnadottir S, Gudjonsson, *et al. Br J Dermatol* 2008;**159:**342-350.

S2. An audit to evaluate service outcome in children with Atopic Eczema attending a paediatric dermatology clinic.

C Devereux, K McKenna, A Bingham, S Hoey

Royal Belfast Hospital for Sick Children, Belfast.

A re-audit was conducted to determine if the service provided at a paediatric dermatology out-patient clinic met the working standards for the management of atopic eczema as defined by the BAD. The re-audit results were compared to the results from the BAD Audit of atopic eczema management in secondary care, Phase 3: Audit of Service outcome, published in 2000. This audit was a prospective study of patients quality of life and disability preconsultation and 6 weeks postconsultation. Standards set were:

1. Of patients reporting sleep loss secondary to eczema, at least 70% should report a favourable change at 6 weeks.
2. There should be a 25% relative improvement in the CDLQI in 60% of patients within 6 weeks.
3. The management process should improve the worst aspect of the disease for 80% of patients.

4. Of those patients who are away from school because of their atopic eczema, 80% should return to school within 6 weeks following their initial assessment.

Standards were evaluated using 2 questionnaires offered to all new patients with a diagnosis of atopic eczema attending paediatric dermatology clinics from January-June 2008. Questionnaire 1 was completed at baseline. Questionnaire 2 was sent by post to the part 1 recruits 6 weeks after their initial consultations.

42 completed Part 1 and 27 completed Part 2 questionnaires were collected, amounting to an overall 64% response rate versus 67% response rate observed in the original audit.

Improvement in sleep loss at 6 weeks was attained in 52% of cases (standard set 70%). There was a >25% relative improvement in CDLQI score in 56% of patients falling short of the 60% standard set. Improvement in the worst aspect of disease was achieved in 67% cases, again not attaining the 80% standard set.

The 2008 re-audit results reveal more favourable outcomes compared to the original results in 2000, although fall short of the standards set. Are original working standards set too high? Is 6 weeks the optimum time to measure improvement in outcome? If non-responders did not reply because they had improved, the working standards may have been achieved.

Several recommendations have arisen following review of these results. These include inviting all new patients to complete a CDLQI; to identify for each individual what is the most troublesome aspect of their disease and re-evaluate at follow up and finally to avail of the input of a paediatric dermatology nurse specialist for all patients

S3. Merkel Cell Polyomavirus (MCV) – a new skin cancer virus.

WL Ho[1], M Carr [2], W Hall [2], GM Murphy [1]

[1]Department of Dermatology, Beaumont Hospital, Dublin, [2]National Viral Reference Laboratory, UCD, Dublin.

Merkel cell carcinoma (MCC) is a rare and aggressive human skin cancer of neuroendocrine origin, with a high mortality and an increasing incidence worldwide. It predominantly affects elderly and immunocompromised individuals, a feature suggestive of an infectious origin. In early 2008, Feng *et al* described the presence of a novel virus in Merkel cell carcinomas (MCC)[1]. Viral DNA was integrated within tumour genome in a clonal pattern in 8 out of 10 MCC samples, suggesting that MCV infection and clonal integration may be the contributing factor in the pathogenesis of MCC. Another study compared MCC tumours from an American cohort of MCC to an Australian cohort, which demonstrated a much higher prevalence of the virus in the American cohort, 69% vs. 24%[2,3]. The regional difference suggests that there may be variable contributions of UV radiation and MCV to oncogenesis.

Our aim was to evaluate the percentage prevalence of MCV in MCCs to further substantiate the above findings, in our Irish cohort. We identified 7 patients who had Merkel cell carcinoma, 3 of whom were renal transplant recipients. Nucleic acid was extracted from the MCC tumour samples and real-time and end point PCR was carried out to determine the percentage positivity.

Results showed 29% positivity in the detection of MCV in these tumours, in keeping with the findings of the Australian cohort. Deletion of viral elements and/or disruption of human tumour suppressor genes could conceivably contribute to uncontrolled cell growth. The highly related polyomavirus SV40 large tumour antigen is known to bind p53 and pRb which are both tumour suppressors and thus contribute to tumourigenesis by cell cycle deregulation. The two previously characterized MCV integration events by Fend et al lead to disruption these tumour suppressor regions in the MCV genome.

The role of MCV in the pathogenesis of MCCs of the skin and other neuroendocrine tumours has yet to be fully elucidated, but ongoing studies should provide new evidence in the near future.

1. Feng H, Shuda M, Chang Y, Moore PS Clonal Integration of Polyomavirus in Human merkel Cell Carcinoma. *Science* 2008;**319(5866):**1096-1100.
2. Kassem A, Schöpflin A, Diaz C, Weyers W, Stickeler E, Werner M, Zur Hausen A. Frequent Detection of Merkel Cell Polyomavirus in Human Merkel Cell Carcinomas and Identification of a unique Deletion in the VP1 Gene. *Cancer Res* 2008;**68(13):**5009-13.
3. Garneski KM, DeCaprio JA, Nghiem PJ. Merkel Cell Polyomavirus Is More Frequently Present in North American than Australian Merkel Cell Carcinoma Tumors. Invest Dermatol 2008.

S4. Aberrant DNA methylation is linked with MTHFR C677T genetic polymorphism in cutaneous SCC.

ME Laing, R Cummins*, EW Kay*, GM Murphy.

Departments of Dermatology and *Molecular Pathology, Beaumont Hospital, Dublin.

Changes in genomic DNA methylation associated with cancer include global DNA hypomethylation and gene specific hypermethylation. We have recently identified a genetic variant in the MTHFR gene involved in the methylation pathway which confers risk for the development of squamous cell carcinoma in renal transplant patients[1]. This genetic variant has also been discovered to confer risk in non transplant patients with low folate status [2]. Our aim in this study was to evaluate global and gene specific methylation status in SCC and non neoplastic skin in renal transplant patients and correlate this to the MTHFR polymorphism. We evaluated 87 skin samples in this study, including SCC and adjacent non neoplastic skin from 33 patients. Seventeen patients had the MTHFR polymorphism, 16 had no MTHFR polymorphism. SCC and non neoplastic skin were microdissected from paraffin blocks. DNA was extracted. PCR was carried out for specific genes p16 and MGMT and also LINE 1 which reflects global methylation. Quantitative evaluation of methylation levels was carried out by pyrosequencing after bisulphite modification of samples. Methylation analysis was evaluable in 40 SCCs and 36 non neoplastic skin samples. Global hypomethylation was evident in SCCs compared to adjacent non neoplastic skin ($p<0.04$). Patients with the MTHFR polymorphism had higher levels of methylation in tumours and non neoplastic skin compared to those without the MTHFR polymorphism ($p < 0.002$). Global hypomethylation appears to be a feature of SCC. Aberrant

methylation of DNA appears related to polymorphisms of MTHFR. In this study we found a functional effect of the MTHFR polymorphism significantly related to methylation of DNA. This might indicate that patients with the MTHFR polymorphism have an overall dysregulation of methylation in the genome of cancer and non neoplastic tissue. Together these findings suggest that intervention in the form of demethylating agents or folate supplementation may be beneficial in the treatment or prevention of SCC .

1. Laing ME *et al.* Association of methylenetetrahydrofolate reductase polymorphism and the risk of squamous cell carcinoma in renal transplant patients. *Transplantation* 2007;**84(1):**113-6. 2. Han J *et al*. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. *Carcinogenesis* 2007;**28(2):**390.

S5. The effect of isotretinoin on depressive symptoms in patients with acne vulgaris – a prospective cohort study 1999-2007

D O'Kane[1], A O'Hagan[2], A McGovern[3], J Dougherty[4], H Acheson[1], K McKenna[1], JR Corbett, DK Armstrong, M Parker[5], C Kelly[4], C McMillan[1]

[1]Departments of Dermatology and [4]Psychiatry, Belfast City Hospital. [2]Departmenta of Dermatology and [3]Psychiatry, Craigavon Area Hospital. [5]Clinical Research Support Centre, Royal Victoria Hospital, Belfast.

Oral isotretinoin is an effective treatment for severe acne unresponsive to conventional therapies. Concerns remain over the drug's safety profile and in particular its effect on mood status.

We designed a prospective cohort study to investigate the role of isotretinoin on mood status in patients with acne. Consenting patients initiating isotretinoin therapy completed a pre-treatment generic questionnaire and a modified Beck Depression Inventory (BDI) at week 0, 4, 16, and 4 weeks post-treatment. The BDI was composed of twenty-one questions, each answer being a score of 0-3, depending on severity. All patients were treated with 0.5-1mg/kg of isotretinoin per day in two divided doses for 16-20 weeks.

486 patients were deemed eligible for inclusion, 58% male, with a mean (standard deviation) age of 21 (5.9). The overall trend was a decrease in BDI scores, with significant differences at all stages of treatment. Compared to baseline, the mean change in BDI was -0.43 ($p=0.02$) at week 4 ($n=474$), -0.628 ($p=0.003$) at week 16 ($n=341$), and -0.945 ($p<0.0001$) 4 weeks post-treatment ($n=183$). No increased risk of depression was identified in those individuals with baseline depressive symptoms (indicated by a baseline BDI ≥10), or a documented personal/family history of depression.

A review of medical notes and pharmacy records revealed that 2 of the 486 patients (0.4%) discontinued isotretinoin after developing mild depressive symptoms. Both reported an improvement in mood status following cessation of isotretinoin. There were no reports of deliberate self-harm, attempted or completed suicide, during treatment or follow-up. A further patient discontinued treatment in response to rectal bleeding.

As far as we are aware, this is the largest prospective study investigating the effect of isotretinoin on depressive symptoms. No evidence of a causal relationship between isotretinoin use and depression was identified. Mild depressive symptoms occurring in <1% of patients may reflect an idiosyncratic side-effect or be unrelated to isotretinoin.

It is difficult to conclusively exclude a link between isotretinoin and depression due to the confounding influence of acne and the risk of depression among the general population. Utilising a depression score such as the BDI when prescribing isotretinoin encourages dermatologists to monitor depressive symptoms, regardless of whether there is a causal relationship to the drug or not.

Book Reviews

SECRETS OF SUCCESS: GETTING INTO FOUNDATION TRAINING

Marc A Gladman, Manoj Ramachandran, Mark J Portou. The Royal Society of Medicine Press. September 2008

Paperback, 182pp. £17.95. ISBN: 978-1-85315-886-5

This textbook, published in 2008, gives advice to Final Year students applying for the National Foundation Training Programme for F1 and F2 doctors. The problems with this application process over the past several years are well known to senior students, junior doctors, programme directors, postgraduate Deans, universities, the public and indeed politicians. This book is timely and is an effort to help students applying for their F1 and F2 positions. The difficulty with this book is that it will become rapidly out of date in such a changing field, but nonetheless it does give basic groundwork and advice on the completion of the application form.

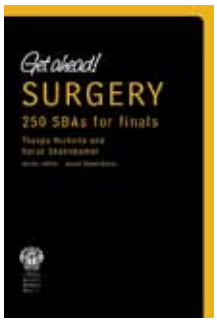
Quite rightly, at the beginning of their textbook, in the preface, the authors have emphasised that the examples which they have provided in their text must not be copied nor modified as this would be plagiarism, which is looked upon very seriously.

While the textbook was published in 2008, in this rapidly changing field, it is probably time for a new edition or at least a reprint with some changes. The book is up-to-date at the time of publication, including giving an overview of the Tooke Inquiry, a guide to the United Kingdom Medical Schools and the number of associated training positions, (Page 9). This is already dated and the next edition will require revision. There then follows a brief guide to United Kingdom Foundation Schools, with the Hospital Trusts associated, and the appropriate contact numbers. Again, in a changing field, these first few chapters will require revision over the next year or two. Thereafter, there is some information on the application process, which is relatively generic and useful. The following chapters relate to likely questions on the application form and how to complete them to maximise the chance of a successful application. While, of course, the questions change year by year, nonetheless many of the questions have a generic core. These chapters are very useful indeed, from such basic advice as reading the question repeatedly, while writing one's answer, to providing samples of topics such as coping under pressure, team working, prioritisation, the patient as a focus of care and professional integrity.

Overall this is a useful little book which can be recommended to senior students preparing for this all-important application. I would, however, finish this review by emphasising the caveat already mentioned by the authors, that on no account should students be tempted to plagiarise directly, or in a modified form, any of the examples provided in this text.

Prof Roy AJ Spence

GET AHEAD! SURGERY: 250 SBAS FOR FINALS



Theepa Nicholls, Saran Shantikumar. The Royal Society of Medicine Press. March 2009. Paperback. 225pp. £14.95. ISBN: 978-1-85315-727-1

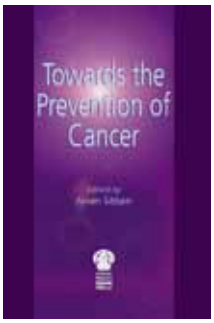
This textbook, published in 2009, is aimed at Final Year students of Medicine sitting their Surgical examination paper. It contains 250 Single Best Answer questions. The layout is that the book contains five practice papers, each containing 50 questions. The student is advised to allow between 1-1½ hours per paper. The book gives the correct answer and, usefully, a brief commentary to that answer. There is a satisfactory, albeit short, examination-orientated discussion of the answer.

As with any textbook of this nature, there can be a few, albeit relatively minor, critiques such as the absence of the mention of laparoscopic surgery when discussing appendicectomy and perforated duodenal ulcer. The description of thyroid cancer would warrant a line or two on the usefulness of fine needle biopsy in most thyroid cancers apart from follicular tumour (in which it cannot distinguish benign from malignant). On Page 45, Question 1, on gallbladder incisions, it would be more appropriate to include a discussion of laparoscopic gallbladder incisions which are, by far, the most common method of surgical access for today's gallbladder procedures. In the index, under Thyroid Cancers, Pages 33 and 123 are given, but on Page 123 there is no mention of thyroid cancer. Leaving aside these relatively minor points, this book is a useful revision text for students undertaking Final Medicine examinations in Surgery.

The authors are relatively young, one being a Registrar in Emergency Medicine, the other being an academic Fellow in Vascular Surgery, and have a sense of the current standards of final surgical examinations in Medicine. The questions are in a modern format and the commentaries are, by and large, timely and up-to-date. The book can be recommended as a revision text in those anxious few months prior to medical finals.

Prof Roy AJ Spence

TOWARDS THE PREVENTION OF CANCER



Dr Amen Sibtain. The Royal Society of Medicine Press. October 2007. Paperback, 80pp. £25.00. ISBN: 978-1-85315-796-7

This book represents the contents of a symposium held in 2007 on the prevention of cancer. There is a slight misnomer in that the first half of the book does examine topics such as smoking, nutrition, alcohol, obesity etc. which relate specifically to cancer prevention, while the second half of the book relates to early detection and screening for particular cancers, such as colon, prostate and breast. Many of the presenters and contributors are well known in their field, such as Bruce Ponder on the genetic aspects of cancer, and Richard Peto on the role of smoking in

the causation of cancer. The textbook was published in 2007, and in this rapidly changing field, while the principles still do hold true, the specific details can become out of date speedily.

In terms of presentation, overall the font size is a little small with very few chapters broken up by diagrams or illustrations. Should, in future years, a report be published from a further symposium on this important topic, the publishers should look at the presentation style, to review font size and the inclusion of illustrations.

The majority of chapters are timely (in 2007). It would be of interest, in the breast cancer chapter, on Page 68, if the author would give his views on the thoughts of some senior breast specialists, that breast cancer screening may be picking up tumours so small (with the associated stresses and workload) that they would be clinically irrelevant in that woman's lifetime. This contrary view to the popularity of breast screening would be of interest to the reader.

The book finishes with the Jephcott Lecture entitled "Cancer Prevention – Vaccine Based Approaches" by Borysiewicz. This is a very useful overview on the current role (as of 2007) of cancer prevention based on vaccines.

Overall, this is a useful little book on both prevention of cancer, early diagnosis and some screening aspects, up-to-date (as at 2007). It is a helpful revision text for those undertaking examinations in Oncology-related subjects. The text would be useful to have on the bookshelves of doctors and health-related professions, as a reference source, on these important topics (with the caveat that the text was published in 2007). A text such as this becomes rapidly out of date over four to five years. Notwithstanding this caveat, this book can be recommended.

Prof Roy AJ Spence

RECENT ADVANCES IN GASTROENTEROLOGY 11

Editor: Christopher Probert. The Royal Society of Medicine Press. December 2008. Paperback, 228pp. £34.95. ISBN: 978-1-85315-710-3

This text, published in 2009, is No. 11in the popular series of "Recent Advances". Many of the authors are based in the Bristol area. While most are senior, established Gastroenterologists, a number are Fellows and Specialist Registrars. Here and there the text is spoilt by spelling errors such as, on the list of contributors, the spelling of "Specialist Registrar", adjacent to Simon Monkhouse's name, is misspelled.

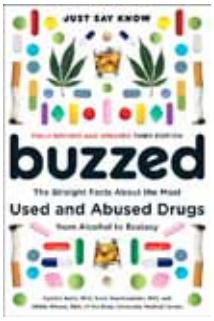
Overall, the text is well laid out although some diagrams, such as Fig. 1 on Page 97, are complex for the non-specialist. The topics include those of current clinical interest and importance, such as management of Barrett's oesophagus, variceal bleeding, obesity surgery and the clinical management of inflammatory bowel disease, along with some newer forms of treatment for irritable bowel syndrome. Most chapters are well supported with current and up-to-date references. The first chapter, on eosinophilic oesophagitis, an emerging condition currently poorly understood, is a useful chapter for both the specialist Gastroenterologist and the trainee. The key points for clinical practice are placed in a useful box at the end of each chapter, such as that for Barrett's oesophagus on Page 25. Most illustrations are satisfactory, although Fig. 1 on Page 33, and also on page 204, the Bristol Stool Form Scale, is difficult to make out through poor reproduction. The chapter on variceal bleeding includes the potentially useful adjunct of treatment, namely self-expanding metal stents, although the data on their use are early.

The chapter on obesity surgery is timely, although perhaps more information on the current role of laparoscopic procedures would be appropriate. Again, a paragraph or two in this chapter on who should be undertaking laparoscopic obesity surgery, in terms of training and specialisation, would be of interest to future practitioners in this field. The liver imaging chapter is comprehensive, although Fig. 6 on Page 122 is difficult to decipher. The chapter on chronic pancreatitis – how should we diagnose it? – is a useful chapter both for specialist and the generalist and is well written with clear conclusions. Similarly, the new treatments for irritable bowel syndrome and recent advances in inflammatory bowel disease chapters are both well written and timely.

In summary, overall this is a useful book with good updates in a number of important clinical areas. This textbook should be on the shelf of the Gastroenterologist for review and should be browsed through by the trainee physician, especially those with an interest in gastroenterology, doing examinations. With some minor caveats, it can be recommended.

Prof Roy AJ Spence

BUZZED: THE STRAIGHT FACTS ABOUT THE MOST USED AND ABUSED DRUGS FROM ALCOHOL TO ECSTASY, 3RD ED.



Cynthia Kuhn, Scott Swartzwelder, Wilkie Wilson, Leigh Heather Wilson, Jeremy Foster.

WW Norton & Company Ltd. September 2008. Paperback, 367pp. £11.99. ISBN 978-0-393-32985-8

The slogan on the cover of this book is "Just Say Know". Aware that the simplistic ("Just say no!") approach of many drug education programmes has failed to deter adolescents from experimenting with and abusing drugs, the authors of this book aim to provide the reader with balanced, objective facts, based on their conviction "that people make better decisions with accurate information at hand."

The authors are involved in the BrainWorks Program at Duke University Medical Centre, and include two professors of pharmacology (Kuhn and Wilson) and a professor of psychology (Swartzwelder). The impetus for writing the book was their recognition of how little most adolescents, parents, lawmakers, - and even medical advisors - know about commonly used and abused drugs.

The book is divided into two main sections. The first part

deals with commonly used and abused drugs. They describe socially acceptable drugs such as alcohol, nicotine and caffeine; abused prescription drugs, such as steroids and analgesics and sedatives; and illicit substances, such as, Ecstasy, cocaine and hallucinogens. The drugs are discussed in terms of pharmacological class, common slang names, pharmacological effect ("The Buzz"), risks in overdose and other adverse effects. The range of drugs covered is fairly up to date, and includes substances such as gamma hydroxybutarate (GHB). Both the positive and negative effects of drugs are discussed – the debate about the dangers of cannabis is covered, along with the arguments for and against legalisation. Similarly they discuss the question of the possible long term neurotoxicity of Ecstasy and other amphetamine derivatives (so called "designer drugs").

The second part of the book is much shorter and provides a simple introduction to neurobiology, pharmacology and addiction. Legal issues are also discussed, albeit from an American perspective.

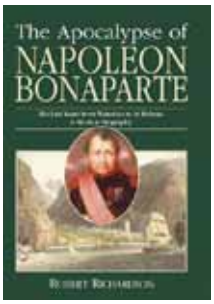
In addition to these two main sections there is also a useful bibliography for those who wish to pursue topics in greater depth, a glossary of drug-related slang, and a colour photographic section which illustrates many of the drugs discussed.

This book is well written and easy to read. It could be used as a resource to be consulted, dipped into simply for interest's sake, or read from cover to cover. Pharmacology is presented in an interesting and accessible manner which does not require the reader to have a background in the life-sciences. And, whilst this is not a pharmacology textbook, the mechanisms of drug action are covered in some depth. However, specifically medical issues, such as treatment of overdose and addiction, are not covered. That this book is written from an American perspective limits the relevance of some sections, especially the discussion of legal issues. In their discussion about the dangers of drugs, whilst coming down hard against Ecstasy, the authors take a softer line than I would with regard to cannabis.

Overall, if you are looking for an up to date, accessible source of information regarding drugs of abuse, this book would be a good starting point.

Michael Trimble

THE APOCALYPSE OF NAPOLEON BONAPARTE



Robert Richardson. Quiller Publishing Ltd. May 2009. Hardback. 288pp. £20.00. ISBN: 978 18468 90635

For those interested in medical history, this book by Robert Richardson is an excellent read. Robert Richardson, who qualified in medicine at Oxford University, has become a freelance medical editor and has written a number of books on medical and surgical history. This book is a splendid insight to the latter years of Napoleon Bonaparte. It is superbly researched and gives remarkable detail of Napoleon's medical illnesses, especially in the latter years of his life. There is a remarkable chapter (Chapter 19) on the postmortem performed on 6th May 1821 of Napoleon, which describes in considerable detail tuberculosis in his lungs and the adjacent pericardium. The examining doctor described how the internal surface of the stomach was taken up by a "cancerous ulcer" along the lesser curvature. The remainder of this chapter describes the intrigue and the various versions of Napoleon's cause of death by those who surrounded him and the historians of that time (and following). Remarkably, it was Napoleon himself who surmised he had cancer of the stomach. It was he who requested (demanded) that he should have an autopsy for the benefit of his son in case he might inherit the cancerous growth. It was stated that, throughout his illness, he never complained and kept his character to the last! His disease was hereditary, his father having died of it, and his sister, the Princess Borghese, was also thought to have had cancer of the stomach.

This beautiful book is remarkably detailed, extremely well researched and gives rise to multiple intrigues which surrounded Napoleon's latter life. For the serious students of medical history, the book is well referenced. I can recommend this book for those wanting a gentle read through medical history and a contemporaneous view of the times of the latter years of Napoleon. I would also recommend it for the student of medicine beginning his or her studies as an insight into the medical times of Napoleon and the remarkable description of his illness and of his autopsy in particular.

I enjoyed reading this text and can recommend it to a wide readership.

Professor Roy A J Spence

THE ULSTER MEDICAL JOURNAL

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Cover legend: Signatures from the visitors book (including Sir Alexander and Lady Fleming) to 12 University square in 1942 – see article by Macafee, page XXX