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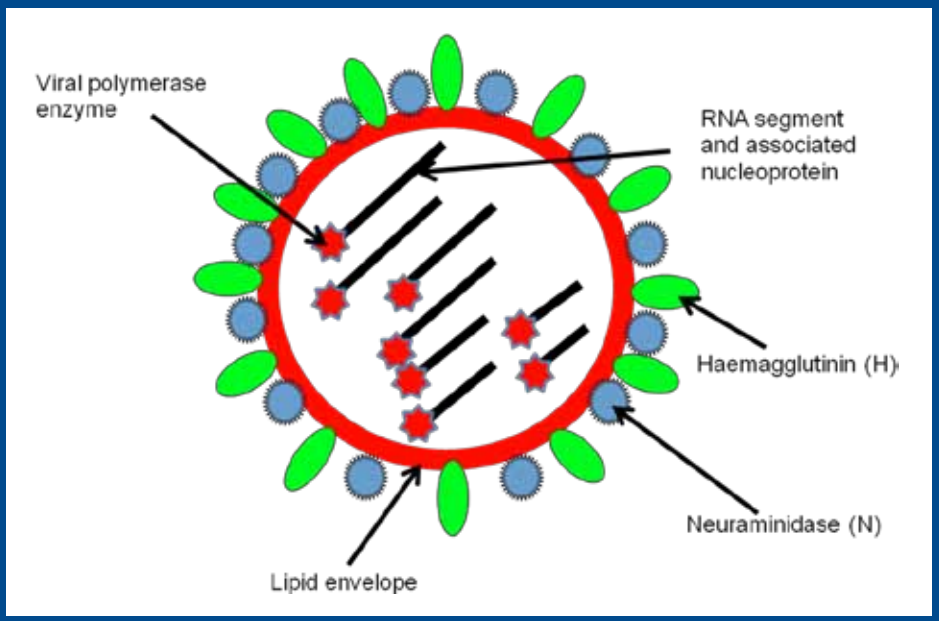

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Editorial

Testing Times

As I write, the inquests have begun. Two natural phenomena, one very large and one very small, have exercised our minds, and our economies, recently. The larger, a volcano under Iceland's Eyjafjallajoekull glacier, comprehensively grounded Europe's commercial airlines, causing chaos and stranding registered voters everywhere. The second was a microscopic villain. The influenza virus H1N1 (Swine Flu) surfaced in the United States, twirled its pantomime moustache menacingly, and ignited the 2009 pandemic. Governments immediately raced to stockpile supplies of vaccine and Tamiflu. In both cases, the question now being asked is whether the official response was over zealous. Many lives were lost to that influenza virus, but none to volcanic ash in jet engines. So far. For both events, however, the outcome might have been very different. Begging Wordsworth's indulgence, our retrospection is, I would contend, drama, recollected in tranquility. Conall McCaughey's superb and timely review considers the biology of that influenza virus. Using it as a template, he expounds on viral structure, its ubiquity and abundance, mechanisms of replication and dissemination, and how anti viral therapies work.

Mature readers will recall diligently writing serial essays, confident in the knowledge that each would be marked with forensic fairness, by dedicated, selfless examiners who, with luck, would overlook minor obfuscations, and score hosanna's to their worthy prose. In the tick of a cosmic clock, those same readers would find themselves *marking* interminable essays; wading though cryptographic handwriting to unearth the morass of random half-learned facts that lay concealed, or perhaps, congealed, beneath. As an assessment tool, the essay is now a thing of the past, in medicine at least, and the multiple-choice question is looking like an endangered species too. In the second of this edition's reviews, Paul McCoubrie considers the assessment process, why it remains essential, and in an encyclopedic exposition, demonstrates just how far we have moved away from foolscap and writer's cramp.

Professor Brew Atkinson's presidential Ulster Medical Society address is also within these pages. Professor Atkinson's masterly article details our understanding of the pituitary gland, from Ancient Egypt, via David and Goliath, to our current genetic understanding of pituitary-related diseases.

My thanks, as ever, for all your papers. Please keep them coming. May I finally take this opportunity to wish you and yours a wonderful summer.

Barry Kelly

Honorary Editor

Ulster Med J 2010;**79(2):**46-51

Review

Influenza: a virus of our times

Conall McCaughey

Accepted 25 March 2010

ABSTRACT

Viruses are successful and omnipresent. Influenza A is a particularly important virus of humans. The article reviews the 2009 emergence of the pandemic influenza A virus, focusing on the potential origin of the virus and the distinctive clinical and epidemiological impact of the 2009 pandemic.

INTRODUCTION

Viruses are extremely successful. They parasitise all forms of life both prokaryotic (bacteria) and eukaryotic (plants, fungi and animals). There is more genetic diversity within viruses than in all eukaryotic and prokaryotic genomes put together. Viruses are, by far, the most abundant life forms on the planet. It has been estimated that there are $>10^{30}$ viable virus particles on our planet, most of which are in the oceans. If we were able to line up all of these end to end it would reach to a radius of 5 million light years, which would include not only the Milky Way but also our nearest 50 galaxies.

At an evolutionary level we still do not understand how viruses originated. It is probable that there are multiple origins relating to different groups of viruses - some ancient, relating to elements of the primordial soup that predate the development of life as we know it, and some more recent in evolutionary terms originating from 'escaped' cellular genetic elements.

For all their ubiquity and success, viruses are startlingly simple. They are tiny, on average about 1/5000th the size of the typical bacterium. Most have fewer than 10 genes coding for proteins specific to the virus and no metabolic system apart from that of the host cell that they parasitise. Yet these simple biological systems are capable of harnessing and subverting the host's complexity to produce viral components, assemble them into new virus particles and eject them from the host in such a way that they can find a next host. The survival of viruses is entirely dependent on a continuous chain of transmission being available, as most viruses cannot survive for prolonged periods outside the host.

At a fundamental level viruses have shaped us. At least 10% of the human genome is made up of elements that originate from viruses and there is increasing evidence that such sequences have had profound effects on the evolution of complex organisms including humans.

The question is often posed; are viruses alive? Essentially the answer simply depends on how we chose to define life. Using standard definitions, viruses cannot be considered to be living organisms. Rather they are biological entities entirely dependent on the cellular functions of the organism that they parasitise.

There are about 200 viral species known to infect humans. In this article I will focus on one of them; influenza A virus, whose profile rose considerably in 2009 with the emergence of a new pandemic virus: Influenza A H1N1 2009.

INFLUENZA VIRUSES

Influenza viruses circulate in humans every year in every part of the world. Intermittently and unpredictably new viruses arise that are capable of causing pandemics (Table 1). The term 'pandemic' refers to the rapid emergence of a new influenza virus that causes an epidemic that covers the whole world.

There are two main types of viruses that cause seasonal influenza –types A and B. Influenza B is an important cause of seasonal influenza but unlike influenza A it does not cause pandemics. Influenza A viruses are further typed into subtypes according to different kinds and combinations of virus surface proteins Haemagglutinin (H) and Neuraminidase (N).

It can be reasonably argued that influenza is the single most significant infection of humans. Typically, each year about 10% of the population will contract an influenza infection. Worldwide, on average, influenza contributes to the deaths of 250 000 people annually. Influenza is the only common infectious agent in the developed world where one can simply look at weekly gross mortality statistics for a country and determine when the virus circulated in a particular year and whether it was a particularly bad year. In a pandemic, mortality can be much higher than for seasonal influenza.

Pandemics occur when a brand new influenza A emerges, to which the human population does not have any pre-existing immune protection. This results in rapid transmission and high attack rates. The definition of a pandemic is to some extent arbitrary and is not well standardised over time; for example the 1977 H1N1 emergence was not then considered to be a pandemic, but using the modern World Health Organisation (WHO) definitions it undoubtedly would be now.

Pandemics are a regular occurrence. Historical accounts suggest that there have been more than 20 since the 16th century, typically occurring every 10 to 40 years. The 1918 pandemic (H1N1) is widely regarded as the single biggest natural disaster documented to have affected our species;

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Table 1

Key examples of past Influenza A Pandemics and antigenic shift events resulting in generalised human circulation

Year of emergence	Influenza A Virus type	Comments
1889	H2N2	Pandemic. Estimated deaths worldwide: 1 million Antigenic type deduced by retrospective serological testing of stored sera.
1900	H3N2	Pandemic. Estimated deaths worldwide: uncertain, <1 million Antigenic type deduced by retrospective serological testing of stored sera.
1918	H1N1 'Spanish'	Pandemic. Estimated deaths worldwide: 20 to 100 million
1957	H2N2 'Asian'	Pandemic. Estimated deaths worldwide: 1 to 1.5 million
1968	H3N2 'Hong Kong'	Pandemic. Estimated deaths worldwide: 0.75 to 1 million
1977	H1N1 'Russian'	Not considered to be a pandemic in the sense that severity and attack rate were lower than with previous shift events. Estimated deaths worldwide: <100 000 Widely conjectured to be a virus of laboratory origin.
2002	H1N2	No pandemic, few documented deaths. Reassortment between the 2 seasonal viruses (H3N2 and H1N1) so not new antigenically.
2009	H1N1 2009 'Mexican' 'swine'	Pandemic Estimated deaths worldwide: <100 000

estimates of mortality range from 10 to 100 million deaths. Notably, over 50% of these deaths were in people under the age of 40. However only the 3 pandemics that happened in the last century and last year's H1N1 2009 pandemic are well characterised in virological and epidemiological terms.

THE ANATOMY OF THE VIRUS (FIGURE 1)

The outer surface of the virus is made of a lipid envelope derived from the cytoplasmic membrane of the host respiratory cell from which the virus budded. The envelope is studded with the H and N glycoproteins (proteins with chains of sugar residues) that extend right through the lipid. This lipid envelope is essential to the viability of the virus. Viruses with a lipid envelope are inherently more delicate than viruses without one, as the lipid is very susceptible to environmental influences such as desiccation. This is the reason that influenza viruses will not survive in the environment for long periods of time whereas, for example, hepatitis A virus (non-enveloped) survives much longer. Most human cases of influenza will be contracted by direct inhalation of fresh wet droplets expelled by a cough or sneeze.

The biology textbook teaches that the perfect parasite is one that causes the host no harm. This may be true of some virus infections, for example those that spread by saliva contact. However the production of a disease process itself may be a key survival advantage for the virus - 'Coughs and sneezes spread diseases'. In animal models, an influenza virus that does not cause disease typically does not spread as well as one that does. Some have conjectured that this evolutionary advantage for a nastier virus is a reason why sometimes a second pandemic wave is of greater disease severity than the first.

'Influenza A H1N1 2009' is the name of the current pandemic virus. 'H' and 'N' are the standard nomenclature for naming influenza A viruses and refer to the type of haemagglutinin (H) and neuraminidase (N) on the surface of the virus. It is worth considering the biological functions of H and N and the resultant opportunities these confer in prophylactic and therapeutic approaches to combating influenza A.

Haemagglutinin specifically attaches to the surface of a respiratory cell. Without this specific attachment the infection of the cell and hence host cannot be initiated. Specific antibody to haemagglutinin can block this attachment and confer immunity. For this reason haemagglutinin is the most important component of an influenza vaccine. The closeness of match between the haemagglutinin in the vaccine and the haemagglutinin in the circulating virus is the most important determinant of vaccine efficacy.

Neuraminidase is also embedded in the lipid envelope of the virus. It is essential for the release of virus particles allowing them to be released from one respiratory cell and hence available for infection of other cells in the same host or shed in droplets to infect another host. Neuraminidase is also important in facilitating the virus penetration of mucus to allow attachment to the cell surface. Without a functional neuraminidase, the virus is not shed from an infected cell and infection in the host is terminated. The two main antiviral drugs, Oseltamivir (Tamiflu) and Zanamivir (Relenza), are neuraminidase inhibitors and act on the neuraminidase protein

TABLE 2

Selected examples of zoonotic transmission of influenza to humans that have not resulted in sustained human to human transmission

Year	Virus Subtype	Location	No. of Cases
1997	H5N1	Hong Kong	18 (6 deaths)
2003	H7N7	Holland	89 (1 death)
2003- to present	H5N1	S&SE Asia, Turkey, Egypt and others	442 (262 deaths) -60% death rate

preventing efficient release of the virus from the host cell.

Influenza virus is particularly well equipped to change its H and N antigens to escape immune detection and infect previously infected or vaccinated people. Two particular features of the influenza virus contribute to its rapid evolutionary capacity to change its antigens and escape immune recognition.

The first feature is the high error rate during genomic replication. The enzyme that copies the viral RNA to make copies to be packaged in new viruses makes a very high number of mistakes. This enzyme is much more error prone that the DNA polymerase enzymes in our cells that copy our chromosomal DNA, facilitating cell division. This generates a very high rate of mutations in the virus. Most of these will be neutral or detrimental to the survival of the virus but some will contribute to the evolution of antigenic change that favours the survival of the virus. The evolutionary selection and accumulation of these mutations causing gradual changes in the H and N proteins ('antigenic drift') happens continuously. This antigenic drift necessitates annually updated influenza vaccines which are matched to the currently circulating strains to render them effective.

The second important feature of the virus is the segmented genome. The virus genetic material is contained in 8 separate RNA segments, each of which codes for one or two proteins. This segmented genome allows the phenomenon of genetic reassortment to occur. Viruses that simultaneously infect the same cell can swap segments - sexual reproduction in viruses: effectively two viruses mating. We know from surveillance studies that this happens frequently, for example, with influenza viruses circulating in wild birds. Genetic reassortment can result in a new H and/or N emerging. This is the phenomenon of 'antigenic shift' where a brand new virus appears.

In nature, there at least 17 different H types. Only H1, H2 and H3 have been recognised in viruses capable of sustained transmission in humans. The rest are seen in a wide range of birds and in some mammals. Occasionally avian viruses have crossed over into the human population causing clusters of cases without sustained human to human transmission (Table 2). The spread of H5N1('Avian Flu') in birds throughout Asia, Europe and Africa is a recent example of a virus that has proven capable of causing severe disease in humans but which has not, so far, resulted in significant human to human transmission.

Antigenic shift results from the movement of one of these H types from an influenza virus, affecting another animal, into a virus capable of transmission between humans. Figure 2 illustrates the process of reassortment which happens frequently in animal influenza viruses. The example in the diagram relates to the pandemic emergence of the H3N2 virus in 1968 which still represents one of the viruses that cause seasonal influenza.

Most influenza genetic diversity is in birds. There are very significant difficulties for an avian-adapted virus to infect a human respiratory cell. This species barrier results from the very different arrangements of sugar residues in the sialic acid chains on respiratory acid chains in mammals and birds. The virus H protein will be adapted to attach either to the mammal or the avian sialic acid chain arrangement. Hence it will be either a mammalian or an avian-adapted virus.

Pigs however, are unusual among mammals in that their tracheal respiratory cell surfaces have sialic acid chains with both the avian and mammalian arrangements. This means that pigs are uniquely susceptible to viruses of both avian and mammalian origin. Pigs have been well documented to contract productive infections with swine, avian and human influenza viruses and have been strongly suspected to be the "mixing vessel" responsible for emergence of reassortant strains that cause pandemics in humans.

H1N1 2009 (SWINE FLU)

Until now, there have been 3 seasonal influenza A viruses circulating in humans: H1N1, H1N2 and H3N2. Perhaps naïvely, based on our short series of three well-documented pandemics, it had generally been assumed that the awaited pandemic virus would require a brand new haemagglutinin type, perhaps an H2 or an H5. Instead, the pandemic virus was another H1 virus, but significantly different from the seasonal H1 virus such that immunity resulting from past infection with the seasonal virus or vaccination did not prevent infection.

The virus was first identified in humans in April 2009 in the southern USA and it was quickly established that it was spreading rapidly from person to person and had been causing widespread disease in Mexico since early March. From the beginning it was recognised that this was a swine origin virus. On June 11th, 2009, with virus transmission documented in more than 70 countries, WHO declared that a global pandemic of novel influenza A (H1N1 2009) was underway. This very rapid spread from North America to the rest of the world was notable as the first pandemic to unfold in the context of post-globalisation modern human travel patterns.

WHERE DID H1N1 2009 COME FROM?

There are many unanswered questions. H1N1 2009 is essentially a reassortment of 3 viruses that have been endemic in farmed pigs over the past 15 years. Where, when and how these 3 viruses reassorted is unclear.

Six of the 8 segments are directly descended from swine H1N2 virus 'triple-reassortant' influenza viruses isolated from pigs in North America around 1999-2000. These triple reassortant viruses emerged in 1999 and had segments of pig, human and avian origin. However the other two gene

segments are from 2 different Eurasian viruses of pigs; the N gene is closest to European H1N1 viruses from 1991-1993, and the MP gene is closest to H3N2 viruses isolated in Asia in 1999-2000. Hence the 8 genetic segments have an origin in 3 different known pig-associated viruses.

There are two difficult aspects to explain. Firstly, the closest relatives for all 8 segments are virus isolates collected more than a decade before the human pandemic started. Where have these segments been in the meantime?

Secondly, how did European and Asian viruses reassort with an American virus, as there is normally little mixing of swine viruses across the Atlantic/Pacific? These two key unanswered questions have given rise to some speculation about the evolutionary origin of the virus and in particular the role of human activity in this. It is possible that the reassortant event occurred 10 years ago and that the virus lineage has been in pigs as a minor unrecognised virus. Lack of surveillance may have resulted in it going undetected until it emerged in humans. However a possible research or diagnostic laboratory origin for the virus has to be considered, possibly related to swine vaccine manufacture. The three parental lines for H1N1 2009 may have been assembled in one place by natural means, such as by migrating birds; however the consistent link for all 8 segments with pig viruses suggests that human activity could be implicated. It is difficult to entirely discount human activity as the possible origin of the virus on current evidence.

If this is the case it would not be the first time that a laboratory source for an influenza virus has been postulated. The 1977 H1 virus (Table 1) is widely regarded as having a likely laboratory origin as it is so similar to viruses from the 1950's that this seems the most biologically feasible source. It is important that further work on the evolutionary origin of the H1N1 2009 virus is carried out and that the origin is eventually understood as this may shed important light on future prevention.

H1N1 2009 – DISTINCTIVE FEATURES

All pandemics are different in their clinical impact and epidemiology. The H1N1 2009 pandemic has displayed a number of interesting features that are worth considering.

AGE PROFILE.

This was unusually young compared to seasonal influenza. It is estimated that only 2% of total cases were over the age of 65. This was undoubtedly a major factor in the clinico-epidemiological impact of the pandemic as older people are, typically, the largest vulnerable group for influenza complications. Serological studies have shown that older people have some cross protective antibody arising from either repeated past vaccination or infection with H1 viruses.

ASYMPTOMATIC INFECTION

The vast majority of pandemic infections were mild. Asymptomatic and very mild infection, especially in children, was much higher than expected. In London and Birmingham, during the first wave of infection in summer 2009, serological testing showed that over 30% of children were infected by the pandemic virus. This was ten times more than was estimated from clinical surveillance.

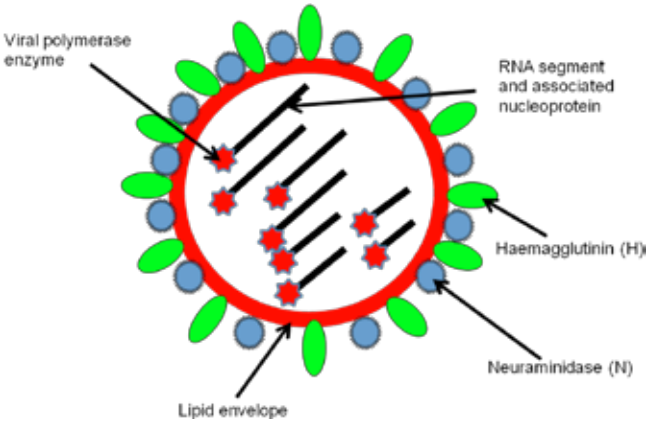

Fig 1. The structure of an influenza virus

NEW RISK FACTORS

Particular risk factors emerged as more prominent in this pandemic than in previous ones, Neurodevelopmental delay, pregnancy and obesity were all recognised as potential co-factors in increased mortality and morbidity in flu infections. However all 3 of these risk factors, previously viewed as of relatively minor importance, came to a prominence in this pandemic as major predictors of severe morbidity and mortality.

HIV INFECTION

This is the first pandemic of the HIV era and there had been concern that HIV would be a significant risk factor. Reassuringly this was not the case and several studies found that HIV status had little impact on the severity or outcome of H1N1 2009 infection, although very low CD4 counts may increase the risk of worse outcomes and opportunistic infections may complicate diagnosis.

INDIGENOUS PEOPLES

The attack rates and severity in indigenous populations were higher than for the general population. They had a three to six-

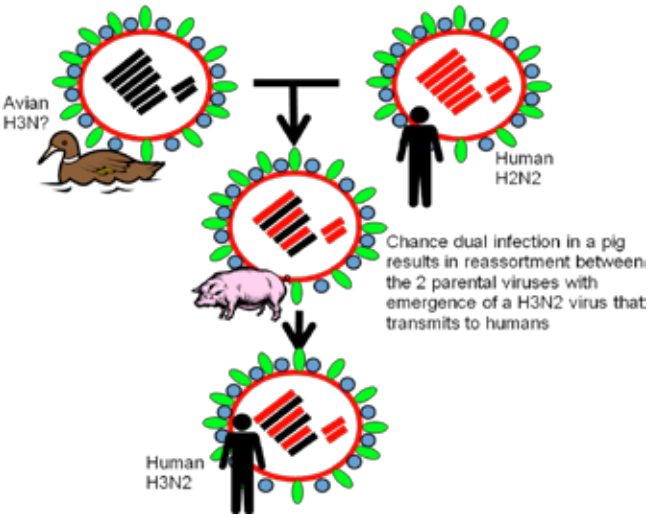

Fig 2. The 1968 pandemic influenza A virus is believed to have originated by reassortment between the H2N2 then currently circulating in humans and an avian H3 virus resulting in a virus that had gene segments from both parents. It is widely postulated that this reassortment event happened in a pig.

fold higher risk of admission to hospital, severe disease and death. This was noted in Native Americans, Inuit, Australian aborigines, Maori and Pacific island people. The mechanism for this is still unclear. It has been suggested that this may be related to the generally higher prevalence of obesity, diabetes, asthma, chronic obstructive pulmonary disease (COPD) or social factors such as crowding, poverty and difficulty with access to health provision. However, it is likely that there are genetic factors involved.

PARADOXICAL INCREASED SEVERITY OF HOSPITALISED CASES

Although the severity of cases was generally mild with hospitalisation rates of 0.3%, comparing very favourably with previous pandemics and even with seasonal influenza, paradoxically a much higher than expected proportion (20%) of hospitalised cases required admission to intensive care units (ICU), placing disproportionate pressure on them. ICU admissions reflected the 'new' risk factors of pregnancy, obesity and neurodevelopmental delay, but over 20% were in patients without clear risk factors. Admission to ICU was typically for rapidly progressive respiratory failure with hypoxaemia. Secondary bacterial infection was less common that had been anticipated.

PCR DIAGNOSIS

This was the first pandemic to occur since the advent of molecular techniques. These were used extensively for surveillance and diagnosis, having many advantages over traditional diagnostic methods. Widespread use of combined nose and throat swab sampling proved very successful.

However in severe cases requiring ICU admission, approximately 20% were found to have a negative nose & throat swab result, despite having detectable virus in the lower respiratory tract (tracheal secretions or lower). The mechanism of this phenomenon is unclear but may reflect some altered tropism of the virus for the lower respiratory tract in more severe cases.

H1N1 2009 INFECTION IN NON-HUMAN ANIMALS

Many countries have reported H1N1 2009 in animals. The source has been regarded as human, with subsequent transmission between farm animals but limited evidence of farm to farm transmission. It is noteworthy that the first European detections of H1N1 2009 in animals occurred in Northern Ireland, affecting pigs on 4 separate farms. Farmed pigs are the animals most recognised to be infected but outbreaks in farmed turkeys and isolated cases in pet cats and dogs have been recorded.

The viruses from these animal outbreaks that have been studied and sequenced, so far have been found to be essentially identical to the pandemic virus circulating in humans. Infections in pigs are probably even more common than the reported detections suggest as the symptoms in the pigs are very mild. Much of the resulting public health message has been reassuring, stressing the obvious safety of eating cooked pork. However the current unique situation of a widespread virus of swine that can transmit equally efficiently from human to human and from pig to pig is worrying. This is potentially the perfect shuttle vector capable of introducing pig virus segments to viruses that can transmit efficiently in humans.

Industrial pig farming has undoubtedly accelerated the evolution of influenza viruses in farmed pigs. There is considerable influenza genetic variability in currently circulating pig viruses. There is also significant evidence of frequent reassortment events in pig viruses. The risk of such reassortment resulting in nastier viruses emerging into humans is one that we should take seriously in the immediate future.

H1N1 2009 RATE OF GENETIC VARIATION.

As discussed, influenza viruses are expected to evolve rapidly and to change antigenicity over time such that their surface proteins are not recognised by antibody resulting from a previous infection or vaccination. However, so far, the H1N1 2009 virus has so far shown very little genetic change. At an antigenic level the virus has essentially remained unchanged from the viruses that emerged in April 2009.

The vaccine for the southern hemisphere winter currently being produced will continue to be made using virus from California (at the start of the pandemic) rather than a more recent isolate. Whether this low mutation rate simply reflects lack of selection pressure in initial pandemic waves, or is some inherent property of this virus, remains to be seen.

ANTIVIRAL RESISTANCE TO TAMIFLU IN H1N1 2009

The H1 seasonal virus circulating up until 2010 was almost entirely resistant to Oseltamivir, and this resistance had emerged over the previous 2 flu seasons. A single aminoacid change in the active site of the N protein can confer resistance.

So far (March 2010), 40 of the 5,462 pandemic viruses tested have been confirmed to carry the mutation which confers resistance to Oseltamivir. The biggest risk for the emergence of Oseltamivir resistant virus appears to be in immunocompromised patients; particularly where lower prophylactic dosages are used after a patient has been exposed to the virus. For example, there have been two recognised outbreaks of drug-resistant virus in haematology units following prophylactic use of Tamiflu in Wales and the USA.

THE FUTURE:

It is generally considered that there will not be any further significant pandemic waves unless we see a very substantial change in the virus. It is likely, based on previous pandemics, that the currently circulating seasonal H1 viruses will disappear to be replaced by the H1N1 2009 virus as a cause of seasonal flu each winter. A key concern is that we are now in an inherently less stable situation with a circulating virus that can transmit to and from pigs and that this has the possibility of allowing segments from pig viruses get into humans with unpredictable consequences.

Future pandemics will occur. As pandemics go, H1N1 2009 has certainly been at the benign end of the spectrum. By March 2010, the documented death toll was 457 in the UK, much less than typically seen in seasonal influenza. Probably ten million people in the UK have had swine flu and most will have had either no symptoms or a mild illness.

We do not know if a '1918 type' event could happen again. The 1918 virus has been reconstructed and studied. Undoubtedly it had distinctive biological properties that made it considerably more pathogenic than any other influenza viruses about which we are historically aware and which are established in humans. However the availability of antibiotics, antivirals, vaccines and intensive care support is likely to have substantial impact on the morbidity and mortality rates even in the face of a very nasty virus.

CONCLUSION

In comparative historical terms, the 2009 emergence of a new pandemic influenza represented an overdue event. In terms of severity and impact on society, it was a best case scenario and an opportunity to rehearse and hone preparations for the inevitable future pandemics that may be less benign. The new dynamic of a circulating human influenza virus that can slip in and out of pigs is concerning as it could lead to future reassortant events between pig and human viruses.

The author has no conflict of interest.

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Review

Metrics in Medical Education

Paul McCoubrie

Accepted 25 February 2010

ABSTRACT

If every doctor is a teacher, then every doctor should be an examiner too. Assessment has a huge impact on learning; more so than most realise. Whilst there have been seemingly endless changes to current assessment strategies, there are some fundamental tenets to fair assessment that have changed little in recent decades. Similarly, whilst the hurdles to good quality assessment seem innumerable, there are lessons to be learnt from the literature that can lessen the impact of assessment on busy doctors.

INTRODUCTION

"It is impossible to overestimate the importance of assessment"

David Newble, 1998

The word physician derives from the archaic noun *physic,* meaning the art or science of treatment with drugs or medication, whereas the word *doctor* originates from the Latin word (genitive case *doctoris)* for teacher. Indeed, countless generations of doctors have recognised the obligation to train others and have, more or less, happily done so since the inception of our trade a few millennia ago. More recently the General Medical Council (GMC) have formally reasserted the educational obligations of all doctors.[1]

I contend that all doctors should also be examiners. At first sight this statement may seem deliberately inflammatory; yet another unwelcome demand on busy medical practitioners. However I will explain that this is neither controversial nor onerous.

Of the twelve widely agreed roles of a medical teacher [2], the one that many doctors gloss over (or frankly ignore) is being an examiner. This is ironic as all doctors already formally and informally assess others; perhaps they don't recognise it as such. Such disparate tasks as interviewing for a new member of clerical staff, giving feedback to a trainee, planning a teaching session or formally examining medical students all entail the same principles of assessment.

This article, therefore, has three aspects. First, it will emphasise the importance of assessment. Second, it will examine obstacles to good assessment. Third, it will review the key issues in modern assessment, carefully distilled from the ever-expanding evidence base. The overall goal is to assist the reader to become more effective at assessment and perhaps to be realistic about what can and cannot be achieved.

THE EDUCATIONAL IMPACT OF ASSESSMENT

"Teaching without testing is like cooking without tasting or writing without reading"

Ian Lang, 1991

Some doctors see exams as a necessary but time-consuming evil, a distraction from teaching and learning. However, in reality, assessment is not only intrinsic to any education endeavour but it is one of the most important tasks. This is simply because of the powerful effect of any assessment on the learner. If assessment is ignored or paid mere lip service then the teacher immediately lessens the impact of their teaching. Bizarre although it may seem, not assessing the learner does them a disservice.

Most assessment is relatively informal and low key. It is to check that learning has occurred, to reinforce particular important points and provide feedback to the learner to help them improve. This style of assessment is commonly known as *formative* assessment. This is in distinction to *summative* assessment which is typified by robust methods, lengthy tests and comparison to a pass / fail standard. Summative assessment includes formal examinations where decisions about career progression are made - so-called "high stakes" exams.

Many authors have documented the tremendous impact that high-stakes exams have on the learner [3]. Some authorities assert simply that "assessment drives learning" [4]. They state that students and trainees feel overloaded by work and hence they strategically learn what they perceive as necessary in the face of exams. From the student or trainees perspective, tests serve an additional, somewhat hidden purpose: they communicate what the "real" course goals and objectives are. Put metaphorically, "The assessment tail wags the curriculum dog", or, more crudely, "Grab students by the tests, and their hearts and minds will follow". [5]

Lambert Schuwirth of Maastricht University has coined the "law" of educational cause and effect. This states "for every evaluative action, there is an equal (or greater) (and sometimes opposite) educational reaction". For example, Newble & Jaeger showed in 1983 that if written testing was

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emphasised, then students focused on book-based learning, whereas if clinical testing was emphasised, students tended to focus on rehearsing their clinical skills on patients.[6]

There are several ways in which learning can be predictably affected. Assessment drives learning through its content, through its format, through the information given afterwards and through the frequency and timing of exams.[3] This effect on learning is often known as *consequential validity*.

The unpredictable side of Schuwirth's law arises because the relationship between assessment and learning is complex. Students and trainees learn subjects that are explicitly not examined [7]. What students actually learn is a very complex social phenomenon; a whole melange of tacit social, cultural and political issues that affect learning. Labelled the "Hidden Curriculum" it was first directly addressed by Benson Snyder in 1971.[8] It can represent a substantial portion of learning. In one study, 75% of final-year medical students sought extracurricular teaching.[9]

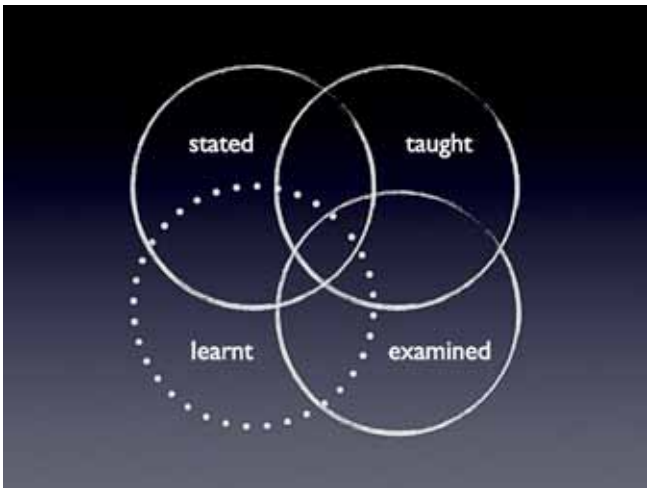

Fig 1. Conceptual map of the Hidden Curriculum

These models of learning can be illustrated as a Venn diagram of overlapping circles representing different ways of looking at a teaching program or curriculum (Figure 1). First, there is a formally *stated* curriculum, often written and widely available. This varies in style, content and format. Second, there is a *taught* curriculum; the subjects covered in teaching sessions. Third, the *examined* curriculum is that covered by assessment processes. Lastly, there is the *learnt* curriculum, the enigmatic and slightly unpredictable subjects that students and trainees actually learn. Of note in this model, the first three are under direct control of the teacher but the latter is not. One always hopes the *learnt* curriculum will overlap significantly with the others. A particularly well-organised teacher will have tight overlap between the stated, taught and examined curriculum, hence making it likely the learnt is too. But the examined curriculum is the one that is mostly likely to have overlap with the learnt curriculum. Perhaps the most important take-home message here is that assessment steers learning and the canny teacher harnesses assessment to do just that.

TRADITIONAL FUNDAMENTALS OF GOOD ASSESSMENT

Assessment's primary role in high-stakes exams should be that of a gold standard test in the diagnosis of incompetence: a test that really sorts the wheat out from the chaff. However in formative tests, the focus is on informing personal development. This doesn't mean that formative assessment should be cursory or brief. Quite the opposite, good quality feedback needs good quality data.

Whilst practical constraints often limit assessment, as a principle it should be appropriate and proportionate. For example, if the purpose were to inform an individual that they have reached appropriate levels of expertise in a particular procedure, it would be inappropriate to set a gruelling written exam. However, such a rigorous and searching written exam would be a perfectly acceptable way of testing knowledge in a formal and important setting such as medical school finals.

Irrespective of its purpose, a good test should follow established methodology. Historically, the focus on a good test was adequate *metrics* within bounds of feasibility; that is mainly achieving a highly reliable and valid test but also one that is easily administered.

Reliability is a fairly straightforward idea: it is the degree to which a test consistently measures whatever it measures. It is a statistical concept, where a stated reliability coefficient or "r-value" is expressed where 0 is zero reliability and 1 is total reliability. Reliability improves with increasing the length of test, where the spread of scores is broad and even, where the level of difficulty is moderately high and the objectivity of marking is high.[10] Reliability can be calculated in a number of ways but the key message is that r=0.8 is an acceptable level for high-stakes exams.

Validity is a complicated concept in educational testing. Simply put, an exam is valid when it measures what it is supposed to measure. This is not a yes / no answer but a degree to which supporting evidence has been produced, or to what degree a theoretical premise supports an interpretation. The modern view is that validity is a single unitary construct with different aspects.[11] To be considered valid, an assessment should: -

- *Sample widely*. This is possibly the most important aspect. Doctors do not perform consistently from task to task. Hence a valid test samples systematically and representatively across what is supposed to be measuring. To do so usually makes a test long. When there is demonstrable evidence, this can be called content validity. Without evidence, it can be called face validity, a poorer measure
- *Differentiate*. It should be able to differentiate between groups of known differences. This can be called construct validity.
- *Agree with other tests*. If the results correlate well with another well-established test, it is said to have good concurrent validity.
- *Predict future performance*. Whilst most tests are administered to find something about future behaviour,

Table 1.

Comparison of different methods of assessment (after Augustine et al [35]).

Assessment	Reliability	Validity	Feasibility	Acceptability	Educational effect
Multiple choice question	+++++	+	+++++	+	Makes trainees revise from written sources
Complex written (i.e. short notes)	++++	++	++++	++	Written sources are favoured but with less emphasis on facts
Oral exam	++	++	++	+++	Trainees rehearse oral skills
Practical skill simulation	+++	++	+++	++	Encourages trainees to practice on models
OSCE or short case	++	+++	++	+++	Mixed effect; skills are rehearsed but can lack context
Long case	++	+++	++	+++	Trainees rehearse total performance
Workplace-based assessment	++	++++	++	++++	Focuses attention on clinical performance
Video assessment	++	+++++	+	+++	Trainees rehearse being recorded
In-cognito simulated patients	++	+++++	+	+++++	Revision emphasizes communication skills

tests rarely perform well as hoped. Furthermore the longer that elapses, the poorer the correlation becomes. This can be called predictive validity.

- *Be real (or very realistic)*. Most testing methods aim to simulate reality but this is clearly second best to testing clinical performance in real life. Simulations and written testing should aim to mimic real clinical practice closely.
- *Guide learning*. As above, consequential validity is crucial.

Having said all this, it is virtually impossible to find a measure that is simultaneously fully valid, highly reliable yet feasible. When the inevitable compromises are made, then validity must remain the number one consideration. A comparison of the commonly used different methods of assessment is given in Table 1.

CONTEMPORARY ISSUES

The focus on adequate metrics and feasibility has moved on a little in recent decades.

Fairness

A fair or authentic exam is a defensible exam. Naturally it should be reliable and valid. In addition, questions should be carefully constructed by experienced examiners and reused with care. Adequate standard setting is also crucial. There are three main ways of setting a pass mark: *holistic, norm-referenced* and *criterion-referenced*.

A holistic model is simplicity itself, involving a fixed pass mark. Obviously the arbitrary nature of this is unreliable and is not recommended. In norm-referencing, the standard is based on the performance of the group being assessed. It is a relative pass mark and thus varies from group to group. Norm-referencing is quick and can be useful for formative assessment. Criterion-referencing refers to an absolute standard, irrespective of the group and is preferred for summative assessment.[12] It is worthy noting that criterion-referencing is relatively laborious. It has also several educational connotations regarding test construction.[13] Furthermore, many "criteria" are based on judgements of individuals or a small group, hence criterion-referencing is not without its critics.[14]

Workplace-based Assessment

Despite improving fairness of traditional medical assessments, they have inherent deficiencies. The recurrent criticism centres around validity; results of traditional tests do not necessarily correlate with what doctors can actually do in their everyday practice.[14, 15] To allow more valid assessment, a number of assessment tools for use in the workplace have become available. These attempt to retain the authenticity of apprentice-style learning and assessment but adapted to modern working patterns. Instead of one master assessing a trainee, snapshots of the trainee in the workplace are taken to build up an accurate picture of their competence. Workplace-based tools enable the following:

- *Multiple perspectives.* A complete assessment of an individual can be achieved by gathering multiple perspectives of professional practice.[16] The use of multiple methods and assessors reduces bias and thus an accurate picture of the trainee is built up like a pointillist painting.[17]
- *Total practice assessment*. Many important aspects of professional practice such as abilities to work in a team,

teach, research and communicate are currently not seriously or formally assessed, mainly as they have been considered difficult to assess rigorously.[18, 19] These generic skills cannot be judged against a simple preordained standard nor can they be quantified easily, but must utilise qualitative and descriptive information. Such assessment is challenging as it relies on professional judgment of the assessor to make decisions regarding the trainee's performance without compromising objectivity.[20]

- *Charting of competence development*. The notion of suddenly becoming "qualified" to do something is illogical.[21] Competence is greyscale not black or white. It is acquired slowly rather than in one sudden epiphanic moment. Accumulation of data over time enables the development of competence to be charted. This can be conceptualised as assessment being a hurdle race rather than a high jump competition.

The Modern Role of Written Testing

The pre-eminence of written testing methods has been questioned. For example, one persistent criticism is that doctors do not answer batteries of complex MCQs in their day-to-day work, yet MCQs feature heavily in exams. The same argument runs that MCQs and other written question formats are therefore not particularly valid. However MCQs are the most time-efficient written test format, hence reliable testing is made feasible. MCQs also allow broad sampling of content that is unachievable in most other testing formats, particularly when dealing with large numbers of students or trainees. This achieves high content validity. Furthermore, they make learners hit the books, swotting up on book-based knowledge. If this is a desired activity, then they have good consequential validity.

One issue that is very clear from the literature is that the one single factor that predicts expertise is knowledge.[22] It follows that assessing knowledge using a written test is a perfectly reasonable way of assessing expertise. So, whilst MCQs lack acceptability and have some validity issues, they are good at testing knowledge, hence one's expertise. The way to improve their validity is to combine MCQs with a more practical or clinical exam to encourage broad learning.

OBSTACLES TO ASSESSMENT

There are many potential reasons why many doctors feel uncomfortable assessing others.

Lack of Training

A lack of training in assessment is a common finding, both at an undergraduate[23] and a postgraduate level.[24] A survey of 529 hospital consultants found that 88% were involved in teaching but only 34% had any teacher training. The majority (67%) indicated that they needed training in assessment and appraisal skills.[25] Another survey of 441 hospital doctors found that, "giving feedback constructively" and "assessing the trainee" were two of the top three most commonly stated themes in which they would like more training.[26]

Time & Resource Constraints

These are ubiquitous in the era of ever-increasing NHS workloads. Further factors demand non-existent time and resources: a 50% increase in UK medical student numbers since 1996; a lack of senior trainees due to the legal constraints of working hours, together with all the challenges of teaching today's generation - "Generation Me".[27] Inevitably the motivation to improve assessment in the UK relies too heavily on the altruism of individuals. John Bligh notes that there are many "well-meaning, earnest teachers facing day-to-day practical problems in full awareness of what should be done, but only too aware of what can be achieved in the circumstances".[28]

Tradition

The current generation of medics have grown up on a steady diet of tests, often sitting up to 100 separate high-stakes examinations in their teenage and adult life. They are unsurprisingly test-weary, with a potential significant toll on their professional health.[29] Senior trainees and established medical practitioners are appropriately cynical about assessment but surprisingly accepting of unfair testing. Perhaps this is realism: whilst learners can walk away from bad teaching, assessment is usually mandatory irrespective of its quality. However, the same individuals are highly test-wise. This can be used to an advantage as their perceptions of an exam, its authenticity and overall fairness are valid and should be sought in any evaluation process.[30]

Technical Complexity

The number of scientific publications on assessment over the last decade has mushroomed. There has been an explosion in the number of proposed instruments, each with its unique TLA (three-letter acronym). The educational literature can be difficult to access and the technical jargon of psychometrics (the study of educational measurement) can further discourage casual browsing.[3] As a result, educational institutions are finding that they need staff with technical knowledge and understanding of assessment issues who can provide guidance.[2] The inaccessibility and complexity of these issues can prove daunting to even the most enthusiastic medical teacher.

Appraisal

Modern performance review tends to blur the boundaries between appraisal and assessment. The two are related but fundamentally different processes. Assessment is an explicit objective evaluation against defined criteria. Appraisal is a confidential, supportive review process of individual and institutional needs. Although appropriate assessment can inform appraisal processes, appraisal outcomes should not inform assessment.[31] Unfortunately, this is the precise basis upon which the GMC plans to base revalidation processes.

Procrastination & Grievances

Dealing with a student or trainee in difficulty can be so problematic that, "...it is far too easy to just pass the trainee and let someone else deal with the problem".[24] Freidenberg recognises this procrastination, leaving this "weeding out" to the certification board, possibly to avoid exposure of inadequate documentation at grievance hearings.[32] Where a student or trainee fails to progress satisfactorily, withdrawal from the programme can be recommended. However, the legal challenge to such dismissal can be extreme; Tulgan et al give

an example where an aggrieved resident mounted a 9-year legal test of dismissal policies, culminating in an appeal to the United States Supreme Court.[33] However, legal challenges to reliable and valid exams have generally been unsuccessful.[34]

CONCLUSION

If every doctor is a teacher, then every doctor should be an examiner too. Assessment has a huge impact on learning; more so than most realise and it can be deliberately used to improve learning. Whilst there have been seemingly endless changes to assessment methods and strategies, there are some fundamental tenets to fair assessment that have changed little in recent decades. Similarly, whilst the hurdles to good quality assessment seem innumerable, there are lessons to be learnt from the literature that can lessen the impact of assessment on busy doctors.

The author has no conflict of interest

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Paper

Diabetic nephropathy and chronic kidney disease at a busy diabetes clinic: A study of Outpatient Care and suggestions for improved care pathways at a subspecialty specialist diabetic renal clinic.

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ABSTRACT

Prior to establishing a specialist diabetic renal clinic in our unit, we studied across 12 months all 1845 patients attending one of our diabetes clinics with a serum creatinine >150µmol/l. Diabetic control was examined along with renal function and cardiovascular risk using current audit standards.

74 such patients were identified (male:female 54:20 mean HbA1c 7.8% (sd±1.45) and age 64.2years (±12.8). 30 patients had creatinine >200µmol/l and 15 >250µmol/l. Using the chronic kidney disease classification, 33, 28 and 6 patients were in groups III, IV and V with 7 patients undergoing renal replacement therapy.

65% of patients met JBS2 audit standards of blood pressure using a mean of 2.93 agents (sd±1.43). Ace-inhibitors or angiotensin receptor blockers were used in 81% and 81% were on regular antiplatelet or anticoagulant therapy. Audit standard for total cholesterol and LDL were met in 89% and 97% of patients respectively.

All patients identified in our study were in CKD class III-V and therefore we considered also alternative inclusion criteria. 136 patients had a urinary ACR ≥ 30mg/mmol. Using this and/or the serum creatinine level above identified 197 patients from the clinic.

This study shows that measurement of serum creatinine alone is not sufficiently sensitive but extended criteria identified a 10% subgroup who will now be offered detailed assessments and intensified therapies at a subspecialty in-house renal clinic. eGFR has recently been added to our computerised proforma and will enable us to further refine inclusion criteria.

INTRODUCTION

Diabetes is an increasingly prevalent condition in Northern Ireland. The prevalence of diabetes in Northern Ireland in 2008 was 4.1% of the adult population[1]. It is estimated that 9% of all patients with diabetes in Northern Ireland have type 1 diabetes[2]. Approximately one third of patients are managed in hospital with type 1 diabetes making up between 10-35% of hospital clinics[2]. The remaining patients are managed in primary care. Our clinic presently comprises 35% type 1 diabetes and 65% type 2 diabetes.

In Northern Ireland there is a 13.9% prevalence of diabetic nephropathy amongst patients with diabetes[1]. Diabetic nephropathy is a major cause of end-stage renal disease affecting 28.9% of new adult patients starting renal replacement therapy in 2007[3]. In these patients, diabetes is a powerful predictor of increased risk of death after the first 90 days of renal replacement therapy[3]. The expanding dialysis population and its associated health and resource implications reinforce the need to prevent or delay the progression of nephropathy in our diabetic patients.

A number of risk factors for progression of nephropathy have been identified including poor glycaemic control, hypertension, smoking, genetic susceptibility, age, race and obesity. The DCCT and UKPDS demonstrated that improved glycaemic control reduces the risk of diabetic nephropathy in both type 1 and type 2 diabetic patients[4,5]. The reduction of proteinuria through the use of ACE inhibitors or angiotensin receptor blockers is also a major intervention shown to reduce progression of renal disease[6-8].

The first sign of renal involvement in patients with diabetes is microalbuminuria. This is defined as a urinary albumin creatinine ratio (ACR) >2.5mg/mmol (men) or >3.5mg/mmol (women) on 2 or 3 occasions[9]. This affects over 20% of type 1 and type 2 diabetic patients 10-15 years after the onset of diabetes and subsequently may evolve to macroalbuminuria or proteinuria (ACR > 30mg/mmol)[10,11]. Once macroalbuminuria is present, glomerular filtration rate declines at an average rate of 10-12ml per minute per year in untreated patients[11].

Screening for microalbuminuria is an important function of diabetes clinics whether this be in the primary or secondary care setting. Patients with moderate established nephropathy often attend hospital clinics for both diabetic and renal care. Frequently both clinics have overlapping responsibilities with regard to blood pressure control with diabetologists primarily addressing glycaemic targets. This is an unnecessary burden

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on patients many of whom may have other co-morbidities for which they also attend hospital. Therefore a single clinic which addresses both conditions would be of considerable benefit. The complexity of patients with diabetic nephropathy may be difficult to manage in a general diabetes clinic setting and a better solution may be a subspecialty clinic focussing on diabetic nephropathy. This would also help in reducing the number of clinics these patients attend. Diabetologists with well defined links to nephrology services are in an ideal position to manage patients with early or moderate nephropathy. This clinic would be designed through careful liaison with nephrologists to ensure smooth referral to nephrology if kidney disease progresses. Prior to establishing such a subspeciality clinic we reviewed our present patient population to establish initial referral criteria.

KEY WORDS

Diabetic nephropathy, subspeciality clinic, microalbuminuria.

AIM

We performed a study to assess kidney function in a group of diabetic patients attending a general diabetic clinic. This was to enable us to plan for a specialist diabetes renal clinic within our own diabetes service. We aimed to:

- establish the prevalence of chronic kidney disease in our outpatient population
- determine if patients with diabetic kidney disease are receiving treatment to help prevent progression of nephropathy and meet targets as outlined by chronic kidney disease guidelines[9].
- identify patients for a new specialist diabetic renal clinic to help patients achieve targets, ensure patients are correctly investigated and managed for all aspects of chronic renal care, to provide necessary dietary support and to ensure smooth pathways to the regional services for nephrology in Northern Ireland.

DESIGN AND SETTING

The Regional Centre for Endocrinology and Diabetes at the Royal Victoria Hospital in Belfast has a large outpatient diabetic population. Until recently our patients with diabetic renal disease have been managed as part of general diabetic clinics. Patient information such as regular medication, clinical examination findings and biochemical results are recorded electronically using the Northern Ireland Regional Electronic Patient Record for Diabetes (DIAMOND system). Further information was obtained from patient notes. At the time covered by this study estimated glomerular filtration rate (eGFR) was not routinely recorded on this system.

Study 1

We performed a search of our clinic database to obtain all patients (1845) who had attended the clinic between January 2006 and October 2007 and who had a serum creatinine >150µmol/l. This value was chosen based on 2002 NICE guidelines which suggested this as a threshold for referral to nephrology. We aimed to assess our management of these patients with established renal disease in a diabetologist led clinic.

Information obtained from Diamond sheets included patient demographics, type and duration of diabetes, oral antidiabetic therapy, glycaemic control (HbA1c), renal function, involvement in nephrology services, blood pressure, use of antihypertensives and cardiovascular risk profile.

Targets used for blood pressure and cholesterol were based on audit standards as outlined by the JBS2 guidelines[12].

Table 1

	Type 1 Diabetes (n=33)	Type 2 Diabetes (n=41)	Total (n=74)
Patients	33 (45%)	41 (55%)	74
Male/Female	21/12	33/8	54/20
Caucasion	33(100%)	41(100%)	74(100%)
Age (mean±sd)	56.2±12.5	70.6±9.0	64.2±12.8
HbA1c (mean±sd)	8.0±1.5%	7.7±1.4%	7.8±1.5%
Duration of diabetes (mean±sd)	33.5±11.5	17±6.0	24.3±9.4
Retinopathy	27 (82%)	17 (41%)	43 (58%)
Blood pressure (mean±sd)	129/69±17/9	136/72±20/10	133/71±19/10
Patients with uncontrolled BP*	10(30%)	16(39%)	23(31%)
BP in uncontrolled patients (mean±sd)	149/84±5/3	160/88±14/6	156/87±12/5
No. antihypertensives (mean±sd)	2.5±1.6	3.3±1	2.9±1.4
On ACEI/ARB	24(73%)	36(88%)	60(81%)

*Blood pressure >140/80mmHg as per JSB2 audit standards[13]

RESULTS

74 patients were identified with serum creatinine >150µmol/l. The demographics of these patients are shown in table 1.

Renal function

Renal function was recorded using both serum creatinine and eGFR. All 74 patients had creatinine >150µmol/l with 30 patients having creatinine >200µmol/l and 15 patients >250µmol/l. The patients were then grouped into chronic kidney disease classes using eGFR as per national guidelines[9]. There were 33, 28 and 6 patients in CKD class 3, 4 and 5 respectively and 7 patients undergoing renal replacement therapy.

In our group of patients 50 out of 74 had urinary ACR recorded over the proceeding year. Of the 24 patients with no ACR recorded, 7 were undergoing

renal replacement therapy and 10 were under regular review and assessment at a general nephrology clinic. There were 17 patients with normoalbuminuria, 20 with microalbuminuria and 13 with proteinuria.

Diabetic control and treatment

(see table 1)

45% of patients achieved a HbA1c of <7.5% (audit standard[12]). Eleven patients (16%) were being treated with metformin. Of these patients creatinine ranged from 156 – 212µmol/l and eGFR from 27 – 41ml/min/year. Of patients with type 2 diabetes, 4(10%) were on diet control only with 13(32%) on oral hypoglycaemic agents, 21(51%) on insulin alone and 3(7%) on both insulin and an oral hypoglycaemic agent.

Blood pressure

51 patients (69%) of our group had a blood pressure of <140/80mmHg (audit standard[12]). The number of antihypertensives required for both controlled and uncontrolled patients are displayed in figure 1.

In our group of patients, 14 patients were not taking either an ace-inhibitor or angiotensin receptor blocker. Of this group, 1 patient had developed hyperkalaemia and 2 had renovascular disease. From surveying the hospital notes no apparent reason was identified for the remaining 11 patients.

Cardiovascular risk

The prevalence of ischaemic heart disease and their cardiovascular risk factors are shown in table 2.

Study 2

In order to identify those with significant early modifiable diabetic nephropathy we widened the search criteria in study 1 to include patients with an ACR > 30mg/mmol (macroalbuminura) and/or creatinine > 150µmol/l. Using this strategy a total number of 197 patients were identified.

DISCUSSION

Although early NICE guidelines recommended renal referral based on serum creatinine >150µmol/l, it is now well recognised that eGFR provides a more reliable measure of renal function. In study 1, all patients had eGFR <60ml/min/1.73m^2 equating to CKD class III. eGFR is calculated using the modification of diet in renal disease equation using serum creatinine, age, gender and ethnicity[13]. For a given creatinine, GFR will be lower in those patients who are older, white and female. Of note only 20 of our 74 patients were female which probably reflects the exclusion of many women with significant renal disease but a serum creatinine <150µmol/l. Serum creatinine alone is an insensitive measure of renal function with a rise in creatinine to just above the normal range reflecting the loss of more than one-half of the total glomerular filtration rate. Using a serum creatinine >150µmol/l identified less than half of patients with significant nephropathy.

Comparable with our results, a recent study of renal disease in diabetic patients showed that the sensitivity of abnormal serum creatinine levels in identifying eGFR <60 ml/min/1.73 m^{2}was 45.3%, albuminuria 51.2% and either an abnormal serum creatinine or albuminuria 82.4%[15]. Therefore inclusion criteria based solely on creatinine will miss a significant number of patients with early nephropathy. We identified 74 patient with a creatinine > 150µmol/l. Given the prevalence of diabetic nephropathy as 13.9% of the local diabetic population we would have expected to have identified at least 256 patients with nephropathy[3]. This is defined as microalbuminuria. Clearly the use of creatinine alone will miss a significant number of patients. However for the clinic to be manageable a more stringent criterion would be needed. It is well established that microalbuminuria is predictive of disease progression in diabetic nephropathy and indeed that progression accelerates with development of macroalbuminuria[11]. We therefore looked at patients with ACR > 30mg/mmol (macroalbuminuria). Including such patients with early modifiable nephropathy alongside our initial group with creatinine > 150µmol/l increased our patient group by more than double from 74 to 197.

In performing these studies, we identified 17 patients (23%) with creatinine >150µmol/l who were also normoalbuminuric. This result confirms the lack of specificity of elevated creatinine in identifying diabetic nephropathy. It has been reported that about 20% of patients with diabetes have reduced GFR but normal ACR[16]. These patients are typically women with a shorter duration of diabetes, a low prevalence of retinopathy, a non-smoking history and a higher haemoglobin and HDL level. It is difficult to identify an underlying cause of renal impairment in these patients. However they typically have a low risk of CKD progression or death[16]. In some cases the kidney disease may relate to hypertension or ischaemic nephropathy secondary to renal artery stenosis. In contrast to the benefits of ACEI/ARB therapy in diabetic nephropathy, treatment in patients with significant renal artery stenosis is associated with an over 30% rise in serum creatinine which is reversible on stopping the drug[17]. The prevalence of renal artery stenosis detected by MRA in patients with type 2 diabetes is 17%[18]. Although not all structural defects are associated with clinically significant disease, this highlights the need to screen for kidney

TABLE 2

	Type 1 diabetes (n=33)	Type 2 diabetes (n=41)	Total (n=74)
Known IHD	11(33%)	20(49%)	31(42%)
Regular antiplatelets/ anticoagulants	23(70%)	37(90%)	60(81%)
Cholesterol <5mmol/l*	29(88%)	36(88%)	65 (88%)
LDL <3mmol/l*	32(97%)	40(98%)	72(97%)
Statin therapy	19(58%)	36(88%)	55(74%)
Smokers	4(12%)	0	4(5%)
Ex-smokers	5(15%)	14(34%)	19(26%)

*denotes audit standards as outlined by the JBS2 guidelines[13]

disease in diabetic patients using a combination of both creatinine (or eGFR) and ACR.

Now that eGFR is being used more commonly, this, combined with estimation of urinary albumin, will be a useful means of identifying patients with early nephropathy for inclusion in a specialist diabetic clinic. All of the patients in study 1 were in CKD class III and one possibility is to include all patients with this stage of kidney disease in specialist diabetes renal clinics. On screening of general practice populations without diabetes, approximately 5% of patients have CKD stage III-V with 97% of these patients in CKD class III[14]. However in a group of patients with diabetes, this percentage will be much higher. Indeed in one study, 27.5% of patients with diabetes have clinically significant CKD, as defined by an eGFR <60 ml/min/1.73 m^2 [15]. This study included patients from both primary and secondary care. At our centre, to include up to one third of our diabetic population in a specialist renal clinic, may exceed the capacity of service provision and therefore we plan to screen initially using creatinine and ACR.

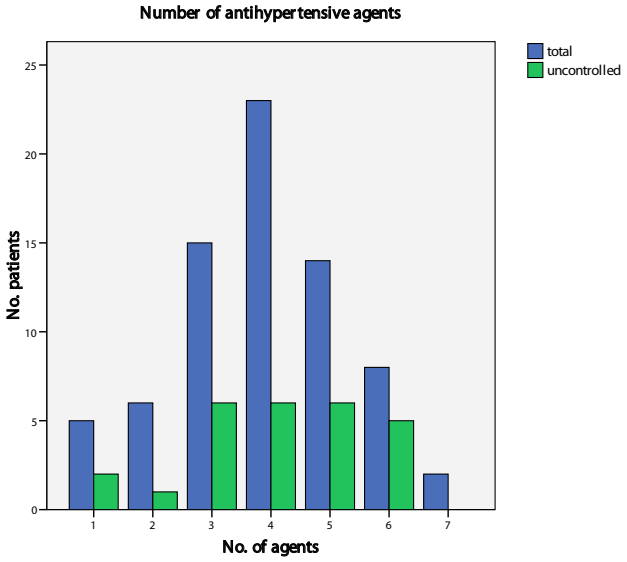

Figure 1

As discussed above patients with diabetic nephropathy have significantly increased cardiovascular risk and therefore attention to cardiac risk factors is an essential part of their care. Only 65% of our patients met recommended audit standards for blood pressure in our general diabetes clinic. This could be improved with increased focus on blood pressure control at a subspecialty clinic. To achieve blood pressure control our patients required an average of 3 antihypertensive agents. Good blood pressure control often needs 2 or more agents. In a study comparing intensive and conventional blood pressure management, the UKPDS group found that 29% of patients in the intensive group required 3 or more agents to achieve targeted blood pressure control[19]. Figure 1 displays the number of antihypertensives used for patients with both controlled and uncontrolled blood pressure. Of note 9 patients with uncontrolled blood pressure were taking 0-2 agents and thus were not being treated aggressively enough. This highlights the need for strict blood pressure control through introduction and titration of new agents if necessary. Cholesterol was well controlled in our study with good use of statin therapy.

It was more difficult to attain audit standards for HbA1C with just 45% achieving HbA1c of <7.5%. However the mean HbA1c in our study was 7.8±1.5% which is similar to mean HbA1c after longterm follow up (8-10years) in other studies such as Steno-2 and UKPDS[20,21].

This study demonstrates a need to improve our focus on cardiovascular risk reduction in this high risk group of diabetic patients. This can be achieved through ongoing education of medical staff and early and appropriate use of antihypertensives, statins and antiplatelets. Rather than refer many patients to a specialised nephrology service we feel that the skills within a diabetes centre should also allow us to intensify and improve glycaemic control and delay progression of renal disease. We feel that this can best be achieved with a subspecialty clinic.

Other guidelines are also in place for patients with CKD stage III-V[9]. In addition to the measures outlined above, patients with established kidney disease require further monitoring, investigation and management. It is recommended that all patients with CKD stage III should have annual measurement of haemoglobin, calcium and phosphate. Those patients who are anaemic may benefit from treatment with iron and/or erythropoietin. In addition, patients at this stage are at risk of renal bone disease. Therefore parathyroid hormone should be checked and if elevated (with an associated low vitamin D level), treatment with vitamin D should be initiated. It is also recommended that patients are referred for a renal ultrasound scan if they describe lower urinary tract symptoms, have refractory hypertension or an unexpected progressive fall in eGFR. Patients should also be immunised for influenza and pneumococcus.

Before this study these measures were not included as part of our diabetic clinic. Thus patients not attending a nephrologist were not routinely screened for these complications of renal disease. As they attend our diabetic clinic on at least a biannual basis, this care can be included as part of their routine review at a specialist diabetic renal clinic.

STRATEGIES FOR CHANGE

We have now established a specialist diabetic renal clinic to run alongside our general diabetic clinic. We have initially included patients with serum creatinine >150μmol/l and/or ACR>30mg/mmol. It is also likely that we will develop additional criteria based on eGFR which is now widely available on biochemistry reports and on our Diamond system. Patients at this clinic will benefit from input from a multidisciplinary team of diabetologists, specialist nurses and dieticians with specialist interests in both hypertension and diabetes. This clinic has been established in collaboration with nephrology ensuring that appropriate referral criteria are set and that patients who perhaps do not need to attend a nephrology clinic can have a "virtual review" if there are any concerns regarding their renal function.

Given the high cardiovascular disease risk of these patients, all risk factors will be addressed during the clinic. In addition, a protocol for screening for complications of renal disease such as anaemia and bone disease has been prepared. This will help

guide clinicians to ensure appropriate treatment. By having a well established renal diabetic clinic, this should enable smooth referral to nephrology if renal disease is progressing towards likely end-stage.

CONCLUSION

In conclusion the results of this survey confirm the lack of sensitivity and specificity of measurement of serum creatinine in the diagnosis of diabetic nephropathy. The use of serum creatinine and with time eGFR alongside ACR significantly improves the identification of patients with diabetic nephropathy and non-diabetic chronic kidney disease. The move to a subspecialty clinic will enable greater focus on aggressive management of cardiovascular risk factors combined with assessment and treatment of chronic kidney disease associated issues such as anaemia. We believe a diabetologist led clinic has the power to enhance patient care although liaison with nephrology remains a key priority.

The authors have no conflict of interest.

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Paper

The Effect of Modernising Medical Careers on Foundation Doctor Career Orientation in the Northern Ireland Foundation School

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ABSTRACT

Objectives Modernising Medical Careers (MMC) emerged in response to acknowledged problems in training in the Senior House Officer grade. The objective of this study was to assess the effect of the Foundation Year 2 (F2) training programme on career orientation in the Northern Ireland Deanery.

Methods A prospective survey-based study was conducted for all F2 doctors participating in the Northern Ireland Foundation Programme. Career orientation was investigated using the Specialty Choice Inventory 45 (SCI45) at the start (Q1) and end (Q2) of the F2 year. Specialty choice was collated after the outcome of specialty recruitment in 2008.

Results There were 231 F2 doctors in programme during the first F2 year in 2006-2007. 147 (M=65, F=82) and 106 (M=55, F=51) completed questionnaires at Q1 and Q2. Male F2 doctors scored significantly higher in the *action orientation* (54.0 vs. 50.0, p<0.001) and *need for assertiveness* (53.0 vs. 48.0, p=0.005) subscales at both time points as well as Q1 *detail is crucial* (57.0 vs. 51.0, p=0.014) and Q2 *independent specialty* (53.0 vs. 46.0, p=0.016). Female F2 doctors scored significantly higher in the *educating patients* subscale at both time-points (44.0 vs. 46.0, p=0.009 and 46.0 vs. 47.0, p=0.03). Analysis of SCI45 subscale scores suggested that males tended to favour the surgical specialties while females favoured the care of the elderly and paediatric specialties. Overall only 29% of doctors were successfully appointed to a specialty in which they had expressed an interest at Q1 whilst 47.8% were selected to specialist training for their declared specialty interest at Q2.

Conclusions Despite introducing MMC with a coordinated UK wide specialty application process (MTAS), a detrimental effect on their career orientation was not evident. Pragmatic career choices based on lifestyle may be the reason why female doctors expressed a preference for care of the elderly and paediatrics while their male colleagues favoured acute, more surgically biased specialties.

Keywords Career, Choice, Doctor, Junior, Specialty.

INTRODUCTION

The introduction of Calman style training in 1995 and MMC more recently, has resulted in a perceived reduction in career flexibility. Generally the view is held that initial career choice is of the utmost importance for doctors in the early phase of their training.[1, 2] Recent reforms in higher specialist training have resulted in a single entry point to a time-limited training programme and consequently foundation year 2 (F2) doctors now feel the need to choose a run-through specialty program immediately after their foundation training.

The first few years of a doctor's career provide clinical exposure, which can influence their longer term choices before they settle on a final career path. This exposure is a major determinant of the future supply of doctors in many specialties. Reports have suggested that the quality and quantity of career advice and information available to junior doctors has been inadequate and in some instances may be misleading in content.[3-6] As a consequence, doctors in training can have a relatively poor understanding of the scope of some specialties and their career opportunities. In particular they may be unfamiliar with consultant-level work in some specialties. The culmination of curriculum and specialty selection modernisation has prompted the need for more specific career advice and support.[7]

Edwards *et al* (1997) reported that 67% of doctors were working in the specialty that had been their first choice towards the end of their first year after leaving medical school. More than 20% were not working in the specialty that had been their first choice at the end of their third year after qualification from medical school.[8] Although it can be feasible to change specialties, this is not easy. The final career choice for a junior doctor is influenced by variables which include the medical school environment and exposure to specialties as an

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undergraduate, personal perceptions of specialties, personal interests and experiences, vocational interests and attitudinal factors.[9-14] In certain situations, the junior doctor may not always have control over their final decision.[15] Baldwin *et al* (1991) reported that career choices in hospital medicine are spread across different stages. Twenty percent make their choice at medical school, while an additional 15% make their choice during the first post-qualification year with a further 20% made in the second year and another 20% made in the third year after qualification. The remaining 25% make their decision up to four years after qualification.[16] These figures support the findings of Isobel Allen (1996) who identified that at 4 years post-registration, 60% of male doctors and fewer than 50% of female doctors were working in the specialty that they had initially chosen when they obtained full GMC registration.[3]

Previously, specialties such as General Practice experienced a decline in the percentage of doctors choosing it as a long-term career choice.[17, 18] However, recent events relating to the medical recruitment crisis experienced in 2007 and the lack of career progression in certain specialties have increased the popularity of General Practice as a long term career choice.[7] Moreover, further evidence has suggested that the quality and quantity of advice and information available in the UK has been generally inadequate and often misleading in content.[3, 4, 6] Fortunately, the incorporation and integration of the Generic Skills course for all F2 doctors has an opportunity to provide both direct career guidance through career symposiums and modules or indirectly through peer and tutor-led career discussion.

When considering selection processes in terms of the specialty, the current system requires decisions to be made without the benefit of having seen the trainee in a clinical setting over a number of years. The specialty committing its training slots and training resources to a junior doctor needs to feel reassured that the doctors they choose, have the attributes and attitudes that will enable them to complete the training process and function well in their consultant roles. More importantly the specialty has to consider that a high attrition rate or failure of trainees to reach the required standard could have detrimental effects on the specialty.

The objectives of this study were to assess the diversity of career intentions at the start of the F2 training programme and to see if junior doctors changed their initial career choices after completion of the F2 training programme.

METHODS

Northern Ireland F2 doctors (2006-2007) were invited to participate in a prospective survey-based cohort study. A verbal explanation of study aims and objectives combined with written information was provided to F2 doctors while attending training modules of the generic skills course which the Northern Ireland Foundation Programme offers to provide these early years doctors a "*head start*". Each questionnaire was administered by a generic skills tutor at the start (Q1-August to September 2006) and end (Q2-June to July 2007) of the academic year at the Northern Ireland Medical and Dental Training Agency (NIMDTA) which is located distant from the clinical environment. A further electronic email trawl was conducted to increase questionnaire completion rates. Due to the assessment of a specific cohort of doctors in a single deanery, there was no comparator or control group assessed.

SUBJECTIVE CAREER INTENTIONS

The current career interest of the F2 doctor was recorded combined with their current F2 rotation divided into 3 periods; August to November 2006, December 2006 to March 2007 and April 2007 to July 2007.

OBJECTIVE CAREER ASSESSMENT

The SCI45 Specialty Choice Inventory was developed by Janet Grant in 1996 as a validated interactive tool which utilises psychometric testing to help medical students and junior doctors select a specialty that best fits with their own attitudes, aspirations, and personal characteristics to assist in career choice or career envisioning for these doctors in training.[7] As F2 doctors also complete other mandatory questionnaires as part of the generic skills programme, it was decided to use only one objective career assessment tool which would be completed at both Q1 and Q2.

The SCI45 Inventory requires the user to comment on 130 statements beginning: "*I want to work in a specialty that ...,"*. The user then has the option of choosing an appropriate response using a Likert scale ranging from "*strongly disagree*," "*disagree*," "*agree*," or "*strongly agree*". The 130 inventory items are organised into 12 dimensions of attributes which act to discriminate between 45 possible medical specialties. From the candidate scores of 12 different subscales, the SCI45 programme recommends approximately 10 specialties which best and least fit that individual's profile (Table 1).[7]

FOUNDATION PROGRAMME COMPLETION DEMOGRAPHICS

In January 2007, the outcomes of the electronic Medical Training Application Service (MTAS) specialty recruitment process for this cohort of doctors were collated by NIMDTA.

STATISTICAL ANALYSIS

This was completed using the SPSS statistical package (Version 13 SPSS®inc. Chicago, USA). Descriptive statistics for baseline variables were presented as mean (standard error of the mean-SEM) or median (interquartile ranges-IQR).

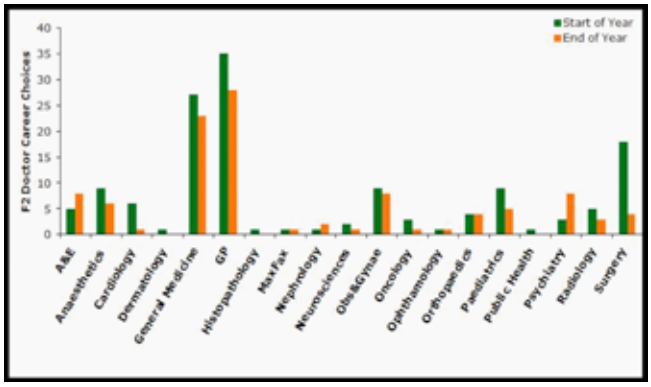

Fig 1. Specialty choices by F2 doctors at the start and at the end of the year expressed as a percentage of F2 doctors interested in the specialty compared to the total questionnaires completed for each time-point.

Table 1

Difference in SCI45 subscale scores for male and female F2 doctors at the start and at the end of the academic year (median, IQR).

FACTOR	START OF YEAR			END OF YEAR		
	Male	Female	P-Value	Male	Female	P-Value
Action Orientation	54.0 (49.0-59.0)	50.0 (43.0-54.0)	<0.001	52.0 (48.0-59.0)	47.0 (43.0-55.0)	0.003
Academic Orientation	52.0 (48.0-59.5)	51.0 (48.0-54.0)	0.10	46.0 (42.0-57.0)	52.0 (43.0-56.0)	0.39
Minor Specialty	50.0 (40.0-55.0)	50.0 (45.0-55.0)	0.30	50.0 (45.0-50.0)	50.0 (45.0-55.0)	0.92
Detail is Crucial	57.0 (48.0-62.0)	51.0 (46.0-59.0)	0.014	54.0 (48.0-59.0)	51.0 (43.0-57.0)	0.11
Working in Teams	58.0 (51.0-63.0)	60.5 (53.3-65.0)	0.29	54.0 (47.0-58.0)	54.0 (51.0-61.0)	0.26
Working with Children	48.0 (43.5-51.0)	48.0 (44.3-51.8)	0.67	48.0 (45.0-51.0)	48.0 (42.0-54.0)	0.82
Educating Patients	44.0 (40.5-47.0)	46.0 (43.0-51.0)	0.009	46.0 (41.0-51.0)	47.0 (44.0-51.0)	0.03
Coping with Uncertainty	47.0 (42.0-51.0)	44.0 (40.0-49.0)	0.30	44.0 (40.0-47.0)	44.0 (40.0-49.0)	0.46
Independent Specialty	53.0 (46.0-59.0)	53.0 (46.0-59.0)	0.54	53.0 (46.0-59.0)	46.0 (46.0-53.0)	0.016
Need for Assertiveness	53.0 (48.0-58.0)	48.0 (41.0-55.0)	0.005	55.0 (46.0-60.0)	50.0 (41.0-55.0)	0.007
Routine Working	53.0 (45.0-57.0)	53.0 (48.0-57.0)	0.69	50.0 (45.0-57.0)	53.0 (48.0-60.0)	0.22
Out-of-Hours Working	50.0 (45.0-57.0)	50.0 (42.0-55.0)	0.32	50.0 (42.0-55.0)	45.0 (40.0-57.0)	0.91

Differences between male and female foundation doctor scores were calculated separately at Q1, Q2 and for doctors who completed the questionnaire on both occasions using the independent sample t-test. The mean percentage change for questionnaire indices at Q2 was compared to Q1 using the formula [(Q2 – Q1) / Q1]. When doctors completed both questionnaires, each parameter was analysed independently for differences between Q1 and Q2 using the paired samples t-test. All statistical tests were 2-sided and differences were considered significant if the p-value was <0.05.

RESULTS

There were 231 F2 doctors in the Northern Ireland Foundation Programme during the 2006-2007 academic year. 147 (63.6%, M=65) and 106 (45.9%, M=55) completed questionnaires 1 and 2 at the start and end of the academic year while 69 (29.9%, M=33) doctors completed both questionnaires. There was no difference in age between male and female F2 doctors with mean ages 26.9 (SEM 0.40) and 26.1 (SEM 0.28) years respectively (p=0.09). The majority of doctors had graduated from Queens University Belfast in July 2005. Most of these F2 doctors had entered University directly from second level education.

SUBJECTIVE CAREER CHOICE

F2 doctors documented a Q1 preference for general practice, general medicine and surgery compared to dermatology, histopathology, nephrology, ophthalmology, orthopaedic and maxillofacial surgery. Nine F2 doctors did not indicate a preference. F2 doctors continued to document a preference for general practice and general medicine at Q2 compared to cardiology, maxillofacial surgery, neurosciences and ophthalmology (**Figure 1**).

SPECIALTY COMBINED INVENTORY SCORES

Male F2 doctors scored significantly higher in Q1 *action orientation*, *detail is crucial* and *need for assertiveness* subscales whereas female F2 doctors scored significantly higher in the *educating patients* subscale. Males scored significantly higher in Q2 *action orientation*, *independent specialty* and *need for assertiveness* subscales whereas females scored significantly higher in the *educating patients* subscale. There was no difference between genders for any of the other subscales at Q1 or Q2 (Table 1).

When the SCI45 scores were compared for all doctors who completed both questionnaires, there was no significant

TABLE 2

Final career destination and training grades for F2 doctors with comparison to initial career choices at the start and end of the academic year.

NUMBER OF DOCTORS	START OF YEAR (Q1)	END OF YEAR (Q2)	FINAL SPECIALTY	TRAINING GRADE
2	GP x 1 Surgery x 1	A&E x 1 GP x 1	**Emergency Medicine (A&E)**	ST1 x 1 FTSA x 1
5	Anaesthetics x 3 Cardiology x 1 Surgery x 1	Anaesthetics x 3 Cardiology x 1 Surgery x 1	**Anaesthetics**	ST1 x 5
17	A&E x 1 Anaesthetics x 2 Cardiology x 3 GP x 4 Medicine x 1 Nephrology x 1 Obs&Gynae x 1 Oncology x 1 Orthopaedics x 2 Psychiatry x 1	A&E x 2 GP x 4 Medicine x 5 Nephrology x 1 Obs&Gynae x 1 Oncology x 1 Orthopaedics x 1 Psychiatry x 1 Radiology x 1	**Core Medical Training**	ST1 x 11 FTSA x 6
13	A&E x 3 GP x 7 Histopathology x 1 Radiology x 1 Surgery x 1	GP x 12 Surgery x 1	**General Practice (GP)**	ST1 x 13
1	Surgery x 1	Obs&Gynae x 1	**Obstetrics and Gynaecology**	ST1 x 1
1	Ophthalmology x 1	Ophthalmology x 1	**Ophthalmology**	ST1 x 1
4	GP x 1 Medicine x 1 Paediatrics x 2	GP x 1 Paediatrics x 3	**Paediatrics**	ST1 x 3 FTSA x 1
3	GP x 1 Medicine x 2	Psychiatry x 3	**Psychiatry**	ST1 x 3
1	Anaesthetics x 1	Radiology x 1	**Radiology**	ST1 x 1
1	Surgery x 1	Orthopaedics x 1	**Surgery**	FTSA x 1
4	Medicine x 2 Obs&Gynae x 1 Paediatrics x 1	Cardiology x 1 Medicine x 1 Paediatrics x 1 Radiology x 1	**No Specialty Training Position**	Home x 4
4	Cardiology x 1 Ophthalmology x 1 Paediatrics x 1 Radiology x 1	Cardiology x 1 Medicine x 1 Paediatrics x 1 Radiology x 1		Travelling x 4
7	Foundation Year 2	Foundation Year 2		Not Eligible for Specialty Training x 7
2	A&E x 1 GP x 1	A&E x 1 Psychiatry x 1		Did not apply x 2
4	GP x 1 Medicine x 1 No record x 2	GP x 1 Psychiatry x 1 No record x 2		Unknown x 5

difference in the specialty subscales between Q1 and Q2, apart from *detail is crucial* and *working in teams* which were significantly higher at Q1 (54.0 vs. 51.0, p=0.022 and 58.0 vs. 54.0, p=0.026). When the mean percentage change from baseline was assessed separately for the male and female F2 doctors who completed both questionnaires, a significantly higher score was identified in the male doctors for *independent specialty* (8.2% vs. -4.9%, p=0.018). There was a trend for an improvement in the *minor specialty* subscale for the males with a mean change from baseline of 15.4% vs. -0.7% (p=0.06) and also for an improvement in the *need for assertiveness* subscale for females of 4.2% vs. -3.8% (p=0.06). However, these trends were not statistically significant **(**Figure 2**)**. There was no difference in the mean percentage change from baseline for the other subscales.

An overview of all three best fit career choices suggested a preponderance for the more elective specialties such as infectious disease, immunology, psychiatry and dermatology in comparison to more acute specialties such as emergency

medicine, anaesthetics, cardiology and surgery. There was no difference demonstrated between these specialty choices at Q1 or Q2. An overview of all three least fit career choices suggested an aversion to specialties associated with a more acute or practical base. These predominantly included the surgical and neuroscience specialties. Surprisingly, general medicine and the non-emergency psychiatry and palliative care specialties were also deemed least fit specialties for a significant proportion of this cohort of F2 doctors. There was no difference demonstrated between the best and least fit specialties at Q1 or Q2.

FINAL CAREER CHOICE

Further analysis of career choice with correlation to final specialty appointments was performed for the 69 F2 doctors who completed both questionnaires. When F2 doctors interested in a specialty at Q1 were compared to the actual number appointed to that specialty, anaesthetics (50%), general practice (43.8%) and core medical training (42.9%) had a higher percentage of end of year appointments. All F2 doctors interested in emergency medicine, obstetrics and gynaecology, psychiatry and radiology at Q1 were unsuccessful in their appointment to their chosen specialty. In total, only 29.0% of doctors were successfully appointed to a specialty that they had been interested in at the start of the year (Table 2).

At the end of the year, an increased success rate of 47.8% was demonstrated for doctors selected to specialist training for their declared specialty interest. Anaesthetics (100%), ophthalmology (100%), general practice (63.2%), core medical training (58.3%), obstetrics and gynaecology (50%), paediatrics (60%) and psychiatry (50%) all had better success rates for chosen specialty appointments than emergency

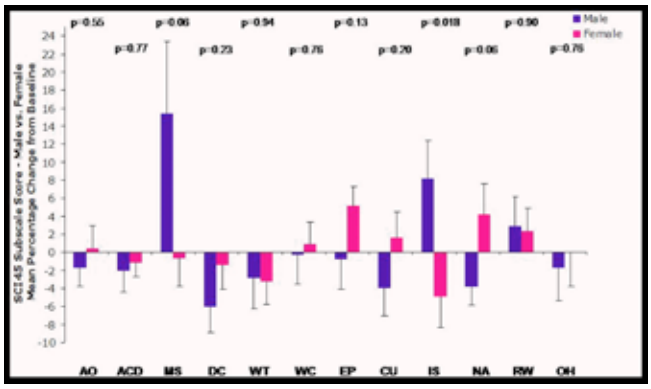

Fig 2. Mean percentage change from baseline in SCI45 subscale scores for male and female F2 doctors who completed both questionnaires at the start and at the end of the academic year (mean, SEM) (AO=Action Orientation, ACD=Academic Orientation, MS=Minor Specially, DC=Detail is Crucial, WT=Working in Teams, WC=Working with Children, EP=Educating Patients, CU=Coping with Uncertainty, IS=Independent Specialty, NA=Need for Assertiveness, RW=Routine Working and OH=Out-of-Hours Working).

TABLE 3

Number of F2 doctors appointed to their chosen specialty compared to the total number of F2 doctors interested in the specialty at the start and at the end of the academic year [Others included F2 doctors who still had to complete their F2 foundation year (n=7) as well as F2 doctors with insufficient data (n=2)].

SPECIALTY	START OF YEAR			END OF YEAR		
	Number of F2 doctors interested in specialty			Number of F2 doctors interested in specialty		
	Appointed	Total Number	% employed	Appointed	Total Number	% employed
Emergency Medicine	0	5	0	1	4	25
Anaesthetics	3	6	50	3	3	100
Core Medical Training	6	14	42.9	7	12	58.3
General Practice	7	16	43.8	12	19	63.2
Histopathology	0	1	0	0	0	0
Obstetrics and Gynaecology	0	2	0	1	2	50
Ophthalmology	1	2	50	1	1	100
Paediatrics	2	4	50	3	5	60
Psychiatry	0	1	0	3	6	50
Radiology	0	2	0	1	4	25
Surgery	1	7	14.3	1	4	33.3
Others	N/A	9	N/A	N/A	9	N/A
Totals	20	69	29.0	33	69	47.8

TABLE 4

Breakdown of specialty training vs. fixed-term training appointments for F2 doctors in Northern Ireland who completed both questionnaires (n=69).

SPECIALTY	SPECIALIST TRAINING APPOINTMENT	FIXED-TERM TRAINING APPOINTMENT	TOTAL APPOINTMENTS	SPECIALIST TRAINING % OF TOTAL	FIXED-TERM TRAINING % OF TOTAL
Emergency Medicine	1	1	2	50	50
Anaesthetics	5	0	5	100	0
Core Medical Training	11	6	17	64.7	35.3
General Practice	13	0	13	100	0
Obstetrics and Gynaecology	1	0	1	100	0
Ophthalmology	1	0	1	100	0
Paediatrics	3	1	4	75	0
Psychiatry	3	0	3	100	0
Radiology	1	0	1	100	0
Surgery	0	1	1	0	100
Total	**39**	**9**	**48**	**81.3**	**18.7**

medicine (25%), radiology (25%) and surgery (33.3%) (Table 3).

Table 4 demonstrates the breakdown of specialist training and fixed-term specialty appointments (FTSA) for the different specialties in Northern Ireland. From a total of 48 potential appointments for this cohort of F2 doctors (n=69), Northern Ireland provided 39 (81.3%) specialty training posts and 9 (18.7%) FTSAs. Most specialties apart from surgery (0%) offered a greater than 50% chance of a specialty training position with the majority providing a 100% rate for specialty training appointments.

DISCUSSION

The Northern Ireland experience with this first cohort of F2 doctors has shown that predominant career choices favoured the consideration of the mainstream specialties of general medicine, practice and surgery. However, other specialties were also considered at the start of the F2 academic year, despite the fact that most of the F2 doctors had not experienced work related patterns in these specialties. Such specialties included emergency medicine, anaesthetics, obstetrics & gynaecology, paediatrics and radiology. With the advent of foundation training, F2 doctors are now exposed to a wider variety of specialties in their second year post-qualification. Despite the influence of these specialties, their subjective career choices remained similar at the end of the year with general medicine and general practice featuring highly in their choices. More specialised disciplines (obstetrics, paediatrics and radiology) were also considered at Q2. However, surgery and its sub-specialties no longer appeared as popular a choice. It is unclear why such a definite reduction was evident but perhaps the experience of longer working hours in a more arduous specialty despite the European Working Time Directive (EWTD) has played a part. However, it may be that knowledge of a reduction in future surgical job prospects accounted for the reduction in surgical interest. It must be acknowledged that completion demographics for the 2 time-points were different with completion rates of 63.6% and 45.9% respectively and therefore a questionnaire completion bias must also be considered.

Lambert *et al* (2003) assessed doctors' reasons for rejecting initial specialty choices as long-term careers. Their questionnaire-based study assessed all graduates, who qualified in 1996 and 1999 from UK medical schools. It was completed during their first postgraduate year with 5633 respondents from a possible 7971 surveyed. At the end of the pre-registration house officer (F1) year, 1,947 (34.4%) of these doctors had rejected previous considered career choices while 1,871 (33.1%) had provided their reasons for career choice rejection.[19] Similar to our study, the mainstream specialties were heavily favoured with 23%, 22% and 21% choosing the medical, general practice and surgical specialties respectively with a lower number of doctors choosing specialties such as anaesthetics (7%), emergency medicine (3%), obstetrics & gynaecology (3%), paediatrics (6%) and psychiatry (4%).[19]

Lambert *et al* (2003) also reported that the medical and surgical specialties were heavily rejected by this group of doctors with 22% and 30% of doctors eschewing these specialties after their first year of qualification.[19] Quality of life was the main reason provided by 50% of doctors who rejected the hospital medical or surgical specialties and paediatrics, whereas only a small proportion of those rejecting GP or psychiatry provided quality of life as a reason. Doctors who rejected general practice or psychiatry cited lack of enjoyment of job content as their reason. Poor working

relationships appeared to be a factor for those rejecting the surgical specialties or obstetrics & gynaecology. Concern regarding training and the examinations required varied by specialty and were highest amongst those rejecting the medical specialties. When considering all 1871 doctors who provided reasons for rejecting their specialty, 48% and 40% cited quality of life and lack of job enjoyment respectively while concern regarding career paths (24%), training and examinations (14%), working relationships (13%), self appraisal (6%) and personal influences (6%) were other reasons cited.[19]

More recently, Stern (2005) suggested possible reasons for career choice amongst F1 doctors at the start, middle and end of their first year post-qualification which included; own personal experiences (40%), house officer working experiences (27%), advice of a senior doctor (7%), consultant work pattern (7%), personal preference (4%), intercalated degree experience (4%), the specialty enjoyment (3%), availability of consultant posts (2%), family reasons (2%), tutor's advice (1%), research (1%) and the influence of an undergraduate special study module (1%).[20] Although our study assessed potential career choices, it was limited somewhat by the lack of assessment of possible career rejection choices or actual reasons for such career choices. However, use of the SCI45 inventory allowed an assessment of both best and least fit career recommendations which revealed a preponderance for the more elective specialties and an aversion to specialties associated with a more acute or practical base.

When assessing career choices objectively, the SCI45 inventory analyses a profile of skills and aspirations of the individual which are then presented in 12 different subscales. When these subscale scores were analysed according to examples of high and low scoring specialties, as described by Borges *et al* (2002), male F2 doctors appeared to favour the surgical specialties particularly plastic surgery and urology as well as obstetrics & gynaecology.[21] These scores further indicated a lower interest in psychiatry, occupational medicine, care of the elderly, genito-urinary medicine and laboratory based specialties whereas female F2 doctors tended to favour care of the elderly and paediatrics rather than the laboratory based specialties.

When the SCI45 scores were compared for doctors who completed the questionnaires on both occasions, there was no significant difference in the specialty subscales, between Q1 and Q2, apart from *detail is crucial*, *working in teams* and *independent specialty* which were significantly higher at Q1. This variation in only 3 out of 12 specialty subscale scores would suggest that an objective assessment of career attributes using the SCI45 did provide an accurate method to assess personal profiles of the skills and aspirations of the individual at a specific point in their career development. However, it should be emphasised that although the subtype scores remained relatively stable there was still scope for variation of specialty subscale scores particularly the *detail is crucial*, *working in teams* and *independent specialty* where a reduction in scores at the end of the year may indicate a trend away from the more surgically orientated disciplines.

The assessment of informal career guidance methodology is more difficult and highly dependant on both the intra- and inter- personal relationship of the F2 doctor with their foundation school appointed educational supervisors. It is also important to realise the influence of work-associated peers, hospital based campaigns and the wider media in career aspirations. From this study it is unclear how influential these factors were and as such these factors should be acknowledged. However, only a single cohort of doctors was assessed and it was hoped that whatever influence did occur would be uniform within the group as we considered our study group to be a single population.

Although this study did not subjectively assess other important means of career guidance, this cohort of doctors did appear to be more privileged than previous generations due to the availability of both hospital and deanery based advisers at the dedicated F2 generic skills course. However, Stern (2005) reported that most young doctors have decided on their future careers around the mid-point of their first year of qualification. Experience in the workplace, both undergraduate and postgraduate helped doctors decide on their future career.[20, 22] They also suggested that formal career advice sessions 6-months into the F1 year added little to final career aspirations. Only 8% of those previously undecided had by that time made a career decision. However, it is important to note that 21% had changed their career choice, subsequently.

Stern (2005) also stated that 89% of junior doctors assessed thought the SCI45 program was useful whilst 43% felt the deanery website was a useful source of career advice.[20] They concluded that these less personal and more computer-based methods of career advice were seen in a more positive light than other activities such as one-to-one tutor led sessions. However, it should be noted that 40% also found career advice sessions useful. Therefore, there does not appear to be any absolute method to impart career advice and that multiple sources may be the most optimal mode depending on the actual specialty.

Although we have subjectively and objectively assessed career aspirations for this cohort of F2 doctors, it is important to discuss and reflect upon their chosen career choices for further specialty training. This study showed that this cohort of F2 doctors were more likely to have a successful appointment to their specialty of choice at the end of the academic year than at the start of the year. It has been demonstrated that that only 29% of doctors were successfully appointed to their declared career choice compared to 47.8% at the end of the year. A higher success rate for appointments of choice at Q1 and Q2 were reported in a number of specialties including anaesthetics and general practice. However, all F2 doctors who declared an interest in emergency medicine, obstetrics and gynaecology, psychiatry and radiology at Q1 were unsuccessful in their appointment to their chosen specialty while appointments based on Q2 choices also remained low particularly in emergency medicine (25%), radiology (25%) and surgery (33.3%).

It is also important to realise the differentiation between dedicated training positions compared to FTSAs. We reported that from a total of 48 potential appointments (n=69), Northern Ireland provided a total 39 (81.3%) of specialty training posts and 9 (18.7%) FTSAs. Most specialties apart from surgery (0%) offered a greater than 50% chance of a

specialty training position with the majority providing a 100% rate for specialty training appointments (Table 4).

It would be useful to conduct this study at the very beginning of medical school with annual assessments rather than completion on multiple occasions in a single year. These assessments could then continue throughout medical school, the foundation programme and further into the junior doctor's career. In the longer term, it would be important to follow this cohort of F2 doctors to ascertain clinical progress and final career disposition. One of the major strengths of this study was the assessment of a fixed cohort of doctors who were exposed to a uniform Foundation Programme. Although this study was limited through confinement to a solitary deanery without randomisation, the authors believe a true representation of the F2 doctors for the period of the study was obtained. However, similar to previous studies, it is unclear as to the influence of a potential selection bias in this selected group of doctors as only 63.6% of the total cohort chose to complete the questionnaires.

Although it would be impractical to attempt to initiate randomisation of foundation doctors to receive or omit the Generic skills careers module, a cross-sectional study incorporating a different deanery would be very useful in investigating the actual effect of a foundation school compared to different methodologies. However, this may also have ethical ramifications as it is important for optimisation of junior doctor training and development particularly within the first few years following qualification. Although we have previously used the SCI45 assessment tool, an updated version SCI-69 is now available. In addition, other aspects of career choice could be assessed using the Career Decision Scale (CDS) which measures anxiety associated with career indecision.[23]

CONCLUSION

There are many factors known to influence a doctor's career choice. Teasing apart the personality traits and aligning these with specific medical specialty interests followed no predictable pattern. Despite the '*triple whammy impact'* of introducing MMC with a coordinated UK wide specialty application process (MTAS) on the first cohort (2005-2007) of Foundation doctors, a detrimental effect on their career orientation was not evident. In the end, pragmatic career choices based on lifestyle may be the reason why female doctors veer towards care of the elderly and paediatrics, while their male colleagues favour more acute surgically biased specialties.

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The authors have no conflict of interest

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Paper

The role of surgery for pancreatic cancer: a 12-year review of patient outcome

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ABSTRACT

Introduction Pancreatic cancer has a poor prognosis with <5% alive at 5 years, despite active surgical treatment. The study aim was to review patients undergoing pancreatic resection and assess the effect of clinical and pathological parameters on survival.

Patients and methods All patients who had undergone radical pancreatic surgery, January 1996 to December 2008, were identified from the unit database. Additional information was retrieved from the patient records. The demographic, clinical, and pathological records were recorded using Microsoft Excel. Survival was assessed using Kaplan-Meier and predictors of survival determined by multinominal logistic regression and log rank test.

Results 126 patients were identified from the database. The majority (106) had a Whipple's procedure, 14 had a distal pancreatectomy and 6 had local periampullary excision. The average age of the Whipple's group of patients was 61.7 years (± 11.7) with most procedures performed for malignancy (n=100). Survival was worse with adenocarcinoma compared to all other pathologies (p=0.013), while periampullary tumours had a better prognosis compared to other locations (p=0.019). Survival decreased with poorer differentiation (p=0.001), increasing pT (p<0.001) and pN stage (p<0.001). Survival was worse with perineural (p=0.04) or lymphovascular invasion (p=0.05). A microscopic postive resection margin (R1) was associated with a worse survival (p=0.007). Tumour differentiation (p=0.001) and positive nodal status (p<0.001) were found to be independent predictors of mortality.

Conclusion Tumour differentiation and nodal status are important predictors of outcome. A positive resection margin is associated with a poorer survival.

Keywords Whipple's procedure, pancreatic cancer, survival

INTRODUCTION

Pancreatic cancer was the eleventh most common cancer in Northern Ireland in 2001, with 160-180 new cases per year in Northern Ireland and 6000 in the UK. Overall it accounts for approximately 2% of all cancer, with an average age of presentation of 69 years old and UK incidence of 10 per 100,000. The male to female ratio in Northern Ireland of pancreatic cancer diagnosis is 1.3:1. It carries a bleak prognosis, with less than 3% surviving three years following diagnosis.[1] The Campbell report "Cancer services – investing for the future", published in 2001, sought to address the provision of treatment for cancer and made several recommendations.[2] Although centralisation of pancreatic surgical services in Northern Ireland has not been fully implemented, there has been an establishment of a multidisciplinary approach to cancer treatment, with clear pathways to incorporate multimodal treatment including palliative care when indicated. This is particularly important for pancreatic cancer, with an increased array of treatment interventions available and adjuvant chemotherapy standard since 2001. The involvement of oncologists, gastroenterologists, pancreatic surgeons, interventional radiologists, palliative care physicians and the primary care team in multidisciplinary discussion has resulted in improved management options and outcome, rendering the former nihilistic attitude to pancreatic cancer outdated.

Although pancreatic cancer is the main focus of this study, four anatomical locations, where cancer can arise to give similar symptoms, have been included, namely the duodenum, common bile duct, ampulla of Vater and the head of pancreas. The purpose of this study was to review patients undergoing pancreatic resection for cancer in any of these locations and assess the effect of clinical and pathological parameters on survival.

Anatomy

The pancreas gland lies transversely in the posterior portion of the epigastric and left hypochrondrial areas. The broad right lateral portion is called the head, which is separated from the body by a constriction known as the neck. The tapering left

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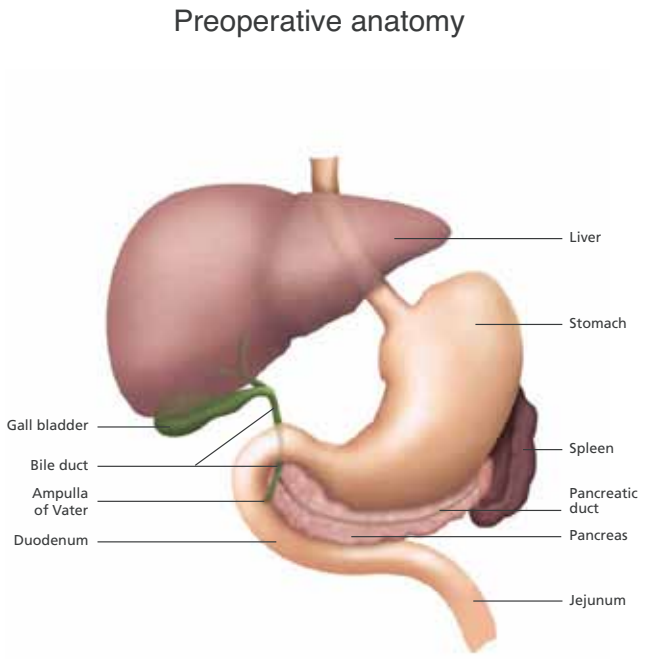

Fig 1. Normal peri-pancreatic anatomy

lateral portion is the tail, while the uncinate process emerges from the head at the angle between its lower and left lateral borders.

The head of the pancreas lies within the duodenal curve, with the upper, lower and right lateral borders lying intimately to the duodenum (Figure 1). The ascending portion of the duodenum lies in front of the left lateral border of the head. The anterior aspect is largely covered by the transverse colon, with the superior mesenteric artery crossing the uncinate process. The corresponding vein travels up behind the neck to form the portal vein. Posterior to the head of pancreas lies the inferior vena cava, the common bile duct, the renal veins, the aorta and right crus of the diaphragm.

The body is covered anteriorly by the stomach, with the aorta, left kidney and vessels and the origin of the superior mesenteric artery lying behind. The duodenojejenal flexure lies inferiorly. The pancreatic tail continues to the left lateral aspect to finish at the lower part of the spleen. All these anatomical relationships are very important, as the degree of local invasion will often determine operative resectability.

The common bile duct (CBD) is formed by the left and right hepatic duct at the hilar confluence. It travels down as described above to drain into the second part of the

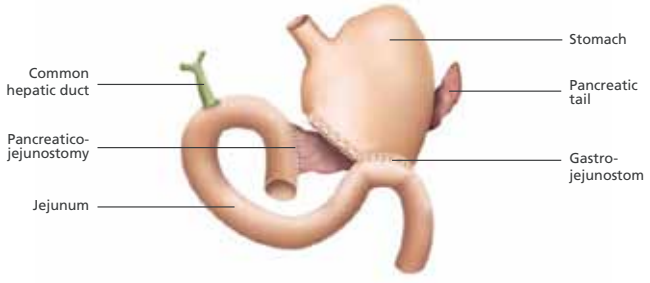

Fig 2. Anatomy and anastomoses after a Whipple's procedure

duodenum, through the ampulla of Vater, beside the pancreatic duct. Periampullary tumours are usually defined as those in the last centrimetre of the CBD, where it traverses the ampullary papilla and duodenal wall.

Presentation and risk factors

Pancreatic cancer often progresses asymptomatically and then presents late, resulting in only a minority being suitable for resection. Symptoms can be quite non-specific and include nausea, anoxeria, jaundice, weight loss and abdominal pain. Pain, when present, is in the upper abdomen radiating through to the back and is often more associated with the body or tail of the pancreas. Alternatively, tumours of the head of the pancreas are more likely to present with painless jaundice and possibly steatorrhoea. Early cachexia is often seen in patients diagnosed with a tumour in the head of the pancreas, with weight loss of at least 10% of total body weight. Other less common symptoms include diabetes, diarrhoea and depression. Tumours arising from the ampulla of Vater are likely to present initially with jaundice and thus at an earlier stage, thus increasing their resection potential. An obstructive pattern to the liver function tests is likely to exist, while it may be helpful to check the associated tumour marker Carbohydrate Antigen 19-9 (CA 19-9), although this lacks sensitivity and specificity, particularly in the presence of obstructive jaundice. Endocrine tumours of the pancreas are less common and presenting symptoms relate to the hormone being secreted.

Similar to many other cancers, smoking makes a well-recognised contribution to the risk of pancreatic cancer. A close relative with the condition doubles the risk, while the synergistic effect of these two gives an eight-fold increase to the risk. Other factors, including dietary, environmental and genetic aberrations have only weak associations.[3]

Pathology

Carcinoma of the pancreas usually arises from the ductal epithelial cells of the exocrine part of the gland. Neoplasms derived from the endocrine component of the galnd, so-called pancreatic endocrine neoplasms, are not uncommon, while acinar cell carcinomas, arising from the enzyme-producing pancreatic cells, are rare. Histologically the vast majority of malignant pancreatic cancers are adenocarcinoma, which can have varying degrees of mucin production. Subtypes of ductal carcinoma include adenosquamous, mucinous, signet ring cell and medullary.[4] Some may arise within intraductal papillary mucinous neoplasms.

The anatomy described above is important to the pathological specimen evaluation tumour staging and assessment of resection margins. Despite guidelines from the pathology professional bodies of the UK and USA, there is as yet no agreed consensus on what constitutes a positive resection margin (R1).[5-7] There are three main surfaces to a typical pancreaticoduodenectomy specimen, namely the anterior, posterior and superior mesenteric vein (SMV) groove surfaces. At pathological evaluation, the specimen is usually serially sliced in a horizontal plane perpendicular to the duodenal axis. A R1 (incomplete) resection is usually defined as tumour within 1mm of a margin microscopically.[7] This may be primary tumour, or tumour within lymph nodes or lymphovascular channels.

Treatment

Investigations of a suspected malignancy in this area include ultrasound, computerised tomography, endoscopic and intraoperative ultrasound. The two important categories of management are chemotherapy and surgery. The latter alone offers potential cure, but the late presentation of disease renders many patients unresectable. The role of chemotherapy can be either palliative or as an adjunct to surgery.

The surgical procedure is a pancreaticoduodenectomy, or Whipple's procedure (Figure 2). This is named after Allen Oldfather Whipple (1881-1963), who pioneered the resection, although it was first described in 1898 by Codivilla. It involves removal of the distal half of the stomach, gallbladder, distal portion of the common bile duct, as well as the head of the pancreas, duodenum, proximal jejenum and lymph nodes. Reconstruction requires three anastomoses, namely pancreaticojejunostomy, choledochojejunostomy and gastrojejunostomy. Total pancreatectomy is not usually recommended and often leads to brittle diabetes. An important modification of the Whipple's procedure is the pylorus-sparing pancreaticoduodenectomy.[8]

The aim of this retrospective study was to determine the survival patterns and pathological predictors of survival in patients undergoing pancreatic resection in one unit in Northern Ireland.

PATIENTS AND METHODS

Patient details

A retrospective review of the Hepatopancreaticobiliary unit database was performed and all patients who had major pancreatic surgery over a twelve-year period were included. Patient demographics were recoded, as well as operation and pathology results. The full pathological report of resected specimens was obtained from the department of pathology. The date of death, where appropriate was obtained from the hospital medical records, and subsequently verified with the patient's General Practitioner. All details were recorded on Microsoft Excel (Microsoft Corporation, USA) and analysed on SPSS (Version 13, SPSS Inc, Chicago, Il, USA).

Statistical analysis

Although some patients with non-neoplastic conditions were identified as having undergone pancreatic surgery, only those with a malignant process were included in the survival analysis and the determination of survival predictors. Survival analysis was performed using Kaplan-Meier for location of tumour, pT and pN stage, type of tumour and resection margin status. In this analysis, only patients who had undergone Whipple's procedure for malignancy were included. Each variable was further investigated using analysis of variance (ANOVA) to quantify the difference. Independent predictors of survival were determined using multinominal regression analysis. A p value <0.05 was considered significant in all tests.

RESULTS

Patient selection

One hundred and seventy-four patients, underwent a pancreatic-related procedure, between January 1996 and December 2008. After exclusion of necrosectomy, pseudocyst drainage and palliative bypass procedures, 126 patients were included in the study cohort.

Spectrum of operations performed

Six patients were managed with local excision of a malignant polyp in the periampullary region of the duodenum. The average age was 75.2 years (± 11.1). There was one peri-operative death and two others have died, at follow-up periods of 3 and 7 months. The remaining three patients were alive 8, 10 and 13 months follow-up post-operatively.

Fifteen patients underwent distal pancreatectomy for either adenocarcinoma (n=4), endocrine neoplasm (n=8) or non-neoplastic conditions (n=3). The average age was 48.3 years (± 19.2). Three of the patients diagnosed with adenocarcinoma died, at a follow-up periods of 8, 8 and 47 months, with one still alive after 18 months.

During the study period 106 Whipple's procedures were performed by three consultant surgeons. The average age of the patients was 61.7 years (± 11.7). The operation was performed for a variety of diagnoses, including chronic pancreatitis (n=3), locally invasive hepatic flexure colonic adenocarcinoma (n=1), inflammatory abscess (n=1), primary sclerosing cholangitis (n=1) and a primary tumour (n=100). There were seven peri-operative deaths (6.6%) following a Whipple's procedure, with a overall median survival of 24 months. The number of Whipple's procedures performed annually has increased during the study period, with a decreasing trend of mortality, with no deaths in the last 3 years of the study period out of 52 operations.

Whipple's patients and survival trends

Histologically 92 of the 100 tumours proved to be ductal adenocarcinoma. The remaining comprised duodenal gastrointestinal stromal tumour (n=1), and well-differentiated endocrine tumours (n=6) and anaplastic carcinoma (n=1). Patients diagnosed with adenocarcinoma had a significantly

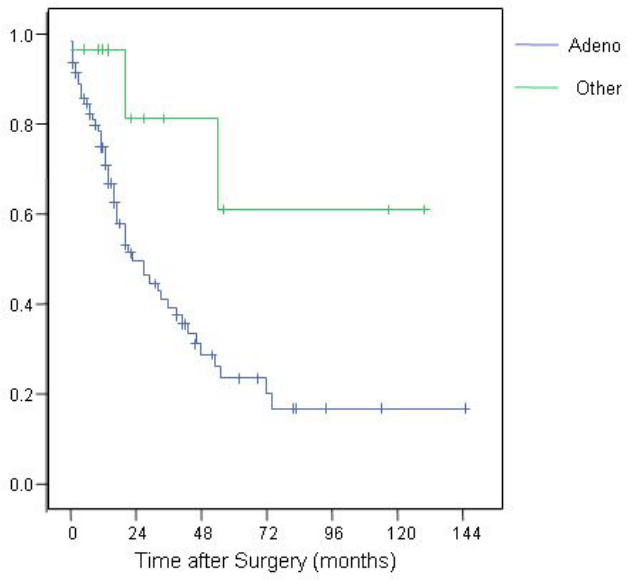

Fig 3. Survival trends of adenocarcinoma compared to other cancers

poorer survival rate than patients diagnosed with the other tumours grouped together (p=0.013; Figure 3).

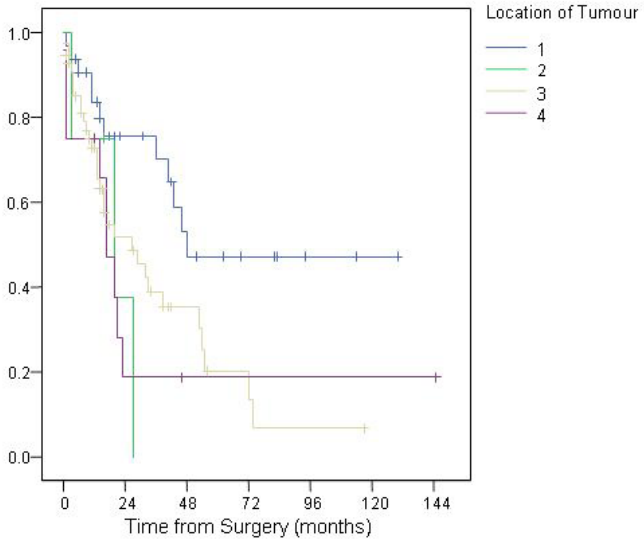

Fig 4. Survival trends after Whipple's according to location of tumour (1=ampulla of Vater, 2=duodenum, 3=head of pancreas, 4=common bile duct)

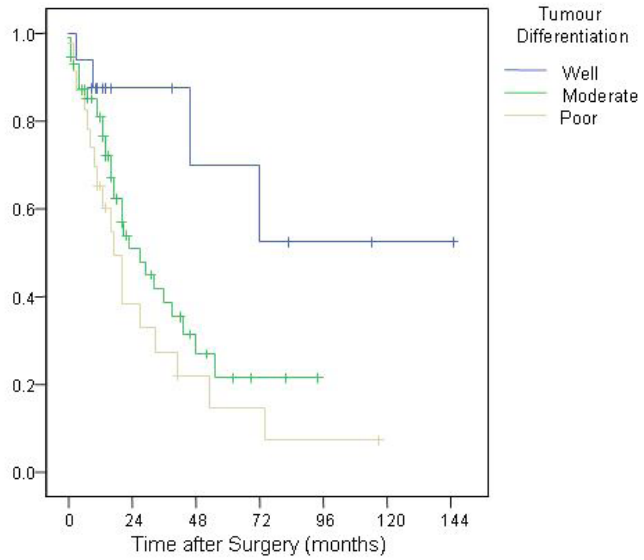

Fig 5. Survival trends according to tumour differentiation

The 92 patients with adenocarcinoma had disease arising from four areas, namely the ampulla of Vater (n=31), duodenum (n=4), head of pancreas (n=45) and common bile duct (n=12). The survival trends according to the four different locations is illustrated in Figure 4 (p=0.019). Tumour differentiation varied from well-differentiated (n=13) to moderate (n=55) and poor (n=21), with survival affected accordingly (p=0.001; Figure 5). The differentiation of 3 tumours was not reported.

Pathological (pT) tumour stages were pT1 (n=4), pT2 (n=20), pT3 (n=63) and pT4 (n=5), and this reflected outcome (p<0.001; Figure 6). The nodal status was positive (pN1) in 58 patients with an associated mortality (p<0.001; Figure 7).

The presence of perineurnal (p=0.044) or lymphovascular invasion (p=0.052) were also found to be poor prognostic indicators. Clear resection margins achieved microscopically in 56 operations improved outcome (p=0.007).

The mean size of tumour was 29mm (±12). Multinominial logistic regression, which included all pathological factors, demonstrated tumour differentiation (p=0.001) and nodal status (p<0.001) were the only significant predictors of mortality. Log-rank test revealed perineural invasion (p=0.012) and lymphovascular invasion (p=0.005) were significant predictors of survival in the months following surgery. In regard to these particular parameters, the relative risk of death was calculated for perineural invasion (1.76), lymphovascular invasion (1.97), positive resection margin (2.01) and positive nodal status (2.79).

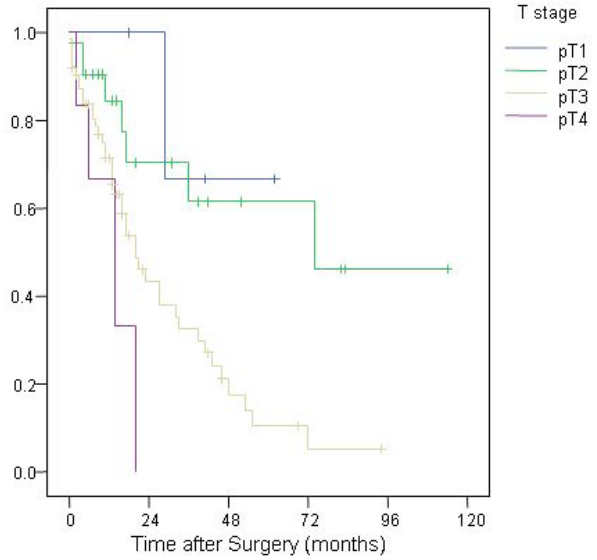

Fig 6. Survival trends according to T stage of tumour

DISCUSSION

Pancreaticoduodenectomy is a major operation, carrying significant risk of morbidity and mortality. Complications include delayed gastric emptying (20%), wound infection (10%) and intra-abdominal collections or fistulae (15%). The latter is often secondary to anastomotic breakdown, particularly the pancreatico-jejunal anastomosis. Most eventualities can be treated conservatively and mortality in high-volume institutions is about 1%.[11, 12] Therefore, patient selection is vital, to optimise the surgical curative rate.

The results of this study indicate that the location of the tumour can influence the survival pattern, where patients with periampullary tumours have a better prognosis. This reflects their earlier presentation and as a result the surgical resection margin was only involved in 3 (9.6%) patients of this sub-group. Consequently, while it was not the practice in these patients, some authors advocate the less radical pylorus-preserving resection to reduce morbidity, without compromise of oncological clearance.[13, 14] Transduodenal local excision was performed on a small number of patients in this study, but carries significant risks, including pancreatitis and duodenal or pancreatic fistula formation. Pre and intra-

operative determination of the site of the tumour is often difficult. However, only 75% of periampullary tumours are truly of pancreatic origin, of which at least 12% are of a more favourable variety than ductal adenocarcinoma of the pancreas.[15] Thus, such patients may have a better than anticipated prognosis.

The involvement of the resection margin, known as R1 resection, is an important factor in prognosis following pancreatic resection.[9, 14, 15] This varied according to tumour location, where 3 (9.6%) periampullary, 1 (25%) duodenual, 30 (54.5%) head of pancreas and 2 (16.7%) CBD tumour patients had a R1 resection. A positive surgical margin is generally accepted as a poor prognostic factor, so it is surprising that in a study of 360 patients, Raut *et al* found no statistical significance in its effect on survival.[16] They attributed this fact to the variable reporting patterns of histology and the lack of differentiating between micro and macroscopically involved margins in other studies. However, evidence from the ESPAC-1 trial indicates that R1 tumours represent a biologically more aggressive cancer.[17] In addition to a poorer response to surgery, the magnitude of benefit from chemotherapy is decreased in patients with R1 margins.

Histological evidence of tumour deposition in lymph nodes removed with the specimen has been shown to be an independent prognostic factor. This is in-keeping with the findings of other researchers and reflects the first step of tumour spread from the primary site.[17, 18,] More recent evidence reveals that the ratio of metastatically involved to retrieved lymph nodes is also an important prognostic indicator.[18-20]

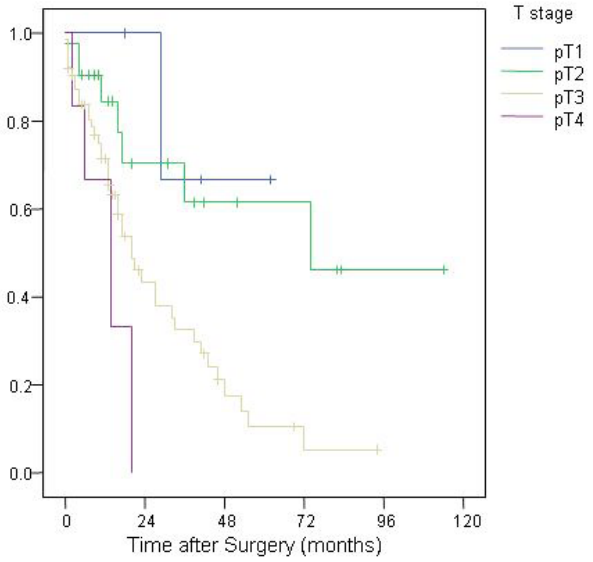

Fig 7. Survival trends according to N stage of tumour

Perineural invasion also emerged as influential in survival. Perineural growth is generally defined as cancer cells growing in close apposition to the nerves. The importance of this is seen in other cancers, such as gastric and breast, as well as those considered in this study.[21-23] It is thought that the tissue plane around the nerve provides a path of least resistance to tumour advancement and dissemination, possibly further stimulated by nerve derived growth factors.[24] It also results in a macroscopically clear margin to be declared involved when identified histologically.

Tumour differentiation is key to understanding the biological aggressiveness of the disease. This was an important parameter in this study and others.[9, 13, 25] This fact is also seen in colorectal cancer, where poorer differentiation is associated with more widely disseminated disease, higher recurrence rates and poorer overall prognosis.[26]

A non-biological factor that is now thought to influence the outcome following pancreatic resection, is institutional experience.[2] A Department of Health document suggested that the population of a pancreatic service catchment area should be at least 2 million.[27] The population of Northern Ireland is projected to increase from 1.70 million in 2008 to 1.84 million in 2031, but it has been acknowledged that geographical constraints made this difficult in the province. Nevertheless, over recent years, centralisation of such surgery has been encouraged.[28] As a consequence of this and of an increase in surgeon numbers, there is a greater proportion of pancreaticoduodenectomies in this study performed in the latter years. A target of 20 resections per institution has been proposed to optimise patient outcome. This is because outcome is influenced, not just by surgical technique, but also by the holistic post-operative care.[28, 29] The requirement of a two million population springs from an incident rate of 1 per 100,000 per year, with a resultant resection rate of 10%. Although hospital case volume and outcome are associated, evidence to support these exact figures is lacking. However, the results of the present study show that with an increased number of Whipple's procedures performed annually for the last 3 years, there have been improved mortality.

In conclusion, pancreatic cancer prognosis improved with better tumour differentiation and a lack of lymph node involvement.

The authors have no conflict of interest.

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Paper

Post-operative telephone review is cost-effective and acceptable to patients.

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ABSTRACT

Introduction Patients undergoing selective minor emergency and elective procedures are followed up by a nurse-led structured telephone review six weeks post-operatively in our hospital. Our study objectives were to review patients' satisfaction, assess cost-effectiveness and compare our practice with other surgical units in Northern Ireland (NI).

Patients and Methods Completed telephone follow-up forms were reviewed retrospectively for a three-year period and cost savings calculated. Fifty patients were contacted prospectively by telephone using a questionnaire to assess satisfaction of this follow-up. A postal questionnaire was sent to 68 general and vascular surgeons in NI, assessing individual preferences for patient follow-up.

Results A total of 1378 patients received a telephone review from September 2005 to September 2008. One thousand one hundred and seventy-seven (85.4%) were successfully contacted, while 201 (14.6%) did not respond despite multiple attempts. One hundred and forty-seven respondents (10.7%) required further outpatient follow-up, thereby saving 1231 outpatient reviews, equivalent to £41,509 per annum. Thirty-nine (78%) patients expected post-operative follow-up, with 29 (58%) expecting this in the outpatient department. However, all patients were satisfied with the nurse-led telephone review. Fifty-three (78%) consultants responded. Those who always, or occasionally, review patients post-operatively varies according to the operation performed, ranging from 2.2% appendicectomy patients to 40.0% for varicose vein surgery.

Conclusion Current practice in NI varies, but a significant proportion of patients are not routinely reviewed. This study confirmed that patients expect post-operative follow-up. A nurse-led telephone review service is acceptable to patients, cost-effective and reduces the number of unnecessary outpatient reviews.

Keywords Telephone review, telephone follow-up, post-operative.

INTRODUCTION

Telephone consultations are increasingly being used as a novel approach to supplement or replace traditional outpatient care for various acute or chronic conditions.[1] The evolving healthcare environment of the past two decades has seen a trend towards shortened hospital admissions with increased patient turnover. Conversely, there has also been a decrease in scheduled, hospital-based, medical follow-up.[2] Traditionally surgeons reviewed every patient post-operatively.[3] However, in a bid to save resources and cut costs many patients undergoing some elective procedures are now discharged without any formal outpatient follow-up. Post-operative telephone review has been proposed as an alternative method of follow-up for patients who have underwent surgical procedures with an anticipated, inherent, low risk of complication.[1] A telephone screening service of carefully selected post-operative surgical patients will help reduce routine out-patient reviews. This should facilitate more rapid appointments for new patients thereby helping meet government targets of time to assessment and treatment.

Patients undergoing selective minor emergency or elective procedures, without any post-operative complication, at our institution are followed up by a structured telephone review instead of the traditional surgical outpatient review. It occurs six weeks post-operatively and is nurse-led. Our study objectives were to review patients' satisfaction of this method of follow-up, assess cost effectiveness over a one-year period and to compare our practice with that of other general surgical units in Northern Ireland (NI).

PATIENTS AND METHODS

A system of telephone review at our institution was established in 2004. The ward for the admission of most elective cases is the Elective Surgical Unit. The most commonly undertaken procedures, which are followed up post-operatively with a telephone consultation include laparoscopic cholecystectomy, inguinal and paraumbilical hernia repair, other hernia repair (e.g. incisional or ventral herniae), varicose vein surgery, circumcision, excision of subcutaneous lesions (e.g. large lipomas), carpal tunnel release and appendicectomies. Structured post-operative telephone review forms are

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TABLE 1.

Patient Satisfaction Questionnaire

Question	Strongly agree	Agree	No strong opinion	Disagree	Strongly disagree
The outcome of your surgery was satisfactory					
Your pre-operative assessment in the outpatient clinic was satisfactory					
You expected to be followed up post-operatively					
You expected this follow-up to be in the surgical outpatient clinic					
You expected to be reviewed by a doctor post-operatively					
You were happy with being reviewed by a nurse					
You were happy with the telephone review					
You were happy with the timing of the telephone review					
You could discuss your worries over the phone					
It would have been easier to discuss your concerns at an outpatient clinic					
Overall you were happy with the service provided					
You would recommend the service to a friend					

completed six weeks following discharge, by trained senior surgical nurses. This consultation addresses pain and analgesia requirements, wound healing and a return to baseline function. It also asks specifically about resolution of symptoms following carpal tunnel release, recurrence of hernias and jaundice, vomiting or diarrhoea following laparoscopic cholecystectomy. Based on the response of the patient they are either discharged back to their general practitioner (GP) or a surgical outpatient appointment is made.

Completed telephone follow-up forms were available for retrospective review for a three-year period from September 2005 to September 2008. The primary outcome was the requirement for surgical outpatient review, while the secondary outcome was the nature of any complication. The cost of a single surgical outpatient review was obtained from the finance department at our institution. The cost of review actually decreased for each year that was studied being £112.04, £111.05 and £95.35 per review for the one year periods between 2005 and 2008. An average cost of review was calculated at £106.15 and for clarity this was used to estimate the cost savings of the telephone review service compared with routinely reviewing all patients at the outpatient centre. The costs involved in running the telephone follow-up service were estimated by the hospital finance department at £2048 per annum based on the salary of a senior nurse for 3 hours per week (52 weeks per year), the average cost of telephone calls (including landline and mobile) and 201 second class stamps.

Fifty patients were contacted prospectively by telephone with a questionnaire (Table 1) to assess general expectation for post-operative follow-up and satisfaction of the follow-up service provided. Responses to both positive and negative statements were recorded using a Likert scale.

Finally, in order to compare our practice with that of other surgical units performing the above procedures, a postal questionnaire was sent to all 68 general and vascular surgeons in NI, assessing individual preferences for patient follow-up. Consultants were asked to simply document how they reviewed these patients, with categories of always, occasionally, subsequent to a complication or never. For simplicity the latter two options were combined within the results section as "no routine review".

RESULTS

A total of 1,378 patients received a telephone review from September 2005 to September 2008 including 459 inguinal, 68 paraumbilical and 38 other hernia repairs; 453 laparoscopic cholecystectomies, 193 varicose veins, 43 appendicectomies, 17 subcutaneous lesion excisions, 22 carpal tunnel releases and 19 circumcisions. One thousand one hundred and seventy-seven (85.4%) of these patients were successfully contacted, while 201 (14.6%) did not respond despite multiple attempts. Of the respondents, only 147 (10.7%) required further outpatient follow-up, thereby saving 1231 outpatient reviews, equivalent to £130,670 or an average of £43,557 per annum. If the cost of operating the service is deducted this leaves a nett saving of £41,509 per annum.

The procedures that most commonly required outpatient review were laparoscopic cholecystectomy (n=47/453; 10.4%), inguinal hernia repair (n=46/459; 10.2%) and varicose vein surgery (n=23/193; 11.9%). In total, 80 (54.4%) of the 147 patients, who required outpatient review, attended for assessment of post-operative pain, where the majority were following laparoscopic cholecystectomy (n=34; 23%), inguinal hernia repair (n=30; 20%), and varicose vein surgery (n=9; 6%). Forty-five (31%) patients required review due to wound healing, complaining of discharge (n=16; 11%), swelling (n=15; 10%), inflammation (n=5; 3%) and numbness (n=9; 6%). Four patients following hernia repair, both inguinal (n=2; 1%) and paraumbilical (n=2; 1%), requested review regarding possible recurrence. Finally, 4 (2%) varicose vein surgery patients requested review to discuss the removal of further veins.

Thirty-nine (78%) patients either agreed, or strongly agreed, that they expected to be followed up post-operatively, with 29 (58%) expecting this in the outpatient department and 30 (60%) expecting review with a doctor. However, all 50 (100%) patients were satisfied with the nurse led telephone review. Forty-six (92%) patients were happy with the timing of the review while only 9 (18%) patients considered it easier to discuss any concerns at an outpatient clinic. Only one (2%) patient was dissatisfied with the outcome of surgery but all 50 (100%) patients were happy with the overall service provided and would recommend it to a friend.

Fifty-three (78%) consultants responded. Only 52 completed consultant questionnaires were analyzed, however, as one of the respondents no longer performed any of the aforementioned procedures. Consultant review practices are summarized in Table 2 but in the vast majority of cases patients are usually offered no routine review. Those who always, or occasionally, review patients post-operatively varies according to the operation performed: inguinal hernia repair 27.6%, paraumbilical hernia repair 34.6%, hernia repair (other) 65.2%, circumcision 21.6%, varicose veins 40.0%, laparoscopic cholecystectomy 33.4%, subcutaneous lesion 13.0% and appendicectomy 2.2%.

Review of the qualitative section of the questionnaire showed a telephone review service is in place in another institution, while a further hospital has a rapid access Surgical Assessment Unit, where patients with complications can be rapidly reviewed. Interestingly, three consultants reported that they review all laparoscopic hernia repairs. Finally, thirteen consultants who review following a reported complication suggested that they routinely discharge the majority of their patients without follow-up. They indicated, however, that patients are provided with an open invitation to contact medical secretaries, the ward or the rapid access unit in the event of a complication.

DISCUSSION

From its inception, the telephone has become increasingly more important in delivering health-care. Indeed, Bell's first recorded telephone call was for medical attention after accidentally spilling sulphuric acid on himself. There is evidence to support telephone consultations due to increased patient satisfaction, less time waiting in outpatient clinics, reduced travel expenses and potential for increased frequency of contact.[1] They are used in the management of asthma, diabetes, epilepsy, traumatic brain injury, rheumatology, mental health and oncology.[3] Both doctor and nurse-led triage services have also been successfully piloted in emergency departments and general practice.[3, 4] Telephone follow-up has also proved successful after ambulatory or day case surgery to reassure patients and manage potential early complications in the first two days.[5]

In the background of a high discharge rate at the initial review following transurethral prostatectomy, Brough *et al*, in 1996, showed that a nurse-led telephone review service was a valuable screening tool to identify patients who require an outpatient review.[6] Since then, the concept of screening patients through the medium of a nurse-led telephone consultation has been successfully implemented in various aspects of surgery. In 2000, Rosbe *et al* stated that a telephone follow-up at 3-4 weeks following adenotonsillectomy is safe and cost-effective in paediatric patients, being also desirable to parents.[7] In 2007, McVay *et al* demonstrated that it was appropriate for other paediatric surgical procedures. For a similar list of surgical procedures to our own, post-operative telephone follow-up was deemed to be safe and preferable to patients' families.[3]

The main benefit of this form of review is the reduction of unnecessary reviews, following procedures with a low risk of complications, when most are likely to be discharged at initial review. This short consultation is frustrating to the patient

Table 2.

Consultant Review Practices. Individual preferences for follow-up recorded as a number and percentage of those surgeons actually performing the procedure. (SOPD = Surgical Outpatient Department).

Operation	SOPD review always (%)	SOPD review occasionally (%)	No routine review (%)
Repair of inguinal hernia	4 (8.5)	9 (19.1)	34 (72.3)
Repair of paraumbilical hernia	5 (10.2)	12 (24.4)	32 (65.3)
Repair of hernia (other)	5 (10.9)	25 (54.3)	16 (34.8)
Circumcision	2 (5.4)	6 (16.2)	29 (78.3)
Varicose veins	10 (25.0)	6 (15.0)	24 (60.0)
Laparoscopic cholecystectomy	8 (17.8)	7 (15.6)	30 (66.7)
Excision of subcutaneous lesion	0 (0)	6 (13.0)	40 (87.0)
Appendicectomy	0 (0)	1 (2.2)	45 (97.8)

and carries a high risk of non-attendance, thereby wasting valuable resources. However, our study confirms that patients do expect post-operative follow-up in some form, if only to provide simple reassurance. Our high patient satisfaction with post-operative telephone review demonstrates that this service can adequately provide the reassurance and review patients expect.

The small numbers (10.7%) of those contacted requiring formal review is comparable to other similar studies. Wedderburn *et al*, in a postal questionnaire, two weeks following inguinal hernia repair and varicose vein surgery found that only 6.7% of patients considered outpatient review beneficial.[8] In this study, due to the implementation of thorough follow-up procedures at our unit, non-responders were included in the group of patients who didn't require further review. The unit protocol is for up to two attempts by telephone at six weeks to be made to contact the patient, followed by a standard letter requesting the patient to contact the unit. The 201 uncontactable patients would have been educated thoroughly on this form of follow-up and been given the ward number to contact if any concerns arose. Therefore it is unlikely they required referal or re-admission to our unit or another surgical unit without contacting the team first. Optimum timing of review is debatable, but since telephone follow-up is intended to replace traditional review it is usually scheduled 4-6 weeks post-operatively. Patients should receive adequate education on discharge, with early complications managed in the usual manner.

Certain procedures require formal review, which explains the low numbers of these in our cohort. The particularly difficult nature of an incisional hernia repair may be a prerequisite for outpatient review. Similarly, following unilateral release of the carpal tunnel, the patient may return for consideration of contralateral release. Finally, the need to communicate histopathology results may be a reason for occasionally reviewing patients.

A limitation of our study is that of the 147 patients reviewed we have not formally assessed whether this appointment added anything to patient care over and above what the GP would provide. We appreciate this is relevant as one could argue whether telephone review is necessary or whether discharging all patients to the care of the GP with review only on request is more appropriate. However, the nurses in charge of the scheme are experienced senior surgical staff and do refer many patients to their GP first, therefore we feel that after screening, these reviews would have been approriate.

The postal questionnaire of consultants had an impressive response rate probably due to its brevity. There are variable preferences in review patterns. For seven of the eight operations studied the vast majority of consultants discharge their patients with no routine review yet we have shown that patients expect post-operative follow-up. A post-operative telephone review service is a cost-effective method of providing the follow-up patients expect but often do not receive. The most interesting point from the survey however, is that for almost all of the operations studied, some consultants still review all patients. This is most striking following laparoscopic cholecystectomy and varicose vein surgery with 17.8% and 25%, respectively. This represents a significant number of reviews, which could be better facilitated via a nurse-led telephone review service and thus free up resources for more appropriate usage.

In conclusion, this study confirms that patients expect post-operative follow-up, even for procedures we would consider as routine. A nurse-led telephone review provides this adequately, is acceptable to patients, cost-effective and reduces the number of unnecessary outpatient reviews.

The authors have no conflict of interest.

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Paper

Childhood Circumcision in Northern Ireland: A barometer of the current practice of general paediatric surgery

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ABSTRACT

Purpose: Studies undertaken in England and Scotland have identified a decrease in the number of circumcision operations being performed during childhood. The aims of this study were two-fold. Firstly, to determine the trend in circumcision operations performed in boys in Northern Ireland over a ten year period. Secondly, to compare the number of operations performed by paediatric surgeons with the number performed by general surgeons over the same period.

Method: Data were collected from the Northern Ireland Department of Health and Social Services and Public Safety. A retrospective analysis was conducted of the number of circumcisions performed in boys aged between 0 and 13 years for the year beginning 1st September 1991 to the 1st of September 1992 and for the year beginning 1st September 2001 until the 1st of September 2002.

Results: 769 circumcisions were performed in the year 1991 to 1992 compared with 264 in the year 2001 to 2002, representing a 66% decrease. In the ten year study period, the number of circumcisions performed by general surgeons fell by 71% whilst specialist paediatric surgeons performed 56% less.

Conclusions: The decrease in rates of circumcision in boys aged 0 to 13 years in Northern Ireland is consistent with trends in the remainder of the United Kingdom. The results also suggest a greater decrease in the proportion of circumcisions being performed by general surgeons in district general hospitals compared to those performed by paediatric surgeons.

KEYWORDS: Circumcision, paediatric surgery, general surgery

INTRODUCTION

Circumcision, arguably, is one of the oldest and most widely practised surgical procedures in the world.[1] From its early origins in religious and tribal rituals, circumcision continues to be practised today worldwide. In recent times, there has been growing concern that too many circumcisions are carried out unnecessarily in neonates and boys. Several studies undertaken in England and Scotland have identified a decrease in the number of operations being performed.[2,3] To date there has been no review of trends in circumcision rate within Northern Ireland.

The aim of this study is to review the numbers of circumcision procedures performed in boys aged 0-13 years in Northern Ireland over a ten year period and to analyse the trend in the procedures performed by paediatric surgeons and general surgeons over the same period.

METHOD

Data were collected from the Department of Health, Social Services and Public Safety in Northern Ireland. The total number of circumcisions performed in Northern Ireland in the 0 to 13-year age group during periods 1st September 1991 to 1st September 1992 and 1st September 2001 to 1st September 2002 was ascertained. Data from the Northern Ireland Census Report [4] were used to calculate the percentage circumcision rates during these years.

Figures specific to each hospital in which the circumcisions had been performed were also available, allowing comparison between the number of circumcisions performed by general surgeons and paediatric surgeons over the same period.

RESULTS

A total of 769 circumcisions were performed in the year 1991-1992, representing 5.7% of boys aged 0-13 years. A total of 264 circumcisions were performed in the year 2001-2002, representing 1.9% of boys aged 0-13 years. Overall, this signifies a 66% decrease in the number of circumcisions performed in the ten year period.

In the year 1991-1992, circumcisions were performed in eleven hospitals throughout Northern Ireland. In total, 257 (33%) operations were performed by paediatric surgeons and 518 (67%) by general surgeons during this year.

In the year 2001-2002 circumcisions were performed in 9 hospitals. Overall, 113 (43%) were performed by paediatric surgeons and 151 (57%) by general surgeons. The number of circumcisions carried out by general surgeons dropped by

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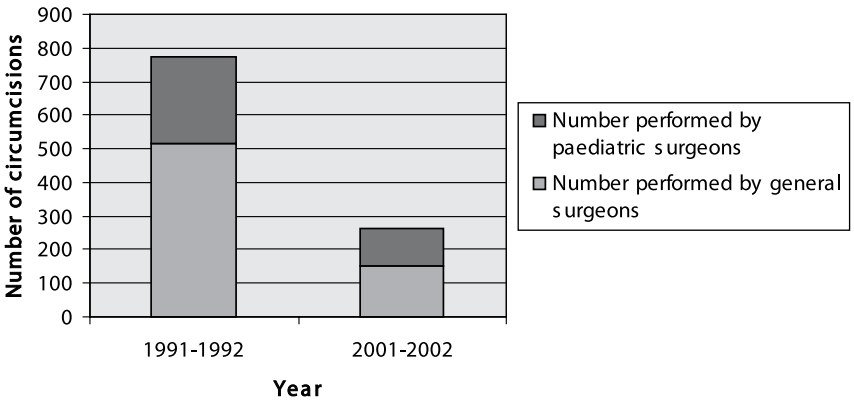

Fig 1. Circumcision Trends in Northern Ireland over the ten year study period

71% in the 10 year period compared with a 56% reduction by paediatric surgeons.

DISCUSSION

The decrease in rates of circumcision seen in this study is consistent with trends noted across the remainder of the UK. Furthermore, circumcision rates in boys within Northern Ireland are currently in line with the target of 2% suggested by Rickwood et al.[2] However, there are a number of limitations to this study. The retrospective data were derived from DHSSPS statistics, a potential source of bias. Unfortunately, the indications for circumcision were not available, making it impossible to evaluate the impact of changes in disease prevalence or trends in non-therapeutic circumcision during the study period. What many surgeons would have considered in the past to be "phimosis" (and treated by circumcision) was in fact physiological non-retractile foreskin. Therefore, the most probable explanation for the reduction in circumcision rate is the improved understanding of the natural history of physiological non-retractile foreskin and the pathophysiology of phimosis.

This study also indicates that the proportion of circumcisions in Northern Ireland being performed during childhood by general surgeons has decreased substantially over the study decade. Circumcision and other general paediatric surgical procedures have traditionally fallen within the remit and interests of both general and paediatric surgeons. Recent increases in the workload of consultant paediatric surgeons have been noted by the British Association of Paediatric Surgeons as fewer general surgeons continue to perform general paediatric surgery.[5] The observed decrease in circumcisions being performed by general surgeons may be due to recent changes in general surgical training, which have reduced opportunities for surgeons in training to acquire experience in paediatric surgery.[6] This highlights an important and potentially worrying trend in the distribution of general paediatric surgery provision in the Province.

The authors have no conflict of interest

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Paper

Rheumatoid arthritis patients with active disease and no history of cardiac pathology have higher Brain Natriuretic Peptide (BNP) levels than patients with inactive disease or healthy control subjects.

Armstrong D J, Gardiner P V, O'Kane M J

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ABSTRACT

Background Rheumatoid arthritis (RA) is associated with increased incidence cardiac failure. It is yet unclear how much the increased incidence is secondary to ischaemic damage, or whether inflammatory cytokines might have a direct effect on the myocardium

Objectives To establish if patients with active rheumatoid arthritis but no history of cardiac disease have higher serum levels of brain natriuretic peptide (BNP), than patients with less active RA, or disease-free controls.

Methods 90 patients with RA and 31 healthy control subjects were recruited. Each was screened to exclude previous history of cardiac disease. RA disease activity was measured using the DAS28 assessment, and other demographic, physical and laboratory tests performed. Serum BNP levels were measured in all subjects.

Results There was no difference in the age, percentage females or BMI between the RA and control subjects. Median BNP in the RA patients was 80.0 pg/ml (IQR 38.0-132.0) compared with 48.5 (26.0-86.0) in the control subjects ($p=0.017$). There was a significant correlation between DAS28 and serum BNP in the RA group, $r=0.37$, $p<0.01$. RA patients were divided into three groups according to DAS28 scores. Patients with very active disease (DAS28>5.1) had significantly higher BNP levels than patients with moderately active disease (3.2<DAS28<5.1) or inactive disease (DAS28<3.2) (both $p<0.01$). Median BNP of RA patients with inactive disease did not differ from Controls.

Conclusion RA patients with no history of cardiac disease have higher serum BNP levels than healthy control subjects. RA patients with active RA have higher BNP levels than RA patients with moderately active or inactive disease, raising the possibility of a directly depressive effect of inflammatory cytokines on the myocardium

BACKGROUND

Rheumatoid arthritis (RA) is now viewed as a systemic autoimmune condition rather than simply an inflammatory arthropathy, with much of the increased mortality attributable to accelerated atherosclerosis and ischaemic heart disease. Alongside coronary artery disease, the incidence of congestive cardiac failure (CCF) is increased in RA[1]. There are several possible explanations for this, including ventricular failure secondary to ischaemic myocardial damage, but inflammatory cytokines produced in RA, such as TNF alpha, have also been shown to have a directly injurious effect on cultured myocytes, including the induction apoptosis and fibrosis[2]. A recent study has shown that serum concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), a hormone produced by the cardiac ventricles in response to stretch and elevated in cardiac failure, are correlated with levels of inflammatory markers and disease activity in RA, and higher than matched controls[3]. However, the study included significant numbers of patients and controls with a history of cardiovascular disease, which might have caused subclinical myocardial impairment. In this study, we tested the hypothesis that serum BNP levels are elevated in RA patients without any previous history of coronary artery disease or cardiac impairment, and that patients with clinically active disease as measured by the Disease Activity Score (DAS28) had higher serum BNP levels than patients with well-controlled disease.

METHODS

Subjects were over 18 years of age and were recruited at rheumatology outpatient clinics in the Erne Hospital, Enniskillen, Northern Ireland. All gave written informed consent.

Control subjects did not have rheumatoid arthritis, any other systemic inflammatory arthritis, or any other condition which might be associated with systemic inflammation (such as chronic chest disease). They were recruited from

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patients referred to a general rheumatology clinic with complaints such as lateral epicondylitis, minor osteoarthritis of the hands and muscular back pain. RA patients fulfilled the ACR classification criteria for rheumatoid arthritis[4], and were excluded if they had a history or either cardiac failure, coronary artery disease or unexplained chest pain, or other chronic inflammatory conditions such as COPD or renal failure. The hospital chart was also examined for any previous diagnosis or investigation of coronary artery disease or cardiac failure. Patients receiving loop diuretics or spironolactone were excluded even if there was not a definite diagnosis of cardiac failure. Patients were also excluded if they were taking medication which might interfere with measurement of BNP levels, such as glitazones or beta-blockers. Thiazide diuretic therapy for hypertension was not counted as a diuretic under exclusions.

The Disease Activity Score based on 28 joint assessment (DAS28) is a validated tool for estimating RA disease activity[5]. Patients with a score of 5.1 or greater are considered as having very active disease, while those with a score of less than 3.2 have inactive disease. A number of other demographic data, treatment history and laboratory tests was collected as outlined in table 1.

Serum BNP was measured on an Abbott Axsym analyzer using a MEIA [Microparticle enhanced immunoassay]. The lower limit of detection for the CRP assay used was <5 mg/l.

Statistical analysis was performed using the SigmaStat 3.1 program (Systat Software Inc). Groups were compared using rank sum order, Spearman's rank correlation and stepwise regression as appropriate.

The study protocol was approved by the National Research Ethics Service (Study Number (08/NIR01/39).

RESULTS

31 healthy control subjects and 90 subjects with RA were recruited. All were Caucasians. There was no significant difference in the age, percentage of females, body mass index (BMI) or use of NSAIDs between control subjects and RA patients. There was however a significantly greater median level of serum BNP in the RA group as compared with the controls (Table 1).

Serum BNP levels in the RA subjects correlated with DAS28 ($r=0.37$, $p<0.01$). We also observed a correlation between increasing age and BNP, although this only reached significance in the RA group ($r= 0.41$, $p<0.01$). There was no significant correlation with disease duration in the RA patients, or BMI in either group. When stepwise regression was performed, neither the introduction of BMI, age or ESR to the equation significantly added to the ability of DAS28 to predict BNP levels.

RA patients were divided into three groups according to DAS28 scores as described under Methods. Patients with active disease (DAS28>5.1) had significantly higher BNP levels than patients with moderately active disease or inactive disease ($p<0.01$). Median BNP of RA patients with inactive disease did not differ from Controls (Table 2).

DISCUSSION

This study demonstrates that even in subjects with no history, signs or symptoms of cardiac disease, RA patients have significantly higher BNP levels than control subjects, and that RA patients with active RA have significantly higher levels than those with moderately active or well-controlled disease. This difference is not explained by differences in age, BMI or disease duration. Although we cannot entirely exclude past ischaemic damage as a cause of cardiac strain in these patients, the higher BNP levels in the most active RA group suggests that the inflammatory milieu might be a exerting a direct effect on the myocardium, separate from any ischaemic damage. There was also a trend towards shorter disease duration and lower BMI in the most active group (data not shown), again suggesting that the higher BNP levels were linked with current inflammation rather than established damage.

There have been a small number of studies examining BNP in the setting of RA, demonstrating that RA patients have higher levels than matched controls. Most of these studies have included patients with a history of significant established ischaemic heart disease, increasing the likelihood of ischaemic ventricular damage contributing to BNP elevation.

A recent paper by Solus et al[3] showed correlations between disease activity, CRP, TNFalpha and IL-6 with NT-proBNP. However 20% of the longstanding RA patients had a history of angina, MI, stroke or coronary artery procedure, compared with just 8% of controls, increasing the risk that their findings in RA patients were related to previous damage, and that their findings between the two groups might have been influenced by more subclinical damage in the RA group. A 10-year longitudinal study in Norway also showed a link between CRP

TABLE 1.

Patient, disease and treatment characteristics

	Controls (n=31) (median, IQR)	**All RA (n=90) (median, IQR)**	**P value**
Age (yrs)	59.0 (50.3-65.0)	62.0 (53.0-70.0)	0.30
% female	77.4%	80.0%	0.83
BMI (kg/m2)	27.6 (25.2-31.6)	25.9 (23.3-31.4)	0.13
ESR (mm/hr)	12.0 (6.8-18.0)	21.0 (13.0-42.0)	<0.001
CRP (mg/l)	<5	8.0 (5.0-23.5)	<0.001
Regular NSAID use (%)	32.3%	46.7%	0.23
Treatment for hypertension	29.0%	34.7%	0.36
Serum BNP (pg/ml)	48.5 (26.0-86.0)	80.0 (38.0-132.0)	0.017

Table 2.

Serum BNP levels in Control subjects and RA patients grouped by disease activity

	Controls	Inactive RA	Moderately Active RA	Very Active RA
n	31	25	33	32
BNP (IQR) (pg/ml)	48.5 (26.0-86.0)	42 * (24.3-90.0)	76** (35.0-115.0)	101.0 (77.5 – 277.5)

Inactive RA – DAS28<3.2, Moderately Active RA – 3.2<DAS28<5.1, Very Active RA – DAS28>5.1

**Serum BNP Inactive v Active, p<0.01 ** Serum BNP Moderately Active v Active, p<0.01*

and NT-proBNP both at baseline and at 10 years, but again did not exclude those with ischaemic heart disease[6].

Although we did not perform echocardiographs on patients, and therefore might still have included patients with subclinical ischaemic damage or diastolic dysfunction, we believe our exclusion of any suspicion of previous heart disease increases the chances that our findings are predominantly due to direct action of inflammatory proteins on the myocardium. Moreover, even in patients with incident heart failure, RA patients are more likely to have preserved left ventricular ejection fraction[7]. The chances of detecting significant heart failure on echocardiograph in a group of RA patients without any history, symptoms, signs or treatment of the disease is very small; median ejection fraction in a group of RA patients without clinical cardiovascular disease was recently found to be 67%, only slightly lower than a control group with 71% (even if achieving statistical significance in the study[8]), and other groups have identified definite left ventrolic systolic dysfunction in only 5% of RA patients in the outpatient setting, many of whom had a history of ischaemic heart disease and would therefore have been excluded from this study[9].

We might have examined other markers of inflammation, such as IL-6 or TNF alpha, but consciously chose DAS28 as our main outcome for disease activity, so as to make the study as relevant as possible to clinical practice. Other control groups, such as patients with psoriatic arthritis (PsA), might also have been chosen, but the different cytokine profile in PsA would make interpretation difficult, until the cytokines chiefly responsible for direct myocardial damage have been positively identified.

Further insights might be gained by re-measuring BNP levels in the same patients once disease activity had been treated; others have shown that the use of ACE inhibitors improves endothelial function in RA[10] and reduces ESR (11). Whether or not early, prophylactic use of ACE inhibitors in RA, as in diabetes mellitus, improves long term morbidity and mortality remains to be seen.

We believe this study adds weight to the argument that chronic inflammation not only accelerates atherosclerosis, but might also have a directly stressful effect on the myocardium in patients without any history of ischaemic heart disease. It provides yet more evidence that prompt and effective suppression of inflammatory activity in RA is essential not only to preserve synovium and cartilage, but also endothelium and myocardium.

In summary, elevated serum levels of BNP are associated with ventricular strain and increased risk of cardiac events and death in the general population. We found that RA patients with active disease have high levels of BNP as compared both with inactive RA and healthy control subjects, despite no history or ischaemic heart disease or cardiac failure.

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Short Report

Screening of clinical, food, water and animal isolates of *Escherichia coli* for the presence of blaCTX-M extended spectrum beta-lactamase (ESBL) antibiotic resistance gene loci

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ABSTRACT

A small study was carried out in order to examine the molecular presence of bla CTX-M gene phylogenetic groups in *E. coli* (n=317) isolated from food (n=54), water (n=7), animal sources (n=69), using consensus bla CTX-M primers and PCR, in addition to human faecal isolates (n=69) and VTEC O157:H7 (n=64). None of the clinically significant faecal VTEC O157:H7 isolates were shown to carry blaCTX-M type phylogenetic groups, nor were such phylogenetic groups observed in any of the food, water and animal isolates. One community faecal isolate (1/69; 1.4%), dating from 1997, carried this phylogenetic group. As recent work has indicated that a significant proportion of such phylogenetic groups are carried in community isolates of *E. coli* with little or no hospital contact, it is important that surveillance is increased to identify potential source(s) and reservoirs of such resistance in the community. Further prospective surveillance is thus required to help elucidate the origins of such phylogenetic group in the community. The significance of this study is that the ESBL-producing *E. coli* associated with local hospital outbreaks is not commonly found in local food, water or animal sources. In addition, given that ESBL-producing *E. coli* is now a significant organism, both in hospitals and nursing homes in Northern Ireland, this report demonstrates that such organisms were present in the community, as early as 1997.

Keywords: esbl, CTX-M β-lactamases, community infections, food, animal, molecular epidemiology, PCR.

INTRODUCTION

Extended spectrum β-lactamase (esbl) producing organisms were first described in Germany in 1983 from *Klebsiella pneumoniae*, following the introduction of the new oxyiminocephalosporins, including cefotaxime, aztreonam and ceftazidime.[1] These enzymes hydrolyze oximino-β-lactams, including the third generation cephalosporins, thereby conferring antibiotic resistant in those organisms which carry the esbl resistance determinant gene loci.[2] Such loci are carried in several genera with the *Enterobacteriaceae*, including *Klebsiella, Enterobacter, Escherichia* and *Salmonella*.[1] For recent reviews on esbls and *Enterobacteriaceae*, please see Rupp and Fey[3] and/or Shah *et al.*[4] and Bonnet[5] for a review on CTX-M mediated resistance.

Recently Woodford *et al.*[6] have described the emergence of a bla CTX-M-15 esbl in *E. coli* from 42 centres in the UK, including Northern Ireland, where overall, 70 (24%) were reported to originate from community patients, many whom had limited hospital contact and where 12 centres had community isolates. Given the widespread distribution of this bla CTX-M type phylogenetic group, particularly from community isolates, it is important to identify the distribution of such phylogenetic groups in *E. coli* in the community, which may be a reservoir and potential sources of bla CTX-M type phylogenetic groups, promoting cephalosporin resistance in *E. coli* associated with community acquired urinary tract infections (UTIs).

Therefore, it was the aim of this small study, to employ molecular methods to screen animal, food and water isolates of *E. coli* for the presence of bla CTX-M type phylogenetic groups, as well as to identify the presence of these phylogenetic groups in a comprehensive collection of community acquired faecal VTEC O157:H7 isolates from throughout Northern Ireland.

MATERIALS & METHODS

Source of E. coli isolates

E. coli isolates (n=317) as detailed in Table 1, were examined

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in this study. All isolates were confirmed phenotypically as *E. coli*, by employment of a combination of biochemical assays and the API20E Identification scheme (Biomerieux Ltd., UK), using standard laboratory identification methods In addition, all verocytotoxigenic *E. coli* O157:H7 were confirmed serologically and by employment of a multiplex PCR assay of virulence gene determinants (VT1+VT2+*eae* gene loci), as previously described.[7]

DNA extraction, PCR amplification & amplicon detection

E. coli isolates (table 1) were subcultured onto Columbia agar base (CM331, Oxoid Ltd., Basingstoke, England), supplemented with defibrinated horse blood 5% [v/v] (Oxoid). All DNA isolation procedures were carried out in a Class II Biological Safety Cabinet in a room geographically separate from that used to set up reaction mixes and also from the "post-PCR" room in order to minimise the production of false positive results and in accordance with Good Molecular Diagnostic Practice (GMDP), as defined in the guidelines of Millar *et al.*[8] PCR amplification of the $_{bla}$CTX-M gene loci was performed in accordance with a previously published method[2]. During each run molecular grade water was included randomly as negative controls and appropriate DNA template from a reference isolate of *Enterobacter cloacae* (CTX-M 9) and a wild characterized *E. coli* (CTX-M 15) obtained from the Northern Ireland outbreak,[6] were included as positive controls. In addition, the MA1/MA2 primer combination were challenged with seven non-esbl producing organisms, including *E. coli* (n=2), *Enterobacter cloacae* (n=1). *Klebsiella pneumoniae* (n=2) and *Klebsiella terrigena* (n=2). In addition, 16 wild type clinical esbl-producing *E. coli* isolates from Northern Ireland, which were confirmed as CTX-M 15 subtype, were also included, as positive controls, as well as an esbl-producing *Klebsiella oxytoca* isolate.

Following amplification, aliquots (15µl) were removed from each reaction mixture and examined by electrophoresis (80V, 45min) in gels composed of 2% (w/v) agarose (Gibco,UK) in TAE buffer (40mM Tris, 20mM acetic acid, 1mM EDTA, pH 8.3), stained with ethidium bromide (5µg/100ml). Gels were visualised under UV illumination using a gel image analysis system (UVP Products, England) and all images archived as digital (*.bmp) graphic files.

RESULTS AND DISCUSSION

Employment of the MA1/MA2 CTX-M consensus primer pair was successful at identifying the esbl gene locus in all esbl-producing isolates, whereas no PCR amplicon was produced on examination of the non-esbl producing organisms examined, including non-esbl producing *E. coli* (data not shown). Examination of the 317 *E. coli* isolates, as detailed in Table 1, produced only one positive result, which was isolated from a faecal specimen of a female patient in the community, where no significant growth or faecal pathogens were detected. None of the VTEC O157:H7 isolates examined were positive for the presence of an esbl gene locus.

CTX-M-producing *E. coli* have been described recently as a rapidly developing problem in the UK, where the study of Woodford *et al.*[6] demonstrated the presence of CTX-M-15 in *E. coli* originating from 42 centres throughout the UK. Another report in the UK by Munday *et al.*[9] demonstrated that surveillance of 1000 faecal samples collected and screened at York Hospital during the last quarter of 2003, resulted in 17 (1.7%) CTX-M phylogenetic groups being identified, including CTX-M-9 (n=9), CTX-M-15 (n=5) and CTX-M-14 (n=3). Both these studies have indicated that such phylogenetic group occur in community isolates of *E. coli*, where there has been no or very limited contact with the hospital environment.

Locally in Northern Ireland, a recent report by Loughrey *et al*[10] demonstrated the presence of ESBL-producing *E. coli* in 120/307 (39%) faecal specimens from 13 long-term care facilities. This report also showed that 60 (50%) of 120 ESBL *E. coli* -positive residents had no hospital admissions since January 2004. The majority of ESBL-producing *E. coli* had phenotypes consistent with production of a CTX-M enzyme. Isolates assigned presumptively to strain A by PCR accounted for 59/120 (49%) ESBL-producing *E. coli*. Although distinct from strain A, most of the other 61 isolates also produced a group 1 CTX-M ESBL; these isolates had varying antibiograms, suggesting multiple strains. In the eastern district of Belfast, 50/175 samples were ESBL-producing *E. coli* -positive, and 38 (76%) of these were strain A; in the other districts 70/132 samples were positive, but only 22 (31%) were strain A. The proportion of strain A isolates varied widely in different nursing homes, ranging from 0/11 ESBL-producing *E. coli* in one centre to 9/9 in another. Epidemic strain A was the predominant ESBL-producing *E. coli* strain among nursing home residents in Belfast and this organism was found in many residents with no history of recent hospital admission.

Although the epidemiology of esbl-producing *E. coli* with the CTX-M phylogenetic groups have been more clearly defined in the hospital setting, the origins of esbl-producing *E. coli* isolates remain unclear in the community. Therefore, any attempts through surveillance studies, to help define these origins should be encouraged.

Recently, two independent epidemiological studies in non-hospitalized patients demonstrated various risk factors for acquisition of an esbl-producing organism in the community. In the first study by Colodner *et al.*[11], 311 non-hospitalized patients with community-acquired UTIs, showed that (i) previous hospitalization in the past 3 months, (ii). antibiotic treatment in the past 3 months, (iii) age over 60 years, (iv) diabetes, (v) male gender, (vi) *Klebsiella pneumoniae* infection, (vii) previous use of third-generation cephalosporins, (viii) previous use of second-generation cephalosporins, (ix) previous use of quinolones and (x) previous use of penicillin, were significant risk factors for the acquisition of such an infection. In the second study by Borer *et al.*[12], 187 *Enterobacteriaceae* bacteremias were detected, of which 119 were community-acquired (63.6%), of which six cases were due to an esbl-producing organism. This study demonstrated that patients suffering from community acquired bacteraemia with an esbl were older and where urinary catheterization and bed-ridden conditions were significant risk factors and where such patients were more likely to suffer from complications and had a higher mortality. Although these studies identify several risk factors for developing an esbl-associated infection, there was no discussion in either study, as to where the esbl-producing

TABLE 1:

Description (origin, date) and presence of extended spectrum β-lactamase bla CTX-M phylogenetic groups in *E. coli* isolates examined in this study.

Description of isolates	Source	Number of isolates examined	Date of isolation of cultures	No. PCR esbl +ve (% +ve)	Comments
Human [clinical]					
Faeces	Human faeces submitted by GPs in the community and in-patient hospital wards	69	1997	1 (1.4%)	CTX-M PCR +ve specimen originated from female patient in the community.
VTEC O157:H7	Human faeces	10	1997	0	VTEC isolates referred to NIPHL* from primary diagnostic laboratories throughout N. Ireland
		18	1998	0	
		15	1999	0	
		11	September – December 2003	0	
		10	January – September 2004	0	
Animal [clinical]					
Clinical isolates	Equine	69	January – July 2004	0	
Environmental *E. coli*	Water Well water (n=4) Swimming pool (n=1) Bore hole water (n=1) Chlorinated tap water (n=1)	7	January – July 2004	0	Isolated from water submitted by Environmental Health Officers from throughout Northern Ireland
Environmental *E. coli*	Food (total)	54	April – June 2004	0	Isolated from foodstuffs submitted by Environmental Health Officers from throughout Northern Ireland
	Shellfish	28			
	Cooked meats	9			
	Rice	2			
	Sauces	2			
	Cooked restaurant meal	10			
	Pastry with cream filling	2			
	Vegetables/salads	1			

organisms originated in the community. Therefore it is important to be able to identify the origins of esbl-organisms in susceptible patient populations in the community.

Recent reports have demonstrated the presence of bla CTX-M phylogenetic groups in animals. Briñas *et al.*[13] demonstrated the presence of a CTX-M-14 from *E. coli* isolated from faecal material of health chickens, and Shiraki *et al*[14] demonstrated the presence of CTX-M-2 in *E. coli* from bovine faecal specimens and suggested that the acquisition of such phylogenetic group in the bovine *E. coli* isolates may have originated from cattle through the use of cephalosporins such as ceftiofur and that cattle could be a reservoir of CTX-M-2–producing *E. coli*. These concluded that continuous and strategic surveillance of antimicrobial-resistant bacteria in livestock is essential to suppress further dissemination of these bacteria into society at large.

Munday *et al*.[9] demonstrated that there was dissemination of CTX-M type esbls into the *Enterobacteraceae* by a variety of mechanisms of horizontal gene transfer. Furthermore, Liebana *et al.*[15] suggested that β-lactam resistance in animal isolates can be generated *de novo* and demonstrated the presence of an AmpC-like esbl in *Enterobacteraecaae* from turkeys, chickens, pigs and cattle. Therefore, it may be postulated that bla CTX-M loci in meat contaminated with viable organisms containing such phylogenetic groups may be one source of such phylogenetic groups for susceptible patients in the community.

Please correct to "In our limited study of E. coli isolates obtained from foods, waters and animal sources, in 2004, during which period, we were actively finding CTX-M-15 phylogenetic groups in clinical E. coli from blood culture, urine and sputum specimens, we were not able to detect the presence of any CTX-M esbl E. coli, from any non-human source. Shellfish were particularly targeted as they were collected from inshore marine waters, where the catchment area included agricultural run-off and sewage treatment works. No CTX-M phylogenetic groups were observed in *E. coli* from any food, water or animal isolate examined and likewise none of the VTEC faecal isolates showed any evidence of bla CTX-M involvement.

As recent work has indicated that a significant proportion of such phylogenetic groups are carried in community isolates of *E. coli* with little or no hospital contact,[6,9] it is important that surveillance is increased to identify potential source(s) and reservoirs of such resistance in the community, particularly in food animals and pets. Further prospective surveillance is thus required to help elucidate the origins of such phylogenetic groups in *E. coli* in the community.

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It is with deep regret and sorrow that the co-authors note the sudden death of their co-worker, Mr. Neville Heaney, who passed away during the preparation of this manuscript. This study was funded by the Research & Development Office, Department of Health, Northern Ireland (Infectious Disease - Recognised Research Group [RRG] 9.9).

The authors have no conflict of interest.

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Presidential Address

From then to now: lessons from developments in our understanding of the pituitary gland

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INTRODUCTION AND EARLY HISTORY

The classical definition of a hormone is of a chemical messenger which leaves one area of the body by the blood stream and, arriving at another part of the body, causes a change in behaviour there. This broad definition has been refined more recently by considerations of local actions at the site of production and of the influence of other agents (such as growth factors) at the site of action. The human pituitary gland is an ovoid structure, approximately six mm in diameter, and consists of two lobes, anterior and posterior. Its anatomical relationships are of importance (Fig 1). It is found above the sphenoid sinus and immediately below the optic chiasm. It is connected superiorly by a stalk to the hypothalamus. The blood supply is complicated and includes one of the portal systems in the body - the veins from the hypothalamus draining into the pituitary gland. Release of the posterior lobe hormones, oxytocin and vasopressin, is controlled neuronally, but release of the anterior lobe hormones, follicle-stimulating hormone, luteinising hormone, thyroid-stimulating hormone, adrenocorticotrophic hormone, prolactin and growth hormone, is controlled by stimulating and inhibiting hormones from the hypothalamus which are carried to the anterior lobe via the portal venous system. The net effect of any one of the anterior hormones does not simply depend on the stimulation or otherwise of its particular releasing hormone (with negative feedback effect) but is influenced by numerous other factors including higher CNS function. The complex regulation of the growth hormone (GH)/insulin growth factor 1(IGF-1) axis is illustrated by Fig 2. Developments of our knowledge of pituitary pathophysiology and management have only been made

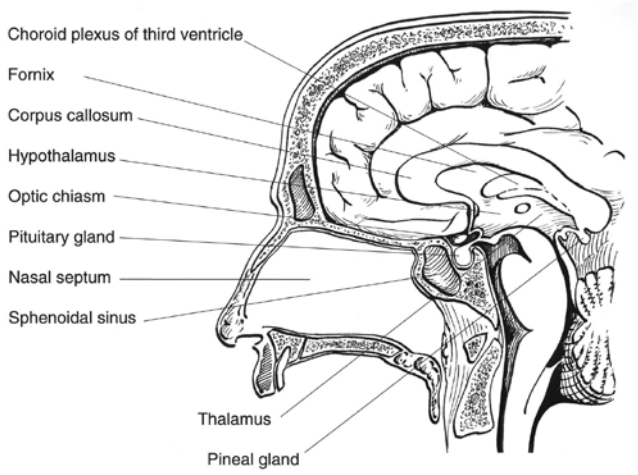

Fig 1. Sagittal section of head showing anatomical relationships of the pituitary gland

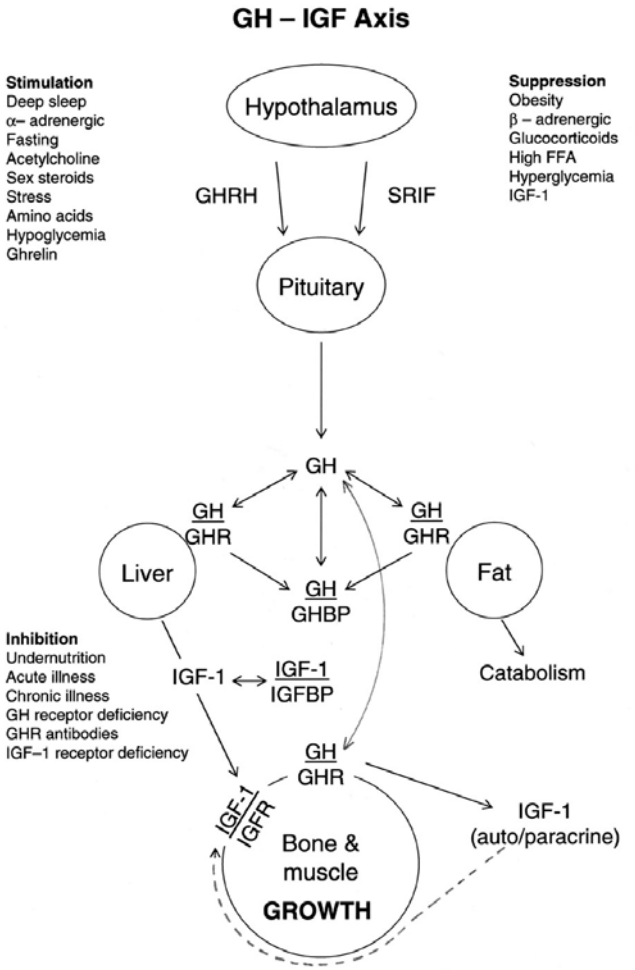

Fig 2. Physiological control of the growth hormone/Insulin growth factor 1 axis

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possible through the interaction of many disciplines with contributions being made by the various groups listed in Table 1. In recent times the contributions of dedicated laboratory staff, and their ability to give reliable, precisely calibrated hormone levels allow us to practice modern endocrinology. Our endocrine nursing staff are key members of the team and their educational input allows people with pituitary disease to look after their illness better because of their increased knowledge of their own disease.

There have been many false ideas and wrong turns during the development of endocrinology although some correct ideas (for example the removal of the ovaries or testes for control of breeding, the use of prolonged lactation to prevent pregnancy) have a long history, dating as far back as the ancient Egyptians and Chinese. Most importantly, Aristotle emphasised the importance of careful examination of the patient. Indeed, he recognised that eunuchs do not become bald and that obesity in females is associated with sterility. He also suggested that the brain is a gland which secretes cold humours to prevent overheating of the body by the fiery heart. His exhortation to careful examination came into its own with the recognition of a variety of endocrine diseases in the 19th century AD. However long before that we can find descriptions of giants in the Bible and it is possible that some had growth hormone producing pituitary tumours. Did Goliath have a classical visual field defect which allowed David to approach close enough to kill him with a stone from a sling? Later, in 2 Samuel 21 we find reference to familial giantism and in 2009 we now recognize a number of syndromes of familial pituitary disease.

Before moving to the history and development of endocrinology from the Middle Ages onward we need to pause and consider a view of Egyptian medicine expressed by Herodotos in the 5th Century BC. He stated "Medicine is practiced among them on a plan of separation: each physician treats a single disease, and not more: thus the country abounds with physicians, some undertaking to cure the diseases of the eyes, others of the head, others again of the teeth others of the intestine…" This is relevant to 21st century medicine where we must take care to use each other's knowledge to cross fertilise specialisms and to remain holistic in our approach to medical practice. General medical societies such as our own Ulster Medical Society can do much to foster this approach.

The middle ages were dark for the development of endocrinology. Galen had suggested that blood flows to and fro in the arteries carrying vital spirit to the various parts of the body. Harvey, to the contrary, recognized that blood circulates. Following on from this the important team of Lower (1631-1691) and Willis (1621-1675) are credited by some for the discovery that substances from the brain move from there through the infundibulum and pituitary stalk to the pituitary and also that the gland itself takes up substances from the blood.

Theophile de Bordeu of Montpelier suggested in 1775 "that each organ of the body gives off emanations - necessary and useful to the whole body. There is no gland which does not draw from the cellular tissue around it a large amount of serosities which co-mingle and inundate the whole region. The pituitary sucks up the superfluous moistures from the brain: they all go to end up in the funnel (stalk) and the pituitary gland receives them and discharges them." He stated that it remained for physicians to "follow up and classify the various reflexes consequent upon the defective functioning of each particular organ." Unfortunately, he was not an experimentalist and had no co-worker to perform the necessary experiments and therefore his ideas were not directly developed. His theories were, however, in many respects remarkably similar to those we hold today (Table 2).Will our dangerous neglect of and low priority for research in Northern Ireland and particularly in the Belfast HealthTrust lead some of our future hypotheses to be untested and hence neglected for many years?

Table 1

Contributors to the development of pituitary pathophysiology and management

- Anatomists
- Physiologists
- Descriptive clinicians
- Chemists and Biochemists
- Neurosurgeons
- Endocrinologists
- Clinical scientists
- Radiologists
- Geneticists and Molecular Biologists
- Radiotherapists/ Oncologists
- Specialist Endocrine Laboratory Staff
- Endocrine Specialist Nurses
- Pituitary Patients

Claude Bernard in 1855 formalised what was probably already accepted for other glands, the adrenal in particular. He recognised that the liver had both external and internal secretions (bile and glucose respectively) and he transferred the idea of internal secretions to the "ductless glands" and, for example, began an analysis of extracts of the thyroid and adrenal glands.

Table 2

A comparison of the thoughts of Theophile de Bordeu in 1775 with our concepts of hormones in 2009

Then
Each organ of the body gives off emanations which are necessary and useful to the whole body
There is no gland which does not draw from the cellular tissue around it a large amount of serosities which comingle and inundate the whole region
Now
Chemical messenger leaving one part of the body and via the blood stream delivering a message to another area or areas and causing an action there.
Refined in recent years by the knowledge of local actions where they are produced, neuronal interactions, and the influence of aspects such as growth factors etc at the site of action

Clinical descriptions of endocrinology syndromes began with those related to underactivity of glands (Addison on hypoadrenalism in 1849, Gull on hypothyroidism in 1873 and Hegar on the effects of oophorectomy in 1878). The diagnoses in those days were made when the clinical changes were obvious and therefore advanced, but nowadays we hope to pick up cases much earlier. Most of the early cases of Addison's disease were due to tuberculosis and the condition was invariably fatal as the patients were not able to mount a satisfactory response to infection without their steroid hormones.

At this stage, a role of the pituitary in the production of end organ disease was not suspected but this followed when experiments in animals showed that the thyroid, gonads and adrenals atrophied when the pituitary was removed. These were vital linkage observations and were an important contribution to endocrine knowledge.

HYPERPITUITARISM

The first over-activity syndrome, acromegaly, was recognised in 1885 by Pierre Marie. It is caused by the secretion of excess growth hormone by a pituitary tumour in adult life. The same excess of growth hormone in children, before fusion of the epiphyses, leads to giantism. Cushing recognized that pituitary tumours could be associated with a moon face, central obesity, buffalo hump and stretch marks but his first series of cases of what is now known as Cushing's syndrome was not published until 1930. He had described one case in 1910 in a paper describing a number of different diseases of the pituitary.

Both acromegaly and Cushing syndrome can cause debilitating physical and psychological disease and are associated with increased mortality. Both initially were untreatable.

Harvey Cushing himself was an extraordinarily tough neurosurgeon who worked relentlessly, wrote continuously and travelled extensively. He made numerous contributions to neurosurgery and did perform pituitary surgery for acromegaly. Curiously he never operated on a case of Cushing's syndrome. He described the classical triple concept of pituitary problems: over-production, under-production, and pressure symptoms (and their combinations). In a famous letter he expressed also a hope that one day, as medicines developed, pituitary surgery would no longer be necessary. That day has still not come though we are edging closer to it.

Hyperprolactinaemia was described by Friesen only in 1971 although syndromes of amenorrhoea and galactorrhoea had long been recognised, and there had been experimental evidence in 1915 that the pituitary was involved in milk production. It was the development of an assay for prolactin which revealed the concept of hyperprolactinaemia and showed how common it was. It was not long before bromocriptine was found to be a useful treatment for prolactin excess and today surgery for hyperprolactinaemia is only rarely required.

HYPOPITUITARISM

Treatment of glandular underproduction by extracts of the glands themselves had been tried in antiquity without success. More recently, Brown-Sequard in Paris in 1889 suggested that testicular extracts contain "an active dynamogenic, invigorating substance which could rejuvenate men." A world-wide response began within months, sometimes with wrong uses and wrong preparations and there was a very mixed medical response in Europe and North America.

George Murray, however, was successful in his treatment of hypothyroidism. He suggested in 1891 in Newcastle that hypothyroidism was due to loss of internal secretion and attempted treatment with sheep thyroid extract. An early patient survived for twenty-eight years with the use of extracts from about thirty-one sheep per year. Not all of his colleagues were initially sympathetic to his idea. One said "It would be just as sensible to treat locomotor ataxia with emulsion of spinal cord." The proof, however, was seen in the great improvement in the well-being of treated patients.

Further work on extracts of various ductless glands followed and in 1950, Kendall, Reichstein and Hench received the Nobel Prize for their work on the nature and function of hormones secreted by the adrenal glands in mammals. They had carried out very detailed experiments and had isolated and studied 28 different compounds from the adrenal cortex. In doing so they identified and recognised the importance of the steroid ring which is characterised by a double bond next to a ketone group. They had painstakingly carried out small animal experiments on the compounds they had labelled as A, B, E and F before attempting to move to assessment in human subjects. Eventually they showed that compound E helped patients with Addison's disease. Hench had observed also that patients with rheumatoid arthritis often improved in pregnancy and this led to the development of a trial of E

TABLE 3

Known familial genetic pituitary tumour syndromes

SYNDROME	GENE	OTHER FEATURES	ANIMAL MODEL
MEN 1	MEN1 11q13	Hyperparathyroidism Pancreatic tumours Carcinoid syndrome	Yes
MEN1-like	CDKN1B 12p13	HPT	Yes
Carney Complex	PRKAR1A 17q23-24	Atrial myxomas, Adrenal hyperplasia	Yes
Familial isolated pituitary adenomas	AIP 11q13.3	None	No

TABLES 4A, 4B AND 4C

Some contributions to pituitary research from the Regional Endocrinology and Diabetes Centre, Royal Victoria Hospital, Belfast, 1954-2009

4a

Growth Hormone

- Visual failure after external pituitary irradiation 1979
- Controlled trial of hGH in adult deficiency 1992
- Some limited efficacy of bromocriptine in acromegaly 1886
- Early dose response studies of octreotide in acromegaly 1990,1993
- First case series of changing glucose tolerance and of gallstones after octreotide in acromegaly 1989
- Efficacy of octreotide LAR in acromegaly 1999
- Effect of Octreotide LAR on tumour size in acromegaly 2002
- Effect of hGH on insulin resistance in hypopituitarism 2002
- Long term efficacy of XRT in acromegaly 2009

4b

Cushing's Syndrome

- First European series of bilateral adrenalectomy for CS 1954
- Early description of CS secondary to a lung tumour (carcinoid type) 1957
- Invasive pituitary tumor developing after adrenalectomy 1959
- Cyclical CS
  - 2 rhythms in the same patient 1985
  - First ever series of patients 1985
  - Importance in assessments after surgery 1992,1999,2005
- Petrosal sinus sampling in the diagnosis of ACTH-dependent CS 1989,1999,2000
- Assessment of remission of CS after pituitary Surgery 1995,1996,2005
- SOM-230(pasireotide) in pituitary-dependent CS 2008

4c

Other Pituitary Disease Research

- Normal puberty and fertility with bromocriptine alone in prolactinoma 1987
- Comparison of cabergoline and bromocriptine in prolactinoma 1984
- Macroprolactinemia as an important cause of hyperprolactinemia 2001
- Assessment of H -P- A axis after pituitary surgery
- Metyrapone and naloxone in H-P –A axis assessment 2000
- Low dose vs. regular dose synacthen vs. Insulin hypoglycaemia response 2000
- Early post-operative serum cortisol to predict need for long term steroids after pituitary surgery 2004

(cortisone) in rheumatoid arthritis. It was the success in this field which would lead to the commercial development of cortisone by drug companies; a spin-off from these being that replacement therapy for adrenal insufficiency then became available, rheumatoid disease being much commoner than hypoadrenalism.

Other advances in our understanding of the pituitary gland in the twentieth century included the recognition that its total removal is fatal (1908) and that necrosis of the gland may occur post-partum (1913). Extracts of anterior lobe were shown to increase growth rates in rats (1921) and to produce acromegaly in dogs (1929). Purification of the hormone occurred in the 1930s and 40s and growth hormone was extracted from human cadavers in 1957. This latter experiment led to growth hormone replacement in suitable short stature patients. This was done using extracted growth hormone, synthetic hormone not becoming available until many years later. The synthetic hormone avoids the contamination with viruses and prions sadly reported in some of the cases who had been successfully treated with extracts.

Currently we have many replacement treatments available for insufficiency of the pituitary gland and its dependent glands. Amongst other things this has led to safer surgery for endocrine over-production syndromes. For example both bilateral adrenalectomy for Cushing syndrome and pituitary surgery for acromegaly became possible very soon after cortisone acetate became available and was shown to prevent death from hypoadrenalism.

The pituitary is difficult to locate as it is a small gland sited deep within the head and is surrounded by delicate and important structures such as blood vessels, the optic chiasm and a variety of other important brain structures. Initial surgery to it carried high mortality and morbidity as it was performed via the transfrontal route. Knowing this, Cushing developed a transsphenoidal approach through the nose but the technical requirements of good illumination and magnification were not then available and he gave up that approach and reverted to his previous transfrontal technique which was then used for many years, despite access to the pituitary being difficult and distant. The fact that it was so often successful is a tribute to our neurosurgical colleagues. Now, with modern equipment and modern sub-specialisation, the transsphenoidal approach is associated with very low morbidity and mortality and our RVH, Belfast figures compare well with those in Europe and the USA.

External pituitary irradiation, when properly given, is helpful in controlling tumour re-growth after operation although care has to be taken with the fields and the dose must given in small fractions over a period of six weeks to protect vision. One remaining disadvantage is the possibility of eventual hypopituitarism due to the non-selective nature of the treatment.

Most pituitary tumours are benign and oncological drugs are generally not required as part of their treatment. However some tumours are locally aggressive and in the past have not responded well to any therapy. Very recently, temozolomide, an alkylating agent, has been demonstrated to be useful in some of these very aggressive cases and further research is eagerly awaited.

Some pituitary disease has a genetic basis and at present we know of four familial pituitary tumour syndromes. The genes involved are also known and animal models exist for three of

the four (Table 3). Genetic testing is surrounded by the usual difficulties of family tracing and sensitivity to the possibility of early and perhaps unwanted diagnoses being made in other family members. Close liaison with laboratory, geneticists etc. is required and rigorous follow up is required. Hopefully the novel animal models will allow basic research to point us to new methods of treatment for all types of pituitary disease.

Research on the hormones of the hypothalamus has also been very successful. The various hypothalamic releasing and inhibiting hormones were not described until the 1960s and 70s. One point of interest is the fact that many of these hormones are released in pulses - if they are infused continuously their effect is considerably reduced or indeed abolished. Knowledge of the physiology of the hypothalamus and pituitary has led to a variety of drug discoveries. LHRH is used in the treatment of prostate cancer and endometriosis while the combined oral contraceptive pill and hormone replacement therapy are used frequently. New drugs have been developed for use in infertility while dopamine agonist and somatostatin analogues are used for pituitary disease and for various other indications (e.g.parkisonism, gut endocrine tumours).

The effect of native somatostatin lasts for a few minutes only but octreotide, an analogue of it, lasts for about eight hours, and by suitable packaging of that peptide in miniature spheres, can have a duration of about one month after an intramuscular injection (Fig 3). These analogues are now widely used in the treatment of growth hormone producing pituitary tumours and can produce a good response including regression of the tumour, in approximately two thirds of patients. There are, in fact, five types of somatostatin receptors present in the pituitary, and octreotide and a similar analogue, lanreotide, predominantly have affinity for ss2. Their effect in acromegaly is good but there is poor responsiveness in Cushing syndrome, where the predominant type is ss5. A new somatostatin analogue, pasireotide, has forty times the affinity of octreotide for the ss5 receptor, and a proof of concept, open-label, single-arm trial has shown good results in Cushing syndrome. Side-effects were common but mild. Further trials are underway and could possibly herald the advent of primary medical therapy for pituitary-dependent Cushing's syndrome.

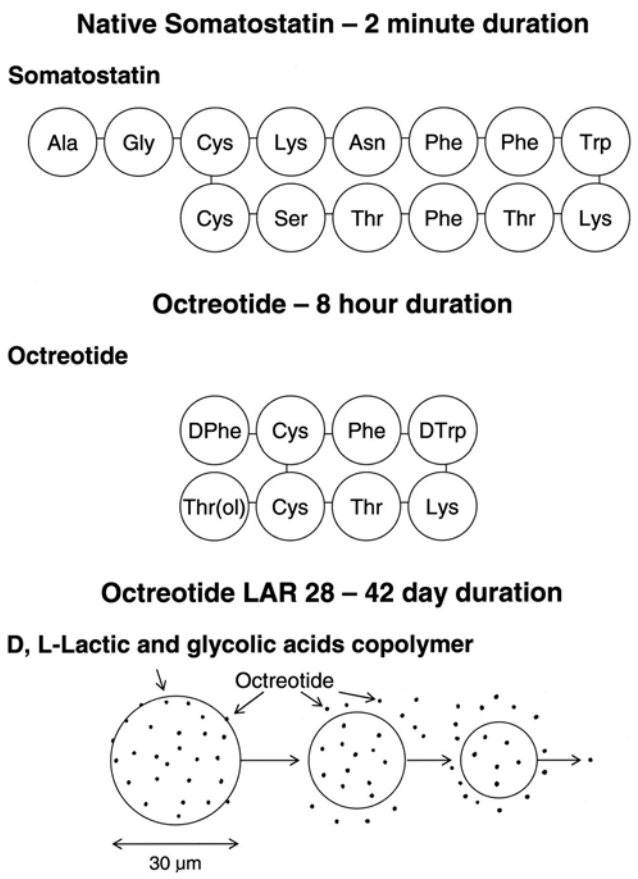

Fig 3. Development of longer acting analogue of native somatostatin and its incorporation by chemists into a preparation which can be given monthly to control GH overproduction

The RVH Regional Endocrinology and Diabetes Centre (Metabolic Unit) has contributed to many of the advances in the treatment of pituitary disease, engaging in its own work and also in many of the international trials (Table 4). This research and the advances in the management of pituitary patients would not have been possible without the skilled assistance of the laboratories, the nursing staff in the unit, surgical and radiological colleagues and many other clinical and research collaborators.

More exciting discoveries lie ahead and our knowledge of the pituitary gland will continue to increase. The experience of the past suggests that many of todays accepted facts and therapies will be shown to be inadequate or wrong but progress in the management of this group of patients will continue unabated as it has done across the years from then to now.

ACKNOWLEDGMENTS

I wish to thank all those who gave me, and maintain my enthusiasm for the science and art of endocrinology. These include my mentors, my consultant colleagues in many disciples including endocrinology, my biochemistry colleagues and all of the excellent junior colleagues who have either worked clinically or researched with me across the years. The nursing staffs of ward 7D and of the old Metabolic Unit of the Royal Victoria Hospital, Belfast have been wonderful colleagues. I thank my secretary Jennifer McDowell for all her help and I dedicate this talk and article to my wife Hilary and my family for all of their outstanding love and support.

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Medical History

A History of Dermatology in Ireland

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The first organised medical relief in Belfast was given by the Belfast Charitable Society in 1774 to persons attending the old poorhouse[1,2]. The Belfast Charitable Society is Belfast's oldest charitable foundation, and Clifton House is the oldest public building in the city still substantially in its original state. The aim of the Society was to grant support to the increasing population of the developing Belfast, with benevolent industrialists helping to assist the voluntary work of physicians, most of whom earned their income from lucrative private practice. In 1797, with the growth of epidemics, including typhus fever, the first hospital in Ireland for fever opened with six beds in a small terrace house in Factory Row, Belfast to be known as The Belfast Fever Hospital, which became the Belfast General Hospital (1847) and later, by royal charter, the antecedent of the Royal Victoria Hospital[2]. Dermatology in Belfast was to ultimately benefit from the Belfast Charitable Society, which provided two grants for land for the first dermatology hospitals, the first being in Regent Street, and later at Glenravel Street, as well as from its allied benefactors.

The Belfast City Hospital started as one of Belfast's workhouses, and built to deal with 1,000 patients, opened its doors in January 1841. Tents had to be used to increase its capacity during the Potato Famine between 1845-7[2].

The first medical school in Belfast was established in 1818 in the Royal Belfast Academical Institute and transferred in 1849 to the newly established Queen's college and later (1908) the Queen's University Belfast. Before this some 300 medical students left Ulster to train mainly in Dublin or Edinburgh, and for some years following the establishment of Queen's University, some students still preferred to receive their medical education outside Ulster, where the standard was still considered superior.

EARLY DEVELOPMENT OF DERMATOLOGY IN NORTHERN IRELAND.

There is no record of any specific provision for the treatment of skin diseases in Belfast prior to 1865, although by this time a skin clinic was conducted in the Adelaide Hospital in Dublin by Dr Walter G Smith[3].

Specialist hospitals began to appear across the British Isles around the 1860's. They treated conditions, which were seen as less glamorous areas of medicine, neglected by the general voluntary hospitals. Relatives of those affected by a disease sometimes started a specialist hospital and more entrepreneurial doctors, with an interest in these conditions started their own hospital, usually in a converted house with a few beds. Success or failure depended on attracting charitable interest, as attracting patients was never a problem. Specialists found that such hospitals gave them the opportunity to study more examples of any single disease than would be found in the general hospital. Common specialist hospitals included those for dermatology, venereal diseases and for "cripples" with orthopaedic conditions. Specialist hospitals caused struggles within the medical profession, and the *British Medical Journal* ran a campaign against them in the 1860's, arguing that they drew away interesting cases from general hospitals.

HENRY SAMUEL PURDON

The first record of dermatology in Belfast is in 1865, when Henry Samuel Purdon (1843-1906), aged 22, established the 'Belfast Dispensary for Diseases of the Skin' at a house in Academy Street[3]. Purdon received his medical training in Glasgow, and when he returned to Belfast, he realised the need for a dermatological service and decided to specialise in skin disease. Finances were always stretched, and at stages Purdon asked his many sisters to donate some of their pocket money to keep the dispensary running. During that time Purdon used his artistic talents to create wax models of skin, particularly that of lupus vulgaris, particularly prevalent at the time. With increasing demand the clinics grew and the house in Academy Street in 1866 quickly assumed the title of "The Belfast Hospital for Diseases of the Skin". Purdon's interests extended beyond dermatology: he was one of the physicians to the original Forster Green Hospital for Chest Diseases, which commenced its career at the corner of Great Victoria Street and Fisherwick Place.

Henry Samuel Purdon (1843-1906)

By 1868 the original building was becoming too small for requirements and the committee were granted funding from the Belfast Charitable Society, to build a new hospital in Regent Street, which was opened in 1869. The new building

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provided mainly out-patient facilities, but also had 8 in-patient beds. The out-patient department and operating theatre were considered adequate, commodious and up-to-date. As reputation spread, patients came not only from Belfast but also from surrounding counties.

Within four years of the opening of the Regents Street Skin hospital, despite increased bed numbers of 14, clinical needs had become too great for the space available. Once again financial restrictions were to become too great and in 1873 a public benefactor; Edward H Benn financed the building of a brand new skin hospital at a cost of £4000[1]. The hospital was regarded as the most complete of its kind in the United Kingdom, and Purdon stated in the preface to one of his books ("Cutaneous Medicine and Diseases of the Skin," 1875), it "contained thirty beds and a suite of baths of every description."[3] It was also well equipped with its own pathology laboratories, operating rooms and pharmacy. The Belfast Charitable Society offered a site for construction at Glenravel Street and in 1875 the new Benn Skin Hospital was opened. Glenravel was the site of the iron ore deposits in County Antrim owned by the Benn family. Professor J.F. Hodges, whose home, Glenravel House, gave Glenravel Street its name, was Professor of Medical Jurisprudence at the developing Queen's University. He was elected president of the Benn Hospital and served in this capacity for 20 years.

Edward Benn, one of Belfast's greatest philanthropists.

In addition to his clinical commitments, Purdon was heavily involved in undergraduate teaching. He became widely known in developing dermatological circles in the UK, Europe and the US, as a corresponding member of the New York Dermatological Society. In 1870, Purdon acquired the position of Editor of the Journal of Cutaneous Medicine at the age of 26 years. Despite his best efforts, financial support for the journal became inadequate and the journal ceased publication, with the *British Journal of Dermatology* taking its place in 1888[1].

Dr Henry Purdon was appointed as an attending physician to the General Hospital in 1870, with an interest in dermatology, though with no designated responsibility in dermatology. Dr Purdon resigned from the hospital staff in 1882, unusually without ever having been made a Consultant Physician. This left a hiatus in dermatology services until McGaw re-established dermatology at the Royal Victoria Hospital in the 1900's.

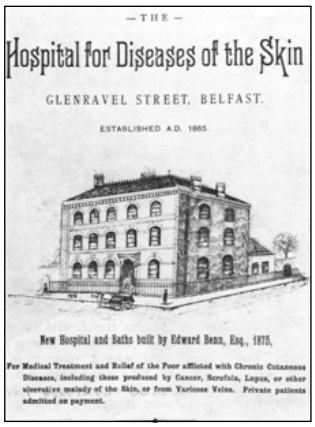
Amid a busy practice Purdon continued active work at Glenravel Street Hospital until about 1900; his assistants were his son, Elias Bell Purdon and Samuel William Allworthy, both of whom were appointed in 1893. The half-century of excellent work carried out at the Skin Hospital by these two physicians is well known, and only ceased there when the hospital was destroyed in an air-raid in May 1941. Elias Bell Purdon, Henry Samuel Purdon's son, was the fourth generation of his family to attend as physician to the Belfast Charitable Society, and at the time of his death, his family had given 143 years unbroken service to the Society[1].

During a bombing raid in the Second World War the Benn Skin Hospital was badly damaged and it was decided not to rebuild it but to use funds for the improvement of the amenities in the nearby and developing Royal Victoria Hospital[3]. Dermatology remained a mainly outpatient specialty, with a few dermatology beds in ward 22 in the Royal Victoria Hospital, introduced in 1951. A dermatology ward was finally established in 1957 (ward 26) and H.S. Purdon's service to dermatology was recognised by naming this in-patient unit, 'The Purdon Skin Ward', a ward which was to become well know to generations of doctors and future dermatologists.

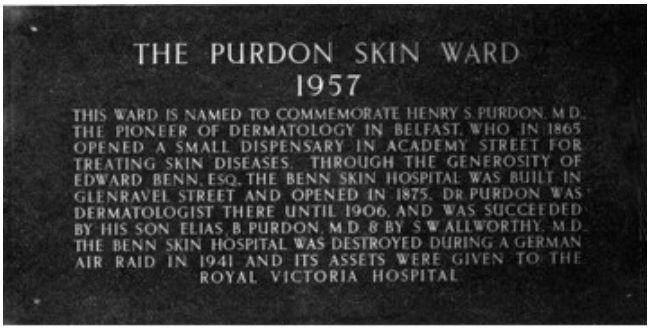
SAMUEL WILLIAM ALLWORTHY

Samuel William Allworthy (1866-1952), a graduate of Trinity College, Dublin, had worked in the Finsen Institute Copenhagen and was instrumental in establishing radiotherapy in Belfast[1]. Like many of that era, he had not shielded his hands nor fingers against the effects of radiation and his hands became disfigured by X-ray burns and required amputation. During

Close up photograph of the front of the Benn Skin Hospital, Glenravel Street.



Sketching of the Benn Hospital, Glenravel Street, Belfast.



Picture 6. Plaque placed outside Ward 26, Royal Victoria Hospital, to commemorate the contribution of Purdon and the generosity of Benn. Alas this plaque has now been since in the Hospital's refurbishment.

the air raid attacks on the Benn Hospital Dr Allworthy narrowly escaped being killed by an air raid on his own home.

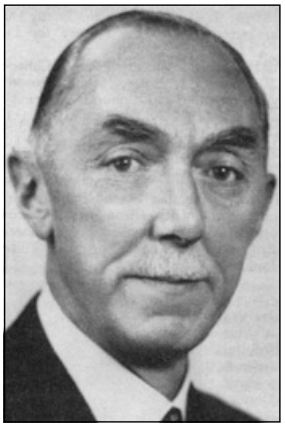
Allworthy combined general practice with dermatology. He was also a consulting physician to the Royal Victoria Hospital and to the Belfast Charitable Institute. He served in the First World War as a skin specialist, and was a vice-president of the section of dermatology when the BMA met in Belfast in 1937[1].

WILLIAM CALWELL

William Calwell (1859-1943) was educated at Queen's University Belfast, and in 1893 he was the first appointed registrar in the Royal Victoria Hospital. He was initially appointed as a physician to the Royal Victoria Hospital in 1895, and established weekly skin clinics in the Royal Victoria Hospital in around 1910, which he continued until his retirement in 1924. He remained however, a general physician but the first at the Royal to be given the title of "dermatologist".

IVAN HENRY MC CAW

Ivan Henry Mc Caw (1897-1961) was the only son of Dr John Mc Caw, a pioneer of paediatrics in Belfast. I.H. Mc Caw had been prevented from a surgical career because of a wound to his right shoulder in the Battle of Messines in 1917. After training in dermatology in Guy's hospital and Vienna, he returned to take charge of the Skin clinics after Calwell, where he single-handedly expanded the skin department at the Royal Victoria Hospital after his appointment in 1933 as its first full time dedicated dermatologist. It was under his stewardship that the Benn Hospital became integrated into the skin department at the Royal Victoria Hospital. He gave the annual lecture to new medical students at the Royal Victoria Hospital in 1944 on the subject of A Synopsis of the History of Dermatology. He became a president of the British Association of Dermatologists in 1948[1].



Ivan Henry McCaw (1897-1961).

JONATHON JEFFERSON

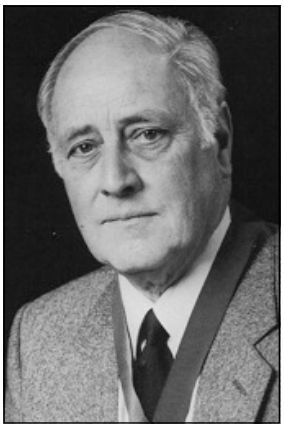
Jonathon Jefferson (1921-1968) after a period of dermatology training in London joined the staff of the Dermatology department of the Royal Victoria Hospital in Belfast where he greatly assisted Mc Caw in the expansion of specialty services in Northern Ireland. His main interest was in industrial dermatoses in which he had a very extensive practice. His early death at 47 years of age was a great loss to dermatology in this area. Jefferson was one of the first people to distinguish between the infective cases of Lyell's syndrome, occurring in childhood and caused, as he showed by a staphylococcal infection, from the largely drug induced toxic epidermal necrolysis of adults[4]. He proposed that the skin splitting occurring in the childhood form of Lyell's syndrome may be due to a staphylococcal toxin, which gave rise to the skin splitting[5] and is probably the first description of the staphylococcal scalded skin syndrome. His paper in the British Medical Journal probably gives the first and best description of the entity of staphylococcal scalded skin in infancy.

REGINALD HALL

Although little is written about Reginald Hall, he was held in the highest esteem by his colleagues. He was responsible for setting up the dermatology department in the Belfast City Hospital and had by far the largest number of beds in Northern Ireland at that time, "having 45 beds at our disposal for the treatment of skin diseases in the Belfast City Hospital, with an experienced nursing staff."[6] Because of his rather retiring personality, he seems less well known than many of his contemporaries, but has been described as an excellent clinician, and as he had qualified as a barrister, he was in much demand for medico-legal opinion. He was the founding member of the Irish Association of Dermatologists, having written to his counterparts in the Republic of Ireland requesting a closer association between dermatologists in both sections of the island.

JOHN MARTIN BEARE

After qualifying in Medicine in 1943 at Queen's University, Dr Martin Beare volunteered for service with the Royal Navy (1943-1946) where he served as a surgeon lieutenant[7]. After the war he spent time at St Thomas' Hospital studying dermatology under the renowned Geoffrey Dowling. He returned to his native Belfast and further trained under the only two dermatologists in Northern Ireland at the time, until his appointment in 1949 as consultant dermatologist at the Royal Victoria Hospital. He developed interests in paediatric dermatology, fungal diseases of the skin and small animal dermatology and contributed widely to the dermatology literature, including several original chapters in the first edition of the internationally renowned "Rook Book", to which he was a regular contributor in subsequent editions. Dr Beare was president of the British Association of Dermatologists in 1984, when he hosted the BAD Annual meeting in Belfast. He was involved in the foundation of the Irish Association of Dermatologists.



Dr John Martin Beare (1920-1998)

PROFESSOR DESMOND BURROWS

Professor Desmond Burrows was the first professor of Dermatology in Ireland, holding an Honorary Chair at Queen's University, Belfast. He was President of the British Association of Dermatologists in 1992 and became President of 6th EADV, in Dublin, 1997. His major interest was in contact dermatitis and he was a world authority on chromate dermatitis, with much of his work on metal dermatitis being cited today. Together with Martin Beare, he was instrumental in the establishment of the Irish Association

Professor Desmond Burrows.

of Dermatologists. Desmond Burrows was the inaugural secretary of the Irish Association of Dermatologists, and struggled hard to get the organisation onto a firm footing.

HISTORY OF DERMATOLOGY IN THE REPUBLIC OF IRELAND.

ABRAHAM COLLES

Abraham Colles (1773-1843) begins the story of dermatology in Dublin. He was a surgeon and is best known for his famous description of the Colles fracture. In 1837, his published work, entitled 'Observations on the venereal disease and the use of mercury' clearly defined and differentiated the spectrum of cutaneous syphilis and his observations on the infectivity of neonatal syphilis, later known as Colles Law. This law was used to describe his observation that syphilitic infants with oral lesions could not transmit the disease to their infected mothers but were infective to previously healthy hired wet nurses, indicating the immunity of previously infected individuals[8].

Abraham Colles (1773-1843)

ARTHUR JACOB

Arthur Jacob (1790-1874)

Jacobs's depiction of a "rodent ulcer" the first description of basal cell carcinoma.

Arthur Jacob (1790-1874) an ophthalmologist, who served his apprenticeship under Abraham Colles, achieved his eponym at the age of 28, like his master, when he published his paper in 1819 on the nervous layer of the retina- Membrana Jacobi. His contribution to dermatology was in 1827 when he published the first description of the basal cell carcinoma, called at the time the 'Jacobs ulcer'. His eloquent observations included the description of 'ulcers with edges which are elevated, smooth and glossy, with a serpentine outline….veins of considerable size ramifying over it….remaining unchanged in size and form for a great length of time'[8].

WILLIAM WALLACE

William Wallace (1791-1837) was probably the first true dermatologist in Dublin. On 1st October 1818, he opened 'The Dublin Infirmary for diseases of the Skin, 20 Moore Street, Dublin, entirely founded and maintained at his own personal expense. In the 17 years the institution was open, 25000 cases of skin disease were reported to be treated. He made two original contributions to medical literature. He introduced potassium iodide to the Material Medica and made experimental proof of the infectivity of the secondary lesions of syphilis. He also introduced the use of a sulphur fumigating cabinet for the treatment of scabies. Unfortunately his pioneering advances and the activity of the Dublin Infirmary for diseases of the skin were brought to an abrupt end with his sudden death from typhus in 1837 at the age of 46. The hospital never re-opened as he had no colleagues and had not had time to train a successor[8].

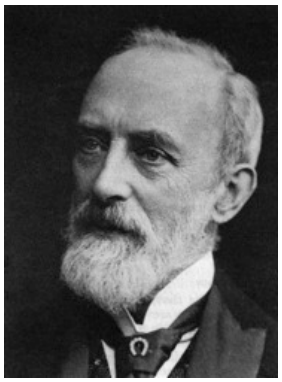
ROBERT GRAVES

Robert Graves (1796 - 1853)

Robert Graves (1796-1853) famous for his description of exophthalmic goitre (Graves Disease) recorded the first accurate clinical description of 'Angioneurotic Oedema' published in his 'Lectures in Clinical Medicine' in 1843. He described how 'tumours rise, run through their course and disappear in the space of a few hours…sometimes on the lips….inside of the mouth and uvula are attacked…On the following day there is no trace of their existence'. His description predates by 40 years that of Heinrich Quincke, a German Professor of medicine in 1882.

JOHN MOORE NELIGAN

John Neligan (1815-1863) a physician at Jervis Street Hospital, was responsible for several dermatological publications, including 'Practical Treatise on diseases of the skin' in 1852 and later in 1855 his 'Atlas of Cutaneous diseases'. He was one of the commissioners to the first British Pharmacopoeia, but he did not live to see the completed work, which was published in 1864[8].



Picture 14. Walter Smith (1844 - 1932)

WALTER SMITH

Walter Smith (1844-1932), who was Assistant Physician to the Adelaide Hospital, Dublin, where he worked from 1866-1881, started the special dispensary for

skin diseases. He was well regarded for his wide knowledge and skill as a dermatologist. He was credited with the first inoculation of Achorion schoenleini into human skin- his own - producing the lesions of favus. In 1879 he published in the British Medical Journal the first description of Monilethrix[8].

WALLACE BEATTY

Wallace Beatty (1853-1923) was Walter Smith's successor in the Adelaide Hospital. He greatly extended the work of the skin clinic and developed a large private practice. He was a popular teacher and was honoured by the University in a special appointment of Honorary Professor of Dermatology. He was on the editorial staff of the British Journal of Dermatology, and was described as "modest, gentle, courteous and beloved by all"[8].

ACKNOWLEDGEMENTS

The authors are grateful for the valuable suggestions from our retired colleagues Professor Desmond Burrows and Dr Andrew TA Dawson for bringing to our attention many of the lesser known aspects of the history of dermatology in Ireland.

The authors have no conflict of interest.

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Letters

AN UNUSUAL CASE OF LOCALISED HYPERTRICHOSIS

Editor

Topical testosterone is now a widely used mode of testosterone replacement therapy. It is well reported that transcutaneous absorption of testosterone may lead to hirsuitism and virilisation.[1,2] We report an interesting case of localised hypertrichosis on the forearm of a female patient and postulate that this was the result of accidental transfer of testosterone gel from the patients' husband.

A 66-year old lady presented with a one-year history of localised hair growth on the right forearm. She denied excess hair growth or alopecia elsewhere and did not report any other signs of virilisation. The patient had no other relevant past medical or drug history. Closer questioning revealed that she had been applying a 5 % testosterone gel (testogel ®) with her right hand to her husbands shoulder, intermittently for 4 years. This was applied daily for hypoandrogenism, secondary to radiation therapy for multiple myeloma.

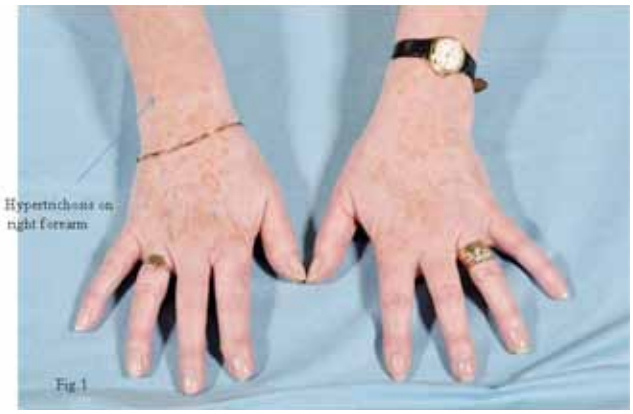

Fig 1.

On examination she had localised hypertrichosis on the right forearm, sparing the right dorsal hand, associated with an eczematous eruption. (Fig.1) There were no other relevant clinical findings. Hormone profile including free testosterone was normal. In view of the temporal relationship between application of the gel and the findings of localised hypertrichosis with a normal hormone profile, we feel that the intermittent application of testogel ® was the causative factor.

In relation to topical testosterone, there have been recent case reports of precocious puberty in children and hirsuitism +/- virilisation in women following accidental transfer of topical testosterone. [2] One recent case report and review of the literature also described progressive hirsuitism in a pre-menopausal woman associated with fluctuating testosterone levels of 1.6-6.7 over a 3-month period (normal range<2.5).[2] This was felt to be secondary to transfer of testosterone gel from her partner during contact, because her hair growth and testosterone levels returned to normal after her partner switched to injectable testosterone. [2] Not all cases are associated with hyperandrogenism however. In one case series of two females applying testosterone gel for treatment of lichen sclerosus et atrophicus, both developed hirsuitism two months later.[1] Hormonal profiles were normal in both cases, however, the gel had been discontinued several weeks before presentation.[1]

Localised hypertrichosis is another known side effect of topical testosterone gel. In a recently published study looking at the effect of transdermal testosterone in female patients, the investigators found that the commonest side effect was dose-related hypertrichosis, predominatly at the delivery site.[3] To our knowledge however, there are no reported cases of localised hypertrichosis secondary to inadvertent transfer of topical testosterone between two people.

Regarding the onset of hirsuitism and virilisation with testosterone, time to development varies between reports, most cases presenting between 8-72 months of use and resolving within 2-12 months.[1]

This interesting case highlights the importance of a thorough history in a patient presenting with hirsuitism, hypertrichosis or virilisation, particularly when the pattern of hair growth is unusual in the presence of normal hormonal investigations.

The authors have no conflict of interest

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PANCREATIC HETEROTOPIA PRESENTING AS A GASTRIC SUBMUCOSAL LESION.

Editor

Heterotopia is the normal tissue of an organ found at an abnormal site without anatomic and vascular continuity from the original organ. It is thought that this arises during embryonic development, where groups of cells differentiate in a manner which is inappropriate for their anatomical position in the body[1, 2]. The usual gastrointestinal sites of Pancreatic Heterotopia (PH) include stomach, duodenum, jejunum, Meckels diverticulum, and gallbladder[3]. The condition is

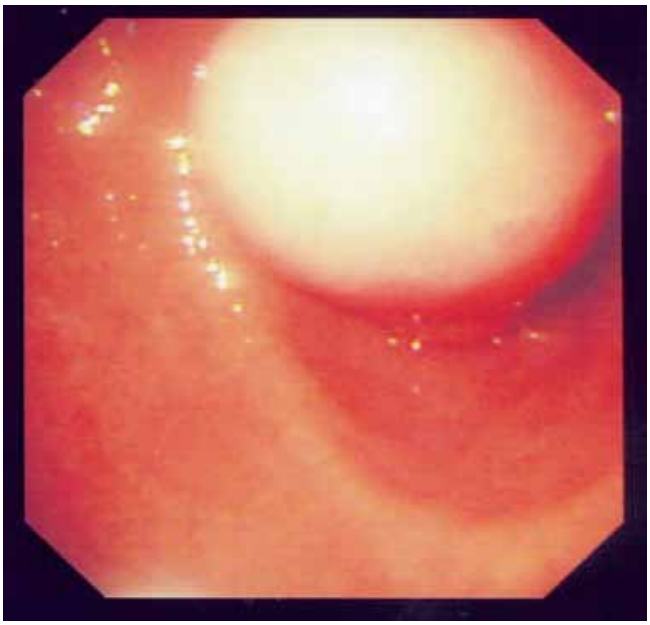

Fig 1. Gastroscopy view

relatively infrequent and usually asymptomatic with post-mortem prevalences ranging from 0.6% to 13.7%[4].

Rare symptomatic cases do arise causing dyspepsia, abdominal pain, melaena, anaemia, nausea and obstruction[5, 6].

We report a case of PH presenting as intermittent gastric outlet obstruction. A 43 year old man presented with a 4 month history of intermittent post prandial epigastric pain and nausea. Complete gastric obstruction was not evident.

An upper gastrointestinal endoscopy revealed a 3cm lesion at the pylorus. (Fig 1) Ultrasound did not highlight any other cause for upper abdominal pain.

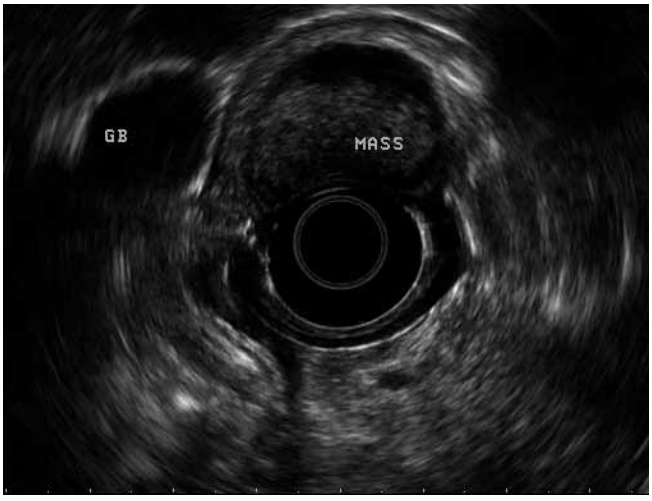

Fig 2. Endoscopic ultrasound of gastric submucosal lesion

Endoscopic ultrasound (EUS) of the lesion confirmed it to be situated within the submucosa having morophological characteristics suggestive of a gastro intestinal stromal tumour (GIST). (Fig 2) EUS can demonstrate echogenic differences between different types of submucosal lesions and the depth of its invasion. Characteristic EUS features highly suggestive of PH tissue are hypoechogenicity or heteroechogenic structure[7]. Anechoic areas usually correlate with ductal structures. These commonly arise from the third or fourth EUS layers of the GI tract or a combination of both.

GIST also originate from the fourth layer of the GI tract and the presence of cystic spaces can indicate a risk of malignant change. The difficulty in diagnosis requires histological confirmation for a definitive answer.

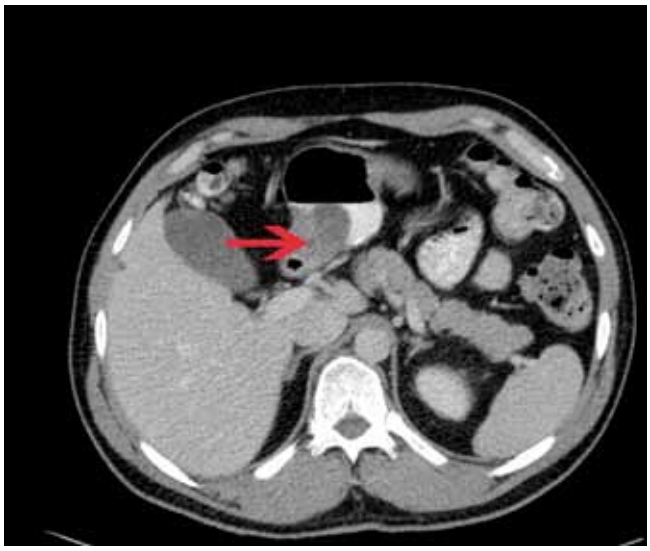

Fig 3. CT scan axial view. Red arrow: gastric submucosal lesion

CT scan confirmed the endoscopic ultrasound findings. There was no eveidence of distant metastatic spread. (Fig 3) Retrospective study of CT appearances of gastric submucosal lesions shows that by using a list of specific CT criteria PH can be differentiated from small gastro intestinal stromal tumours or leiomyoma with a high degree of accuracy[8].

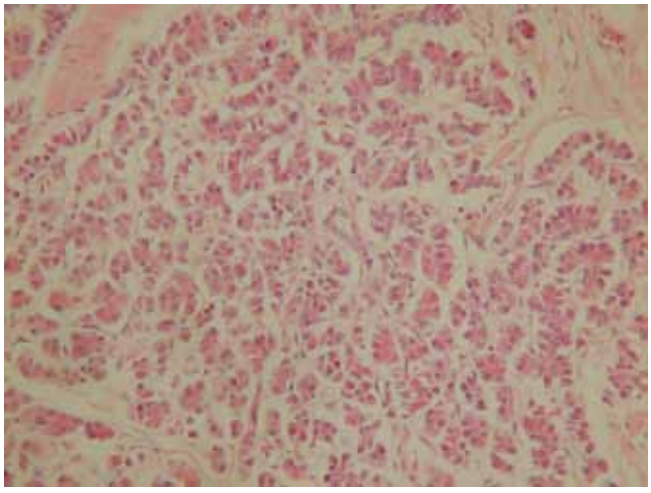

Fig 4. Pancreatic exocrine glands

Subsequently the patient proceeded to laparotomy where a 3cm lesion was located in the pyloric channel. A distal gastrectomy was undertaken and the patient made an uneventful recovery. Review in the outpatient department several months following surgery confirmed the relief of his symptoms. Histology revealed the lesion to be consistent with a focus of PH encompassing a cystically dilated duct. (Fig 4)

COMMENT

PH is part of the differential diagnosis of gastric submucosal nodules. The likely aetiology of PH is congenital and usually asymptomatic. However if symptoms occur they are usually in the fourth and fifth decades[5]. PH is a rare differential diagnosis of a submucosal gastric lesion.

The distribution of PH is 25% in the stomach and 30% in the duodenum[9] with the rest distributed at other sites throughout the gastrointestinal tract. There is also the exceedingly rare possibility of malignant change[10, 11].

This case highlights the rare aetiology of a symptomatic gastric submucosal lesion as well as the difficulty in making a preoperative diagnosis even with modern imaging modalities such as CT and EUS.

The authors have no conflict of interest

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POST-OPERATIVE PYODERMA GANGRENOSUM IN ASSOCIATION WITH ILEAL CARCINOID TUMOUR

Editor

Pyoderma gangrenosum (PG) is an uncommon, progressive ulcerative condition of skin. It presents with deep ulceration characterised by an overhanging violaceous border, which can occur on any body surface. It is frequently confused with other more common ulcerating skin conditions such as necrotising fasciitis, vasculitis, pustular drug reactions and skin infections. Since surgery may be used to treat some of these conditions, but is relatively contraindicated in PG, early diagnosis is critical and is usually made in conjunction with a dermatologist.

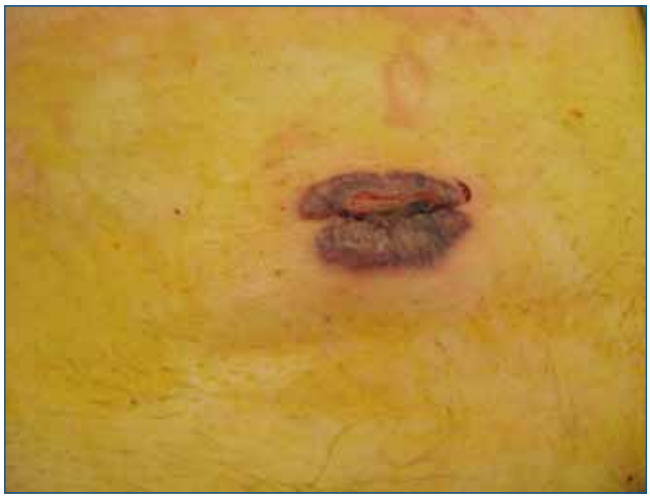

Fig 1. Early violaceous change around a laparoscopic port site

This 76-year-old male had a laparoscopic assisted right hemi-colectomy for an apparent ascending colonic tumour, however histology actually revealed a well differentiated neuroendocrine tumour of the terminal ileum. Serum pancreatic polypeptide, N and C-terminal glucagon, chromogranin A and urinary 5-HIAA collection were all elevated.

On day 7 this man's left iliac fossa port site was noted to be indurated and erythematous. Cefuroxime was empirically commenced for a presumed wound infection. He became pyrexic with a leukocytosis of 30,000 mm^3 and skin at the port site quickly became sloughly and ischaemic (Figure 1). Following debridement he required transfer to intensive care as a case of suspected necrotising fasciitis.

The patient's necrotising skin condition progressed relentlessly. He required 4 further debridement's with intermittent returns to the intensive care unit for supportive therapy (Figure 2). Microbiology of the skin specimens was insignificant and pathology described neutrophillic abscesses with no evidence of vasculitis, granulomatous inflammation or metastatic tumour. Following a dermatological opinion a diagnosis of PG was made.

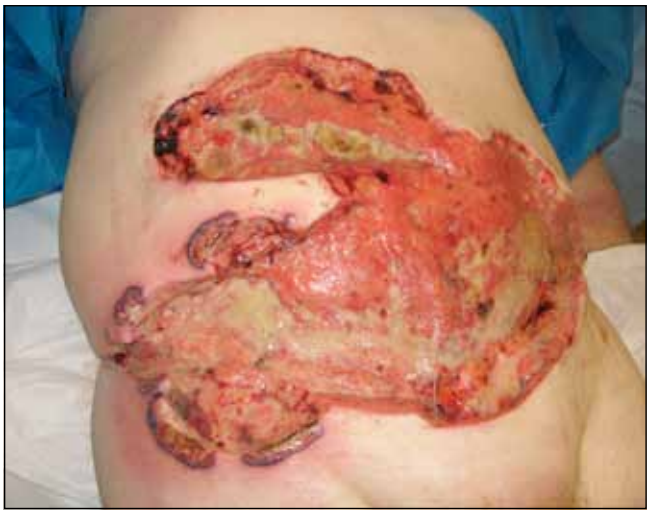

Fig 2. Extensive abdominal wall debridement with classical violaceous borders seen at the wound periphery

Intravenous antibiotics were stopped and high dose prednisolone was commenced in addition to the already prescribed somatostatin (Octreotide®). The patient was maintained on azathioprine (Imuran®) once the prednisolone had been tapered. His large abdominal defect was dressed with Activon tulle® honey dressings. He progressed well and was discharged. Follow up revealed satisfactory recovery of the wound.

DISCUSSION

The literature yields only one other case connecting PG with carcinoid tumour[1], while most reports correlate the occurrence of PG to trauma, typically surgery[2]. The delay in the recognition of this serious dermatological condition was associated with increased morbidity for our patient. PG is a serious and potentially fatal skin condition when correct treatment is not quickly commenced. Management is relatively simple once recognised with the use of corticosteroids and immunosuppressant. Surgery is not thought to be beneficial and in many circumstances can worsen the condition[3].

We recommend that in any significant skin condition, particularly post-operatively or in one not responding to treatment effectively, one must seek the early advice of a dermatologist and not be guided primarily by histology.

The authors have no conflict of interest.

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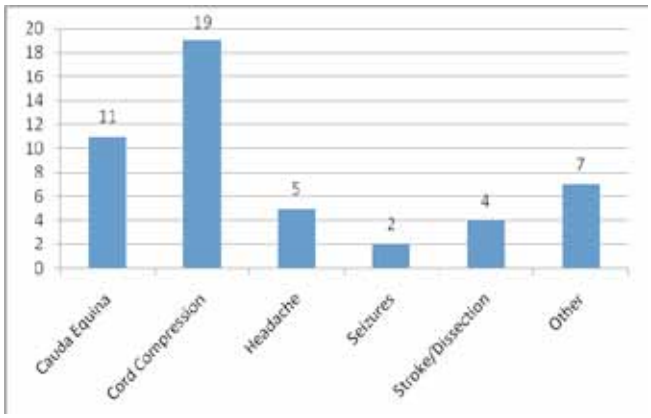
USE OF OUT OF HOURS MRI IN THE ROYAL VICTORIA HOSPITAL – A 6 MONTH RETROSPECTIVE REVIEW

Editor

Through the ongoing development of the Critical Care Centre, it is anticipated that the region's principal trauma receiving unit at the Royal Victoria Hospital will attain Level 1 Trauma Centre status. However an essential criterion for this is the provision of 24 hour access to MRI, as stipulated by the American College of Critical Care Medicine[1]. Out of hours MRI is currently provided as a time-limited, daily service on a consultant to consultant referral basis. Within the UK, it has been reported that only 32 out of 88 (36.3%) trauma units with MRI provide an out of hours service[2].

We undertook a 6 month retrospective review of all patients requiring out of hours MRI between November 2007 and May 2008. Records were assessed for referral information, imaging result and clinical outcome. 74 patients in total had out of hours MRI. Of these, 48 were regarded as emergency (scan performed <24 hours from referral).

Of the 48 emergency requests, the majority came from neurosurgery (n=27) and neurology (n=14), with orthopaedics (n=5), general medicine (n=1) and A&E (n=1) making up the remainder. Figure 1 illustrates the categories of clinical referral, with the majority for either suspected cauda equina syndrome or cord compression.



Out of hours MRI had the greatest impact in suspected cauda equina syndrome, as all scan positive patients (n=5) had surgery on the day of scanning, and made good neurological recovery, with only 1 having ongoing pain at 6 month follow-

up. Early surgery (<24hours) is felt to be of most benefit to those presenting with incomplete cauda equina syndrome[3]. However, it should be noted that suspected cauda equina syndrome contributed to 15% (11/74) of the total out of hours MRI caseload.

Of the 19 patients investigated for cord compression, 7 were confirmed on MRI. A further 2 patients were diagnosed with cord ischaemia. The remainder were either normal, had degenerative change or disc protrusion not causing compromise of the cord or nerve roots. 2 patients with confirmed cord compression were treated conservatively. Of those who had decompressive surgery, 2 were operated upon within 24 hours of their scan but neurological deficit persisted upon discharge.

It is anticipated that a modern, safe and comprehensive out of hours MRI service to Northern Ireland could be achieved with the 4 district general hospitals which have MRI capacity adopting an out of hours service similar to the current at the Royal Victoria Hospital, coupled with expansion of the Royal Victoria Hospital service to provide 24 hour access. Demand for out of hours MRI is anticipated to further increase with full implementation of NICE guidelines for stroke imaging and suspected metastatic cord compression.

The authors have no conflict of interest

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OLANZAPINE INDUCED HYPONATRAEMIA

Editor

We report a case, a 48 years old woman, presenting with life threatening severe hyponatraemia caused by the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) secondary to Olanzapine use. A Medline search revealed no publications of Olanzapine induced SIADH or hyponatraemia. However, online, there were three cases with hyponatraemia been reported at a Dutch pharmacovigilance centre[1].

A 48 years old Caucasian female, obese (BMI 32), smoker with medical history of mixed bipolar affective disorder, schizoid personality disorder and hypercholesterolaemia was admitted to the hospital in a postictal confusional state following an episode of generalised tonic clonic seizure at home with biting of the tongue and urinary incontinence. There was one day history of generalised muscle aches, anorexia, lethargy, irritability, confusion and unsteady gait prior to the episode. There was no history of polydipsia or polyuria. Shortly after admission, she had respiratory arrest for which she was intubated, started on mechanical ventilation and transferred to ICU.

She was on Olanzapine 20 mg daily for last two years. Her concomitant medications included Diazepam 5mg and Simvastatin 40 mg per day. She had not used any other medication known to cause SIADH during the previous two years. Laboratory investigations revealed hyponatraemia with sodium value of 114 mmol/l, serum osmolality 240 mos/kg, urinary sodium 49 mmol/l and urinary osmolality 220 mos/kg.

Diagnosis of SIADH was made. Olanzapine was incriminated as the causative agent since no other apparent cause of SIADH was found. With discontinuation of Olanzapine and treatment with hypertonic/ normal saline, her serum sodium levels normalised, her respiratory functions improved dramatically and soon, she was weaned off the ventilator, extubated and sent to general ward. In the ward, she continued to maintain normal sodium levels with the discontinuation of Olanzapine. Causality assessment using the Naranjo Nomogram revealed a probable association, with probability score of six.

DISCUSSION

Hyponatraemia (serum sodium concentration < 136 mEq/L) is a prevalent and potentially dangerous medical comorbidity in psychiatric patients[2]. Hyponatraemia is known to occur as a rare but clinically important adverse reaction to treatment with different psychotropic drugs[3]. In these patients, it is important to rule out psychogenic polydipsia, a clinical disorder characterised by polyuria and polydipsia, as it occurs in 6% to 20% of psychiatric patients and is more likely to be seen in schizophrenia[4].

In our patient, diagnosis of hyponatraemia secondary to SIADH was made as the biochemical blood and urine test results were consistent with SIADH. SIADH is suspected in any patient with hyponatraemia, hypoosmolality, and a urine osmolality >100 mOsm/kg. It causes hyponatraemia by preventing the excretion of ingested water[5].

Usually, rapid and complete recovery of drug-induced SIADH occurs when the offending agent is discontinued. In our patient also, the correction of hyponatraemia, combined with the discontinuation of her Olanzapine, resulted in resolution of hyponatraemia, without any further recurrence.

CONCLUSION

Clinicians should be aware that patients being treated with Olanzapine can develop hyponatraemia and it is important to check serum sodium levels when patients on Olanzapine develop symptoms suggestive of hyponatraemia.

The authors have no conflict of interest

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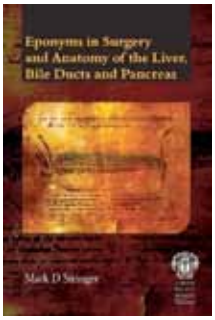
Book Reviews

EPONYMS IN SURGERY AND ANATOMY OF THE LIVER, BILE DUCTS AND PANCREAS



Mark D Stringer, The Royal Society of Medicine Press. October 2009. Paperback. 208pp £35.00 ISBN: 978-1-85315-985-5

This is an excellent little book written by Professor Stringer, based in the Department of Anatomy in the University of Otego, in New Zealand.

The book is a well researched summary of 'Eponyms' related to the anatomy and surgery of the liver, bile ducts and pancreas.

The book is laid out in alphabetical order beginning with Abernethy each section begins with a short summary of the surgical or anatomical details of the eponym.

There then follows a page or two on the biography of the person upon whom the eponym is based.

The book is an easy read and there are a number of amusing anecdotes - for example on page 3. Abernethy's proposal of marriage was as follows "My time is essentially occupied, and I have therefore no leisure for courting ..... reflect upon this matter until Monday." This lady subsequently became Mrs Abernethy and they had two daughters!!

The book is useful for anyone interested in the history of medicine. However I would also recommend this book to students as the little piece of anatomy or surgery at the beginning of each section is of educational value.

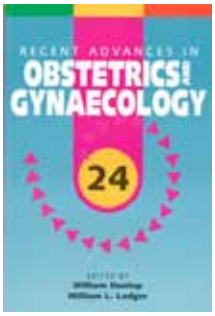
For the more serious students of history each section is followed by a brief bibliography.

The book is liberally illustrated throughout with photographs of the persons after whom the eponyms are named with many historical photographs of instrumentation, theatres etc.

The book is an excellent read for one's leisure time or when travelling for the student of medicine, the anatomist the general physician, the general surgeon or the hepatobiliary specialist. I enjoyed the book immensely and can recommend it thoroughly.

Professor Roy Spence

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY 24



Edited by William Dunlop and William L. Ledger. The Royal Society of Medicine Press. June 2008. Paperback, 288 pp. £35.00 ISBN: 978-1-85315-699-1.

Recent Advances in Obstetrics and Gynaecology 24 is another high quality volume from the 'Recent Advances' series. It brings together eighteen chapters by over thirty authors, of topical analysis of developments in Obstetrics and Gynaecology in one handy volume.

Within obstetrics, nine chapters deal with a wide range of topics. A chapter on gestational diabetes highlights the back to basic principles of high carbohydrate low glycaemic index diets and yet makes reference to the introduction of insulin or oral hypoglycaemic therapy in women with incipient fetal macrosomia, even in those with apparently adequate glycaemic control.

Further maternal issues covered include a comprehensive chapter on management of shock. The importance of the team approach and well-rehearsed 'fire drills' in each unit is emphasised.

A very informative chapter on HIV and pregnancy from an African perspective not only explores the role of antiretroviral treatment but also discusses the more general issues such as the risks associated with breast feeding infants in low-resourced areas. Breast-feeding doubles risk of infection for an infant, yet the risks of replacement feeding may outweigh the risk of HIV transmission.

Additional fetal issues discussed include the associated problems with recreational drug use in pregnancy. Reference is made to the 2.1% of British women whose alcohol dependence subjects their fetuses to risks of growth retardation, neurodevelopment problems including behavioural problems, specific dysmorphic features, cardiac and joint anomalies.

Further fetal issues specifically dealt with include fetal macrosomia and abnormalities of the fetal urinary tract.

The place of operative vaginal delivery is discussed. This is an area of considerable interest due to training issues influencing the choice of instrument used to aid vaginal delivery. Resultant effects on Caesarean section rates are discussed as well as the likely shortfall of availability of expertise in complex operative vaginal delivery in the future.

The complexities of trophoblastic disease is described as is the success of the centralised registration and treatment system in the UK. This registry was established in 1973 and has enabled the development of effective and safe management policies which are now used worldwide.

Gynaecology is awarded a further eight chapters. The role of serum anti-Mullerian hormone (AMH) in the prediction of ovarian reserve and of ovarian response to gonadotrophin stimulation is discussed. Indeed, its role as a potential marker of obstructive azoospermia in male patients may have significant clinical relevance.

The difficult subject of conservative management of fibroids is discussed with reference to magnetic resonance guided thermal ablation therapy. Although still within the realms of research, this technique, as recognised by NICE, is showing promise for patients wishing to conserve their uterus.

A fascinating chapter is given to the ethically challenging area of pre-implantation genetic diagnosis (PGD). With the indications being continually extended, the debate regarding

the place of PGD in late-onset disorders is highlighted. Its controversial role is explored with reference to parents of children needing haematopoietic stem cell transplants who are trying to ensure that their next child is free of disease or indeed are trying to provide a good tissue match for an existing sick child.

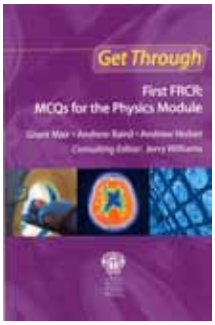
Excellent up-to-date accounts are given of clinical practice in endometriosis, recurrent miscarriage and post-menopausal bleeding. Moreover, the historical practice of ovarian surgery for polycystic ovarian syndrome is re-examined with the benefits of laparoscopy. Two thirds of women can ovulate after ovarian surgery with half conceiving within twelve months. However, women with raised BMI or infertility lasting greater than three years appear to be resistant to surgery. The role of insulin resistance in polycystic ovarian syndrome is afforded a further detailed chapter for those with an academic interest.

Of particular note is the concise but highly relevant chapter on Risk Management. This chapter gives a synopsis of all the buzzwords commonly used in this topic. It provides a useful framework for a subject which encompasses an extensive array of theories, thus enabling the reader to form a basis upon which to question preventable errors in medicine.

In conclusion, the eighteen chapters are presented in an accessible and easy to read format, which are all well referenced. Each topic incorporates a comprehensive overview, which emphasises the salient points of interest and, just as importantly, highlights areas that remain ambiguous, making this a very user-friendly aid for both busy clinicians and those sitting RCOG membership examinations. In all, this is a bookcase essential for all grades within the speciality.

Dr David Glenn

GET THROUGH FIRST FRCR: MCQS FOR THE PHYSICS MODULE.



Grant Mair, Andrew Baird, Andrew Bisset. Consulting Editor Jerry Williams. 1st Edition, The Royal Society of Medicine Press. October. 2010. 156pp. £24.95. ISBN 978-1-85315-951-0.

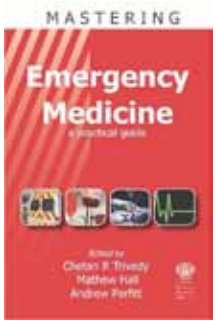
This book is part of the Royal Society of Medicine Press "Get Through …" series aimed at doctors in training. It's a pocket size book of multiple choice questions with answers and a mock examination at the end to test yourself. The First Part FRCR exam has gone through some renovation recently so this book is timely and comprehensive. It is written by three specialist registrars in Radiology (all passed their exam first time) and edited by Jerry Williams, Head of Radiological Physics Training for South East Scotland. The book will appeal to trainee radiologists who are sitting their FRCR part 1 exam, lecturers in Physics for Radiologists and also Radiology tutors.

After a contents page and useful list of abbreviations, the book is structured into sections each focussing on key sections of the FRCR part 1 physics syllabus. The questions follow the format of the examination closely and I wasn't able to identify any errors in the samples I attempted. One of the key strengths of this book is that each answer has a short explanation (sometimes up to a paragraph) which immediately commends itself. Also, the questions are graded with a star system to give you an indication of the difficulty of each question. The questions ranged from the basic "The atomic number of iodine is 53" (True - and I'm sure you knew that) to the more challenging "The photoelectric effect occurs at a maximum when the incident photon energy is just less than the k-edge" (False – and I'm sure you knew that too!). The book is not all basic physics, there is lots applied science and technology too. For example, "The centre of the patient receives the highest radiation dose when using a helical scanner" (False) or "Modern plastic cardiac pacemakers are safe for MRI (False – it is not just what things are made of that may make them hazardous in MR scanning). One of my favourites was "Photon starvation occurs in obese patients" (False - even the physicist has a sense of humour!). I wasn't able to identify any missing sections although in some cases there was a limited supply of questions. For example, in the area of contrast agents or imaging modality quality assurance, there tended to be one question only. This is a minor quibble, as these questions serve to help the candidate identify areas for revision rather than cover the whole spectrum fully.

A candidate who is able to answer the questions correctly in this book, and has their knowledge supported by thorough revision, will very likely do well in their FRCR Part 1 Physics exam. It is certainly worth the £24-95 to see you through the exam.

Dr John Winder

MASTERING EMERGENCY MEDICINE: A PRACTICAL GUIDE. 1ST EDITION.



Editors: Chetan Trivedy, Mathew Hall, Andrew Parfitt

The Royal Society of Medicine Press. November 2009. Paperback.

£39.95 ISBN 978-1-85315-744-8

This is a welcome 1st edition text for trainees in Emergency Medicine. Never before has there been such a concise, revision-focused text that aids preparation for the Emergency Medicine clinical exams, at both Membership and Fellowship standards.

This well-designed text is in a format closely based on the College of Emergency Medicine (CEM) syllabus. In the 34 chapters, there is coverage of the core curriculum with sections including: Resuscitation, Wound Management, Infectious Diseases, Acid-Base Disorders, Toxicological Emergencies and Psychiatric Emergencies. A chapter on Medico-Legal Aspects of Emergency Medicine encompasses all relevant issues such as: consent, capacity, children in the emergency department, living wills, complaints procedures and confidentiality. Northern Ireland trainees should be aware that the Mental Health Act 1983 applies only to Great Britain and the Mental Health Order 1986 (not covered in this book) applies in Northern Ireland.

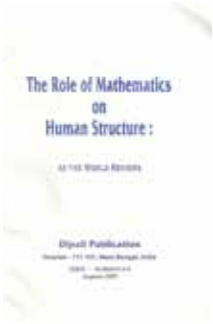
Each chapter begins with a list of the 'core topics' relating to the chapter title. The core topics are then individually covered using clinical scenarios similar to those encountered in previous OSCE exams. The sample scenarios cover the 5 broad categories encountered in the CEM examinations: clinical examination, skills examination, teaching-based OSCE, communication skills OSCE and the history-taking OSCE. A '*suggested approach'* outlines why the topic is pertinent to Emergency Medicine and describes a methodical approach to the scenarios enabling the reader to learn a template on which to base further revision and clinical practice. A non-official mark sheet at the end of each scenario may be used as a guide to the expected OSCE standard.

The layout of this book includes shaded boxes highlighting important learning points such as relevant scoring systems, complications and risk factors. The authors use useful mnemonics as a learning aid for those of us who prefer this style of learning. Where relevant, there are external references quoted such as NICE, Toxbase and the Resuscitation Council for further reading.

In summary, no book is a substitute for clinical experience and the coverage of topics in this text is not exhaustive but reading this well-presented and up-to-date text, which has been written specifically for the MCEM and FCEM clinical examination is undoubtedly an excellent adjunct to seeing patients in the emergency department in preparation for the college exams.

Dr Andrew Dobbin

THE ROLE OF MATHEMATICS ON HUMAN STRUCTURE: AS THE WORLD REVIEWS.



Kumar Adhikari. Dipali publication. August 2009. Paperback. 48pp. RRP £10.95

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Over the past few years, I have been asked to review quite a number of books and manuscripts but none as unusual as The Role of Mathematics on Human Structure: As The World Reviews.

A publishing house uses the term "vanity publication" to describe books that are not commissioned, but instead, the author will pay for the printing of the manuscript.

On occasion, such books may have some merit, perhaps overlooked by sales-hungry literary agents and publishers. Generally though, such publications are books without commercial appeal and have little or no intrinsic merit.

When asked to review this publication, I expected a book about the mathematics and biomechanics relating to Human Anatomy. Imagine my surprise to find that the book is in fact, a summary of the reviews of the author's 2003 publication, 'The Role of Mathematics on Human Structure'. I was in fact, being asked to review a book of reviews, which had been published, at his own expense, by the author himself.

Let me be clear: the author's initial publication is not the book that is now under review. The Role of Mathematics on Human Structure was apparently a book that considered the application of mathematical methods to aid more precise surgery, and produce better surgical outcomes, particularly in the orthopaedic population. The Role of Mathematics on Human Structure: As The World Reviews, the book currently under review, reproduces 33 reviews of his earlier publication and presents them to the reader. To be fair, it would appear that the majority of the reviews are favourable, but not all the reviews are in English. Several of the more detailed reviews outline the original book's structure in considerable detail.

Why is there a need for the follow up publication? The term 'vanity publication' could have been coined specifically to describe this book. Why would anyone publish a book detailing reviews of an earlier book? More curiously, who would buy such a book? It is little wonder that this was published at the author's own expense. Who are the potential readers of such a publication? (I can't, for the life of me think that anyone would waste their time or money on purchasing, let alone reading it).

Surely, in this day and age, any potential purchaser would choose the cheap, fast option. Simply Google the title and author, check out the Amazon reviews, and make a decision on whether or not to buy. I can think of no reason to recommend this publication to anyone, unless of course you are the doting mother or devoted partner of Dr. Kumar Adhikari.

Dr Tom Lynch

THE ULSTER MEDICAL JOURNAL

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