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Submissions to submissions@RCSIsmj.com
Access and innovation

Last year’s journal received overwhelmingly positive feedback and I think it is safe to say that students and staff were greatly impressed by the high quality of the first issue, both in terms of the excellent content, and its appealing presentation. You should expect nothing less from an RCSI publication, so it is with a tip of our hats to all of last year’s journal staff and contributors that we are now delighted to present to you the second edition of the RCSIsmj. Last year’s journal set the bar high for us, but everyone working on this year’s edition has certainly been up to the task. We have endeavoured to achieve the same high standard as was set last year, and also to include a few new ideas of our own.

The new ‘in the pipeline’ section strives to provide interesting reviews of cutting edge research into new treatments – whether drugs, procedures or other technologies – which I believe medical readers should become familiar with (p.73). The medical school curriculum is sometimes slow to incorporate information on preclinical or new treatment strategies, and I hope that this section will help to keep the perspicacious reader in tune with the very latest.

Our Senior Editor, Erik Vakil, has collaborated with Prof. David Smith to create the ethics challenge (p.5). Ethical dilemmas are a quintessential aspect of all medical practice. While you might one day know everything there is to know about your specialty, that knowledge alone will not see you through your ethical quandaries. We hope to encourage everyone to take a minute and think critically about the scenario we have presented. Moreover, we hope that some of you will take a little more than a minute to write down your thoughts and make some critical arguments to submit to the competition. The best argument as judged by a faculty panel will be published in next year’s journal.

Another new feature is the ‘editors’ pick’ (p.37), the article that stood out to both of the editors as being a truly excellent piece of work in every respect. We felt that as a tribute to such excellent work, the topic of that work should inspire the cover art. We think you will agree that this year’s editors’ pick is indeed an excellent offering, and thus understand why we chose the cover theme.

RCSIsmj Director Laura Cullen and Vice-Director Kristl Vidya Dorschner have chosen the theme of the journal this year: ‘access to healthcare’. Kristl’s original research on foetal screening (p.22) touches on this issue, and in the ‘access to healthcare’ section (p.49) we have published three articles, each of which provides a very different perspective on the issue. Laura Cullen has written ‘Health and homelessness: an Irish perspective’, which looks at the unique challenges faced by the homeless population in accessing health services. ‘Mountains to climb – healthcare challenges in rural British Columbia’ provides a look at the challenges of delivering care to vast areas of rural Canada. Finally, ‘The global evolution of medical tourism: the American perspective’ examines the recent phenomenon of medical tourism, and the impact of globalisation on the worldwide healthcare industry.

This year we received a large volume of excellent contributions and we feel that this issue highlights the very best. Unfortunately we cannot publish everything we receive, but we would like to sincerely thank all those who submitted for their hard work. We would also like to encourage all our readers to keep us in mind in future years. We are proud to showcase the great work being done by everyone at RCSI, so read on and enjoy!

James Young – Chief Editor

Faculty Editor’s message

I am very happy to welcome readers to the second edition of the RCSIsmj. James Young, Erik Vakil, Laura Cullen and their editorial team are to be congratulated on building upon the success of last year’s inaugural issue. The high standard of content and publication quality is evident throughout this second edition. Once again, diversity has been embraced in terms of the coverage of articles, with a mixture of original articles, case reports, topical reviews and perspectives across a broad range of medical areas. RCSIsmj reflects the diversity of medicine and the opportunities that await our current undergraduates. Other articles show that we now live in a global medical community. Equity and access to healthcare are issues throughout the developing and developed world. As the RCSI is a multinational and multicultural medical school, many of our graduates will be faced with these challenges during their professional careers. I hope readers find the articles as informative and interesting as I do.

RCSIsmj is an undergraduate-led journal that is a showcase of a vibrant and diverse medical school.

Professor Tom Fahey
Head of the Department of Family Medicine and General Practice, RCSI
RCSIsmj ethics essay prize

Ethics challenge

The RCSIsmj Ethics Essay Prize is a new feature of the 2008/2009 edition of the journal. We are inviting all students to submit an essay discussing the ethical questions raised in the case study presented here. Medical ethics is an essential aspect of the medical curriculum and we hope to encourage RCSI students to think critically about ethical situations that arise during their education and their careers in healthcare.

All essays will be reviewed by a faculty panel of experts, and the winning essay will be published in the 2009/2010 print edition of the RCSIsmj. This is the perfect opportunity to get published and the only officially guaranteed publication in the RCSIsmj. The deadline for submissions will be March 31, 2009, and the winner will be announced on June 1, 2009. Submissions should be made as an attachment to submission@rcsismj.com and must adhere to the submission guidelines available on our website at www.rcsismj.com/ethicsprize. All inquiries should be made to editor@rcsismj.com.

Good luck!

The case
You are a GP in a rural town. Richard, a 35-year-old patient, presents with a dry cough, having recently returned from a four-month-long business trip to Botswana. As he is about to leave the room, he says: ‘By the way, I’m a bit concerned – I slept with a woman while away, and I’m worried I might have picked up something’.

You counsel him before taking blood for a HIV test. He returns a week later and you have to advise him that the results show him to be HIV positive. He is married with two children, and his wife is also one of your patients. He is very upset when you raise the question of discussing the results with his wife. He says: ‘No way! Our marriage is in enough trouble as it is!’ They are not currently sleeping together, although his wife has noticed that he’s been trying to avoid any form of intimacy and wonders why. He then threatens to sue you for breach of confidentiality if his HIV status becomes known to his wife.

Submission guidelines
Your essay should include an introductory section that identifies the key ethical questions raised in the case study. These questions should then be addressed in a logical fashion underlining how you might deal with this situation satisfactorily. Please also include a section where you address weaknesses in your arguments.

Your paper should not exceed 2,500 words.

Please note that this should not be written as an opinion piece. It will be expected that you discuss ethical issues academically, making sure to reference where necessary.

Your essay will be evaluated on three major criteria:
1. Ability to identify the ethical issues raised by the case.
2. Fluency of your arguments (note that there is no penalty for which side you discuss, just be sure to develop your arguments in a clear and logical fashion).
3. Academic quality with regard to depth of research, appropriateness of references and quality of sources.
AOIFE MORRIS tells the story of the RCSI’s involvement in momentous events in Irish history.

RIGHTS AND REVOLUTION: the RCSI in Irish history

The RCSI has a long and distinguished history where medical education, innovation and research are concerned. What is less well known is that it has, both as an institution and a building, witnessed and participated in many significant historical events.
Revolution – 1916

The RCSI’s most popular historical association, certainly in the mind of the Irish public, is its unwitting participation in the historic events of Easter Week 1916. From Tuesday April 25 to Sunday April 30, the College housed a garrison made up of 109 male and 10 female members of the Irish Citizen Army, led by Commandant Michael Mallin and his Second-In-Command, Countess Constance Markievicz. Initially, on the afternoon of Monday April 24, the garrison took up position in St Stephen’s Green, but Mallin was forced to re-evaluate his position when the British forces occupied the Shelbourne Hotel and United Services Club. Thus, Sergeant Frank Robbins and Countess Markievicz, together with a small party, were sent to secure the RCSI, both as an escape route and to search for arms and ammunitions belonging to the Officer’s Training Corps, which was attached to the College at the time.

Their arrival at the front door of the college coincided with that of Dr John Knott, described as an “elderly, erudite and eccentric” Fellow of the College who was accustomed to spending his day in study in the Library (now the Anatomy Room). Oblivious to the sounds of battle and the flying bullets, he made his way up York Street only to be told by the bedel (caretaker), door ajar, that the College had been closed by order of the Registrar. The rebels seized the opportunity and rushed in, “one of the rebels firing at close range, a rifle” to secure the building for their purposes. As for Dr Knott, he continued on his journey to the Library, seemingly unfazed by the chaos and gunfire surrounding him.

Heavy fire by the British on the 25th forced Mallin and his troops to withdraw from St Stephen’s Green and join the small contingent in the College. JDH Widdess, renowned Irish medical historian and former RCSI Librarian, described the scene: the examination hall (now the College Hall), being surrounded by four solid walls and lit only from the roof, provided safe sleeping quarters. “Space beneath the seats of the chemistry lecture theatre in the rear of the building was fitted up as a mortuary. In the Entrance Hall, barricades were constructed with books from the Library”. Despite this, “neither the fabric nor contents [of the College] suffered serious harm”. Although the College was spared much of the destruction that befell other strongholds of the Irish rebels during Easter Week, the bullet holes in the façade and, most remarkably, the neat depression of a bullet hole in the brass plate on the inside of the College Boardroom door, bear silent witness to their presence.

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This sporting life

Prior to the events of Easter 1916, the College of Surgeons Lecture Room witnessed an important event in Irish sporting history: the formal adoption of the original rules of hurling. Under the chairmanship of Dr Hugh Auchlinek, they were adopted at a meeting of the Dublin Hurling Club on January 3, 1883. In attendance at this meeting was Michael Cusack, who was appalled at the style of hurling.
prevalent in Dublin at the time. The version of hurling concerned was a genteel form known as ‘hurley’, much closer to hockey than to the ancient Irish game. It was practised by such individuals as Edward Carson of Trinity College (a prominent unionist who went on to lead the Ulster Unionist Party at a crucial time in Irish history, and a key player in ensuring England kept their rule over Ireland – an attitude at odds with the philosophy of Gaelic Games) and was “effeminate in the extreme”; for example, kicking the ball and pushing an opponent were forbidden. Michael Cusack went on to found the Gaelic Athletic Association (GAA) on November 1, 1884.

Here come the girls

The RCSI has also played an important role in social history. In addressing issues of equality, the RCSI, through its medical school, has been very progressive over the centuries. In the late nineteenth century, female Irish medical students found themselves frustrated and their careers hampered by the negative attitudes of professional men. While these women were fortunate enough to be encouraged to pursue a medical education by their parents, they were not allowed to sit examinations or obtain degrees. The Medical Qualifications Act of 1876 made it optional for any medical examining body to admit women to their examinations and, thus, become licensed to practise medicine. In 1877, the King’s and Queen’s College of Ireland (later the Royal College of Physicians of Ireland [RCPI]) was the first body to respond and vote, by a majority of one, to admit women.6

In 1885, the RCSI opened its educational facilities “that all provisions of the Charter, Bye-Laws, and Ordinances as to education, examination, and granting diplomas to Fellows or Licentiates shall extend to women” and agreed to recognise the examination results from the London School of Medicine for Women.7 The first female Licentiate of the RCSI, Mary Emily Dowson of London, was presumably a pupil of that school. The RCSI was the first College in Great Britain and Ireland to admit women to their medical school. There was one entry in the winter session of 1885-1886, a Miss Agnes Shannon. It seems, however, that she did not persist with her studies, as the first female graduate was Mary Josephine Hannon, who took a post in India. One of the most distinguished of the early female graduates was Emily Winifred Dickson (Martin). She won numerous medals before graduating as a Licentiate of the Royal College of Physicians in 1891. Following training in the Rotunda Hospital, she qualified with a MB BCh BAO Gold Medal in 1893 and, in 1896, was elected the first female Fellow (FRCSI) of any of the Colleges of Surgeons in Britain or Ireland.

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Present day endeavours

Such equity, in both access to and further opportunities in medical education, is something that the RCSI strongly advocates through its many enterprises both here and abroad. The RCSI continues to cultivate its long-standing historical involvement in honourable endeavours through the conferring of Honorary Fellowships. Notable recipients acknowledged for their contribution to humanitarian causes and human rights have included Mother Teresa of Calcutta (1995), President Nelson Mandela (1996) and Bob Geldof (2007). This is in keeping with the RCSI’s efforts to constantly perform beyond the boundaries of its medical charter. Whether intentional or unwitting, RCSI, in its presence on St Stephen’s Green, has witnessed movements and beliefs that have had a significant impact on the landscape of Irish history.

References
Located in the heart of Dublin City, the Royal College of Surgeons in Ireland (RCSI) is an internationally acclaimed school of medicine and medical sciences, renowned for its undergraduate and postgraduate professional and research programmes. Another aspect of the school that is often unknown to students is the contribution that the RCSI has made to the wider community since its foundation. Over the years, these have ranged from fundraising events for breast cancer research to senior citizens’ Christmas parties. One specific area that stands out is RCSI’s devotion to education programmes and health promotion in the local community.

The Research Outreach Programme

The first programme to be formally established was the Research Outreach Programme, which began in 2000. The Programme’s objective is to educate the general public, teachers and students about scientific research in a way that is comprehensive, interesting and enjoyable.

Beginning at primary school level, the RCSI hosts an annual ‘Science Hands-On Workshop’ (SHOW) that involves a one-day visit to the College. The purpose of this event is to make science more accessible and fun for children. Over the course of the day the children get to visit some of the laboratories on campus, participate in basic experiments and, as a group, they get to interview a ‘real scientist’. Students are provided with a workbook to take home that includes photographs of the day’s events and directions for basic experiments that they can carry out with their teacher in the classroom. RCSI researchers are also available to give talks and interactive presentations to schools on general scientific topics.

Schools programmes

the RCSI has also created a ‘mini med school’ for Transition Year students, which was launched this year. The aim of this programme is to encourage students to pursue a career in the healthcare field by giving them a taste of ‘real-life’ medicine. A total of 150 students attended the week-long programme, which took place on the RCSI campus and in Beaumont Hospital. Students participated in a variety of clinical skills workshops and lectures, and were given the opportunity to view live surgery. Because of its overwhelming success and the enthusiasm expressed by both students and staff, the college has doubled the number of places in the programme for 2009.
Another activity aimed at Transition Year students is the annual ‘Focus on Science’ programme. Each year, 25 students who have a specific interest in pursuing a career in science and scientific research are invited to participate. The programme provides hands-on experience in laboratory investigations and experiments, bringing to life the students’ ideas for their possible future careers. For secondary school students, the RCSI Research Outreach Programme supports and co-hosts the ‘Debating Science Issues’ annual national debating competition. The aim of this competition is to develop students’ interest and increase their knowledge of advances in biomedical scientific research.

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Public access
An outreach lecture delivered by a leading scientific expert is also held every year to promote science and technology to the general public. Last year Dr Michael Stebbins, Director of Biology Policy for the Federation of American Scientists, gave an interesting lecture entitled ‘Bring US Science Policy Back from the Brink of Insanity’. For members of the public with a specific interest in the field of medicine, the opportunity to broaden their knowledge is provided by the original ‘mini-med school’. This has been hosted in Dublin by the RCSI for a number of years. Medical professionals from the RCSI deliver talks on a variety of topics such as forensic medicine, human anatomy, and diseases of the young and old. Any member of the public can apply to the course, which takes place every two years. This year saw the introduction of the ‘Mini-Med School Road Show’ to provide people outside the Dublin area with the opportunity to take part in the programme. Waterford was chosen to host the inaugural event.

The REACH Programme
REACH (Recreation, Education, and Community Health) is a community outreach programme established in 2007. It brings the various RCSI community activities together into one programme led by a dedicated programme manager. The main function of the programme is to encourage primary and secondary school students to enter tertiary education programmes, particularly those students who have been traditionally under-represented at these institutions. The hope is that by interacting with third-level students in a college environment, primary- and secondary-level students will feel that they can belong in these third-level institutions.

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Community health
The REACH programme also promotes health and fitness in the community. The Community Health and Fitness Day is an annual event hosted by the RCSI in association with Mercer Medical Health Centre. In 2007, the event held workshops and educational talks on topics such as diabetes, cancer, and the importance of blood pressure and cholesterol monitoring. Mercer Medical Centre also provided free health checks to members of the community over 50 years of age. In addition, members of the RCSI paramedic programme provided defibrillator training to coaches of local football teams.

Conclusion
The REACH programmes help to show that the RCSI, while focusing on educating tomorrow’s healthcare professionals, also accepts responsibility for providing educational services and opportunities to the community, from primary school students to our elderly population. This commitment evolves with each passing year and it is obvious that there is a huge reliance on RCSI staff and students to donate their time to nurture this vital component of the RCSI’s ethos.

Acknowledgements
The author wishes to thank Dr Kate Johnson and Maria Kelly for providing the information for this article.
We drove a truck for four to five hours into the countryside of Malawi. It was a four-wheel drive where we had removed all the seats to fit about 30 people on the floor. We only had enough resources to visit once a year. We travelled to four centres, usually schools or health clinics, to pick up patients for cataract surgery. They had to be legally blind with a vision of 3/60, which is worse than legal blindness in Ireland (6/60). Once they were 3/60 in both eyes, they were eligible to get into our truck.

One man I saw was 45 years old, with a vision of 6/36 in his better eye. He had five children and could barely walk into the room unassisted. Yet we had to tell him: ‘Sorry, we can’t put you in the truck. We can only take people who are worse and we don’t know when we can come back to get you’. He just sat down and cried on the spot. This would never happen anywhere else. It was absolutely heartbreaking.

Ms Coleman’s initial inspiration came from an astounding lecture about the ability to solve the global crisis of blindness, which was given by Professor Allen Foster, one of the founders of the Vision 2020 (V2020) initiative, in 2000. V2020 estimates that approximately 75% of world blindness is avoidable. It also defines “avoidable blindness” as blindness that can be successfully treated or prevented by known cost-effective means. Cataracts, defined by the WHO as clouding of the lens of the eye that impedes the passage of light, is the single most important cause of avoidable blindness in developing countries, and cataract surgery has been shown to be the most effective treatment.

As a specialist in cataract and oculoplastic surgery, Ms Coleman was especially keen to develop a cost-effective and rapid method to bring cataract surgery to Africa. “50-75% of blindness in Africa is due to cataracts. It does not matter how much money is raised for the problem, because unless there is a programme to train surgeons to treat cataracts, there is never any hope of helping the people. Only a surgeon can train a surgeon; therefore, it would have to be a surgeon who set up the programme, and I knew that was what I had to do.”

Ms Coleman immediately began her quest for a cost-effective and self-sustainable system to deliver cataract surgery to Africa. The answer was found when she travelled to Aravind Eye Hospital in India. “They [Aravind] were using the latest techniques in the developing world,” praised Ms Coleman. “They had already developed a solution. Therefore, I decided to work with them to bring the solution to Africa.”

Excited by her findings, Ms Coleman proposed her solution for blindness in Africa to RCSI CEO Professor Michael Horgan at an alumni reunion and immediately gained full support from the College. A board committee, composed of corporate executives, field academics and enthusiasts, was later put in place. RTS was finally registered as a charity in January 2006.
Making the dream a reality

RTS is currently working closely with the Aravind Eye Institute (LAICO) and LV Prasad to adapt the model of eye care developed in India to the African context. In its 18-month start-up phase, RTS established 27 projects in India and eight in Africa – in Angola, Kenya, Ethiopia, Congo, Cameroon, Rwanda, Malawi and South Africa. All of the projects were based on a similar concept, where RTS would seek local partnerships with hospitals, clinics or companies to provide high volume, high capacity and sustainable eye care through the introduction of capacity building and cost recovery. Ms Coleman explains: “The idea is to provide the latest technology – for example the newest intraocular lens – to people who can afford it, and the revenue generated will then pay for treatment for poor patients”.

“In our hospital in Lumbashi, Congo, a mining company pays $400 to the hospital for each cataract surgery done on their employees. Revenue generated from one surgery on a mining company employee can cover three surgeries for a poor patient. In September 2007, we performed 200 cataract operations and saw 200 outpatients. The programme cost US$39,000 to run, US$37,000 was earned and no poor patients were turned away. The programme is expected to operate at a profit in six months and the profit will be used to expand the training service. Several Indian surgeons and nurses are currently training two local Congolese surgeons and their nursing staff.”

Where now?

In the next phase, Ms Coleman wishes to focus on developing surgical training programmes for locals and surgeons who wish to volunteer. In developed countries, there are two main types of cataract surgery: the conventional extracapsular cataract extraction and the preferred high frequency ultrasonic probe approach, known as phacoemulsification (phaco). The dilemma is that most surgeons are no longer trained to perform extracapsular cataract extraction and phaco requires expensive equipment. This makes both approaches difficult to apply in a self-sustainable manner in a developing country. Fortunately, there is a quick and inexpensive alternative known as small tunnel incision. Ms Coleman claims that this procedure only requires three to eight minutes to remove a cataract. However, this technique is difficult to learn if the surgeon has not first mastered the extracapsular approach. Hence, RTS is working to develop a ‘rapid transfer training programme’ to train surgeons who are only trained to perform phacos to master small tunnel incision as well.

A role for students

Near the end of the interview, when asked if RCSI students can take part in such an exciting programme, Ms Coleman gave this reply: “Medical students can play a significant role in helping with the transfer of skills to local people, for example teaching shopkeepers how to give out reading glasses, or teaching local doctors to screen for CMV retinitis and to perform basic dilated fundoscopy”. Transferring skills is more beneficial than actively volunteering those skills, as it allows locals to generate an income and promotes self-sustainability. The role of skills transfer may eventually extend to other areas of the programme depending on the necessity, response, and level of competency of students.

Many of us are aware of the resource disparity that exists in this world and many agree that something should be done. Yet few people act upon their dissatisfaction with the status quo and actively search for a solution, as Kate Coleman has done. With her leadership, RTS has entered the field of international eye care at a time when the industry can exploit recent technological and clinical advances to treat avoidable blindness. “We could not have done this 10, 15 years ago because Aravind had not proven the case and because technology has changed so rapidly that it allows a cataract operation to be done in three to eight minutes. This is the time. Everything in the world is coming together to eliminate this crisis.”
An independent healthcare provider

Professor Mark Redmond is one of the leading cardiothoracic surgeons in the country. He completed his training at Johns Hopkins Hospital in Baltimore, Maryland, and has held a number of prominent positions, including Director of Paediatric Heart and Lung Transplant, Co-Director of the Albert Broccoli Centre for Aortic Diseases, and Director of The Cardiac Research Laboratories, at Johns Hopkins. He returned to Dublin in 2000 where he founded the Beacon Hospital and Medical Group in Stillorgan. Professor Redmond continues to lead as a consultant cardiothoracic surgeon and is active in developing and promoting alternative models to public healthcare.

Q. How do you think the RCSI contributed to your success?
A. I think the College contributed dramatically to my education, not just in terms of a medical school, but also in the overall development of healthcare and how it was due to evolve, particularly in regard to education and research. I think it is probably in these two areas that the College was at its strongest and contributed most to helping me develop as an academic surgeon. I also did research in anatomy at the end of my second year, I did research in biochemistry at the end of my third year, and the College was able to support me in securing some internships in the US in the subsequent years.

Q. You’ve said that the Beacon Hospital uses a platform of education and research to deliver quality healthcare. Could you tell me a little bit more about these activities?
A. It is just a vehicle to provide healthcare. We traditionally think of hospitals as a bunch of rooms with beds in them, but the hospital is a dynamic place where the whole concept should revolve around delivering a service to a patient, and that patient doesn’t necessarily have to be in a bed. This is no longer a novel concept but it would have been when it was introduced in the ’70s and ’80s. For a hospital to deliver healthcare, it constantly has to reinvent itself; it has to evaluate what it does and how it can do it better in terms of service delivery. I like to say “introduce disruptive technologies”, which means introducing new ways of delivering healthcare, introducing new forms of treatment that can usurp traditional thinking, introducing new ways of doing things, and in that way moving healthcare forward.

I believe that healthcare will soon become undeliverable in terms of finance because it is becoming too expensive, too cumbersome and isn’t patient-focused enough.
that is where research in healthcare delivery is so important to us. We are trying to develop a kind of translational research mode where we can bring advancements in treatment processes to fruition in the setting of the medical campus, which is designed to be flexible, quickly embracing new ways of treating patients in a successful fashion.

In terms of education, there is no point in delivering all this care to patients without it benefiting the next generation of doctors and nurses. It is vitally important to us that we educate the new generation of healthcare providers in an open-minded way, with novel concepts and new ways of introducing care, to avoid this idea of getting stuck in a rut by delivering care in a way that was successful in the past, because it certainly isn’t going to work in the future. We’re trying, in our way, to influence the next generation of healthcare professionals so that they can be ready for the new advances that are made now and over the next 10-15 years, and come up with their own ideas about new ways of doing business for surgeons and doctors.

Q. How important is the interface between primary and tertiary care?
A. That is the key. The patient’s introduction to healthcare and first point of contact tends to be their GP. After that the experience can be quite mixed depending on what the GP believes is wrong with the patient. They can access healthcare through the emergency rooms or they may access it by trying to obtain consultations with doctors in their consulting areas in outpatient departments and hospitals. There is a whole mix-and-match of ways of accessing care and it is haphazard. It can be dependent on social standing and ability to pay. We see that as a real flaw in the healthcare system, not just in this country but also in many other countries. We want to work on that interface to bridge the gap between patients developing symptoms and getting the appropriate care. It is only by doing this that patients may receive a more seamless chain of care that brings them to where they need to go to get well.

Q. What was the biggest lesson you learned in America and how have you applied that to the Beacon?
A. We were encouraged at Johns Hopkins not to accept the status quo, even if it was comfortable. Once you are comfortable in delivering care to patients, in your research, or in your education of medical students, once you’ve formulated a strategy for doing all of those things and are comfortable with it, it is time to think and say “wait a minute now, this isn’t right”. We need to be constantly evolving, and constantly trying to challenge ourselves and others around us. This is apart from learning how to be a cardiac surgeon, which I sometimes take for granted. I felt very strongly about this undercurrent of reinvention and it is something we’ve worked hard to achieve at the Beacon.

Q. What is the greatest crisis facing the Irish healthcare system?
A. The big concern that I personally have for the Irish healthcare system is budgetary constraints. There is also a lack of co-ordination in the public sector between healthcare delivery and healthcare finances. Often those involved in the financial end are not trying to co-ordinate delivery of care and it is a lack of co-ordination that has led to our current problems. We have what we call a triple nationalised healthcare system, where the Government is responsible for funding healthcare, for regulating it and for delivering it. I think this leads to long waiting lists, and difficulty in accessing healthcare. Once a patient is in the system, it tends to be a relatively good system. But then when we move on from there into the community, there aren’t the services designed to prevent patients coming back into hospital with similar problems. So the problem is that when you’re triple nationalised, you’re budget-oriented, and the only way to save money is to cut budgets to hospitals in a clinically unsophisticated fashion. The Government is saying: “sorry your budget is dropping by 10% next year” without helping hospitals to co-ordinate how they deliver their healthcare between different hospitals to try to allow savings in one area and increased delivery of healthcare in another. It is that lack of clinical sophistication that is leading to many of the current problems in the public healthcare system.

The concept of the Beacon was to become an independent provider of healthcare so that the Government would have the option to purchase very high-level healthcare from an independent provider. Public budgets could then buy that healthcare and it would be the responsibility of the provider to deliver the care in a very efficient and value-for-money fashion. The Government would then be in a position to purchase healthcare where it wants and not just from public hospitals; that way they would have a real alternative. That would allow them to drive efficiency into the system, and allow them to move from inpatient to outpatient care in certain situations without having to worry about interfering with unions or staffing levels.

Q. What is the role of private healthcare in Ireland?
A. I think this is a controversial area. Personally I don’t like to use the word private. I use the word independent because the word private has connotations of exclusivity and ability to pay and I don’t see that way. If you have been to our renal unit, all those patients are public patients, if you like to use that term. In other words, it doesn’t matter what your ability to pay is, but that these are patients that need healthcare in the form of renal dialysis. The Government has used our renal facility and has purchased the services there, and obviously we do a very good job at providing that care, and this has given them a great option for their patients. If the Government finds a way of doing things differently or somebody finds a better way of delivering renal dialysis, the Government can move on to a different provider who does it better. The challenge for the independent provider is to come up with a way of responding to any changes that occur. It’s not up to the Government to do it, so the Government can spend its time directing healthcare, which is best done by just spending the money in whichever way it wants and not worrying about human resources and capital expenditure.
The effects of seizures on the brain: transcriptional profiling using a DNA microarray database

Abstract

Background: Epilepsy is one of the most common neurological disorders, affecting people of all ages. In recent years, important advances have been made in the study of mechanisms underlying the development of epilepsy using large-scale gene profiling. Changes in the expression of genes involved in neurogenesis, astroglialosis, and axonal and/or dendritic plasticity, and the loss of selective neuronal populations, are some of the significant findings made in previous microarray studies.

Aim: To categorise the biological function, cellular compartment localisation and molecular function of genes altered by seizures.

Methods: A mouse brain gene expression database containing the results of the effects of seizures on around 35,000 genes was investigated.

Results: Genes whose expression was altered at least two-fold as compared to controls, once corrected for multiple comparisons, were included in the analysis (929 genes in total). Gene ontology analysis revealed that cellular activity, immune system, biological adhesion and localisation were the most highly represented processes in the biological function category. Within the cellular component category, genes associated with intracellular organelles and the synapse were most abundant. Finally, within the molecular function category, genes involved in binding and transporter activities (particularly glutamatergic ion channels) were most highly represented.

Conclusion: This analysis provides a comprehensive ontology profile of gene expression changes in response to seizure activity in the brain, and may yield new insights into molecular mechanisms underlying the development of epilepsy.

Keywords: Seizures, mice, epilepsy, microarray analysis, gene expression.
Convulsive status epilepticus (SE) in rodents has been used extensively to understand how seizures affect the brain and the pathological processes by which epilepsy develops (epileptogenesis). In rodents, systemic administration of the cholinergic agonist pilocarpine or the glutamate analogue kainic acid (KA) are frequently employed to model SE. Both produce bilateral and widespread hippocampal and extra-hippocampal damage, which reflects some, but not all, neuropathological aspects of human TLE. In contrast, focally evoked seizures in rodents replicate more faithfully the unilateral pathology of TLE. For example, microinjection of KA into the mouse basolateral amygdala nucleus evokes a prolonged seizure within the limbic system that culminates in unilateral damage to the hippocampus (principally the pyramidal neurons of the CA3 subfield). The insult is also epileptogenic, with mice developing spontaneous recurring seizures within the first week along with longer-term hippocampal changes including astrogliosis and increased neuropeptide Y immunoreactivity, which is suggestive of mossy fibre (axonal) reorganisation. These changes were the primary reason for our investigation of the neurons in the hippocampal region. Identifying genes that influence seizure-induced neuronal death and the cell and molecular changes underlying epilepsy development is an important challenge facing epilepsy researchers.

DNA microarrays (‘genechips’) are a powerful technology for large-scale analysis of gene expression changes in the brain. The latest microarray chips can analyse over 35,000 genes. Microarrays have already been successfully applied to study gene expression changes in a variety of models of experimental epilepsy including electroconvulsive stimulation in rats, intra-amygdala injection of KA in mice or rats, and intra-peritoneal injection of PTZ (pentylentetrazole) in mice. In the rat model, changes in the expression of specific genes involved in the loss of selective neuronal populations, axonal and/or dendritic plasticity, astrogliosis, neurogenesis, changes in the arrangement of the extracellular matrix and reorganisation of neuronal circuits have been observed. Gamma-aminobutyric acid (GABA), sodium channel, voltage-gated, type 2, beta subunit (Scn2b), sodium channel, voltage-gated, type 2, alpha subunit (Scn2a), and glial fibrillary acidic protein (Gfap), are some of the genes previously implicated in epileptogenesis. GABA is the main inhibitory neurotransmitter in the brain and activates Cl⁻ channels, hence hyperpolarising the target neuron. However, Scn2a and Scn2b encode for sodium channels to allow the propagation of action potential by causing an influx of Na⁺ into muscles and neurons. Finally, the Gfap gene encodes for intermediate filament (IF) protein, which is found in glial cells such as astrocytes. In hippocampal sclerosis, dentate granule cells sprout mossy-fibre axons that are directed back into the inner molecular layer, possibly because the neurons they usually extend to have been lost. There is some evidence that these aberrant mossy fibres instigate a recurrent excitatory circuit by forming synapses on the dendrites of neighbouring granule cells, and also form synapses on inhibitory interneurons as part of a feedback mechanism. The aim of the present study was to comprehensively profile the genes regulated by damaging seizures in order to gain insights into the pathogenesis of seizure damage and the development of epilepsy.

Methods
Experimental seizure model and sample preparation for microarray
Methodology for microarray analysis of gene expression following experimental seizures has been recently described. RNA was extracted from the ipsilateral hippocampal CA3 subfield of male C57Bl/6 mice (9-10 weeks old) 24 hours following an episode of status epilepticus triggered by intra-amygdala microinjection of kainic acid (1µg) using the TRIzol reagent (Invitrogen Corporation, Carlsbad, CA, USA), as described. Control and seizure mice were adult male C57Bl/6 (from Harlan, UK) and weighed 20-22g. A group of C57Bl/6 mice, vehicle-injected, served as controls.

Samples were processed by an Affymetrix authorised service provider (Almac Diagnostics, Craigavon, Northern Ireland). RNA was subject to one-round amplification and the labelled target cRNA was then hybridised to the Mouse Genome 430 2.0 GeneChip arrays, which detect over 39,000 transcripts. Affymetrix GeneChip image files were analysed by robust multi-chip analysis (RMA) using RMAExpress 0.5 to determine background adjustment, perform quantile normalisation, and calculate expression values. Replicate arrays (n = 5 for control, 4 for injury) were included in the analysis. The normalised data was filtered to select for genes with an average raw expression value of greater than 50 in at least one of the three conditions, then uploaded to Genesifter® (VizX Labs, Seattle, WA, USA) for statistical analysis. Data was adjusted logarithmically and the threshold for significant regulation was set at two-fold in order to include genes that exhibit a biologically meaningful change in expression but not exclude certain genes that, because of high constitutive expression, may show lower degrees of change. A t-test was applied followed by the Benjamini–Hochberg algorithm to correct for multiple comparisons. Gene ontology and function were assigned using Genesifter®, which uses genetic information available in Entrez Gene, Kyoto Encyclopedia of Genes and Genomes (KEGG), and the published literature. Z-score analysis, which indicates whether a process or ontology term is significantly (p<0.05) over-represented (≥2) or under-represented (≤2) was performed using Genesifter® software.

Results
Overview of transcriptome analysis
We have previously reported that of 39,000 gene transcripts investigated by microarray analysis, expression of a total of 929 genes was significantly different compared to the control group. Of these, 686 (74%) were upregulated compared to 243 (26%) that were downregulated. In the present analysis we used the most recently updated Genesifter® database (interrogated June-July, 2008), to explore the biological and molecular functions of

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FIGURE 1: Z-score representations of genes involved in different biological processes, cellular components and molecular functions: Ontology of genes regulated by experimental seizures in the hippocampus. The graphs represent gene Z-scores that were up- or downregulated, and are grouped according to: (A) biological process; (B) cellular component; and, (C) molecular function. Ontology assignments were through Genesifter®.
these genes and reveal the cellular compartments with which they are associated. In addition to overall gene numbers, Z-score analysis was applied in order to avoid drawing erroneous conclusions about important processes based on high numbers of regulated genes alone by taking into account the overall abundance of genes in a particular category. Note that in some cases, individual genes were represented more than once within each ontological term (for example, the same gene may be associated with both nucleus and cytoplasm).

Analysis of expression of genes implicated in biological processes
In terms of biological processes, we analysed genes involved in cellular processes, metabolic processes, adhesion and its regulation, cellular localisation, cell killing, response to stimuli, and the immune response. Genes in the categories of cellular and metabolic processes had the highest representation of both upregulated and downregulated genes. The most represented in the list of upregulated genes were involved in adhesion, biological regulation, response to stimuli, and the immune response (Figure 1a, red bars). Genes involved in transport and metabolic processes were most represented in the list of downregulated genes (Figure 1a, green bars).

Analysis of expression of genes implicated in diverse cellular components
The cellular site of function of altered genes was explored, including the nucleus, organelles, extracellular matrix, and synapse. Genes associated with nuclear activities, such as genes of the nucleocytoplasmic shuttling complex, and those associated with the extracellular matrix were most represented in the list of upregulated genes. Genes implicated in synapse and neuron projections, and in dendrites and axons, were most represented in the list of downregulated genes (Figure 1b). Metabotropic glutamate receptors, GABA-B-like receptors, and potassium:chloride symporters were also highly represented among downregulated genes.

Analysis of expression of genes implicated in molecular function
In the category of molecular function, we focused on binding, catalytic, transcriptional regulator, enzyme regulator, structural molecule, motor, antioxidant and chaperone functions. Binding and transcriptional regulator activity comprised the most common functions of genes that were upregulated (Figure 1c). Genes associated with antioxidant activity were highly represented in both the upregulated and downregulated list of genes. Genes associated with binding (Figure 1c), particularly protein and ion binding, were most represented in the upregulated group of genes. Among downregulated genes, the most altered category was that of transporter activity (Figure 1c), particularly voltage-gated channels such as potassium channels (Kcncl) and sodium channels (Scn2a and Scn2b).

Analysis of expression in significant genes in various categories
Finally, we undertook a summative analysis of the most significant processes and functions regulated by seizures, compiled from all three ontological categories. Results of this analysis shown in Figure 2 highlight the abundance of genes associated with regulating cellular process, apoptosis, transcription regulation, developmental process and differentiation, signal transduction, transport and synaptic transmission, metabolism, and immune and stress response. Genes involved in cellular processes and cellular metabolism make up almost 50% of the total genes altered, either by upregulation or downregulation.

Discussion
The focus of our study was to explore the ontology of genes whose expression was altered by experimental seizures to obtain insights into the mechanisms of injury after seizures and the development of epilepsy. Our analysis provides new information on the widespread biological effects of seizures on the brain.
Of particular interest, genes associated with the immune system and immune cell localisation were among the most upregulated genes. Regulation of the immune system has become a major focus of interest as a mechanism contributing both to the initial reactive responses to brain injury, but also contributing acutely and chronically to seizure generation. Among genes found in our study were CD14, CD44, and CD9, which have established roles in inflammatory processes. Inflammatory reactions in the brain can enhance neuronal excitability, impair cell survival, and increase the permeability of the blood–brain barrier to blood-borne molecules and cells. For example, CD14 is known to interact with apoptotic cells, triggering phagocytosis of these cells.

We also found that Gfap, a gene expressed in astrocytes, was strongly upregulated in the present model. Astrocytosis is a long-established pathological hallmark of human TLE and astrocytes may contribute to seizure generation by disrupting normal ionic balance in the seizure focus, or by quenching availability of endogenous anticonvulsants, including adenosine. Our data is therefore in line with expected findings in human and experimental models of seizure damage. Interestingly, we also detected upregulation of IL-6. At low levels, IL-6 has been associated with astrocyte proliferation and neuron regeneration. However, overexpression of IL-6 has been shown to result in loss of GABA- and parvalbumin-positive (calcium-binding albumin protein) neurons in the hippocampus.

We detected downregulation of brain-derived neurotrophic factor (BDNF) after seizures. BDNF has been described as having a role in the growth and survival of neurons. Lack of BDNF has been shown to result in the degeneration of neurons and contributes to the development of Huntington’s disease.

At a cell compartment level, upregulated genes associated with organelles were of particular note. These included the mitochondrial associated genes Slc25a25, Dhrs1, and Acs4. This category included solute carriers (Slc25a25) used for transport of electrons, and the dehydrogenase reductase family (Dhrs1), involved in combating oxidative and metabolic stress. This supports an effect of seizures on neuronal metabolic function. Indeed, seizures cause metabolic dysfunction and oxidative stress to mitochondria, and mutations in mitochondrial genes have been linked to epilepsy. Prime examples of metabolic disorders that have an epilepsy component are myoclonic epilepsy with ragged-red fibres (MERFF) and mitochondrial myopathy encephalopathy lactic acidosis with stroke-like episodes (MELAS) syndromes. Both of these syndromes are associated with point mutations that lead to defects in the mitochondrial respiratory chain enzyme complexes.

Our group has previously identified roles for genes associated with programmed cell death in the pathogenesis of seizure damage. Here, we found upregulation of Bcl-2 associated atanogene 2 gene expression (a pro-apoptotic gene), suggesting that seizure activity contributes to neuronal apoptosis. Thus, the present analysis identifies potential new gene targets that regulate cell death and survival signals in neurons. Based on this, targeting of genes regulating apoptosis or cysteine protease cascades may be a useful strategy for neuroprotection. Indeed, other pro-apoptotic members of this family have been shown to be induced following damaging seizures, including Bim, while loss of anti-apoptotic Bcl-w increases seizure-damage vulnerability.

The cell compartment associated with the most downregulated genes was the synapse. This included metabotropic and ionotropic glutamate receptors. Thus, neuronal excitability may be initially suppressed after an episode of status epilepticus. GABA receptor and potassium:chloride symporter genes were also downregulated in this compartment, suggesting an effect on both excitatory and inhibitory neurotransmission. Potassium:chloride symporters are used to regulate Cl− concentrations in the neuron and their regulation may also contribute to altered neuronal excitability. The sodium channel genes Scn2a and Scn2b were also found to be downregulated. This supports the hypothesis that seizures cause bi-directional modulation of genes associated with neurotransmission, which may influence post-seizure epilepsy development.

At a molecular level, the most overexpressed genes in the upregulated group were involved in binding, particularly receptor and protein binding. Serine (or cysteine) peptidase inhibitor, clade E, member 1 (Serpinel1), Synaptopodin, Tropomyosin 3 and Tropomyosin 4 were some of the genes upregulated and they are involved in actin binding. This may reflect early changes to neuronal cytoarchitecture in the seizure-damaged tissue. Among downregulated genes at the molecular level, transporter activity was most represented, particularly genes encoding voltage-gated channels such as ATPase dependent Ca++ transporter, plasma membrane 2 (Atp2b2), potassium voltage-gated channel (Kcncl1) and Kv channel interacting protein 2 (Kcnip2). This may translate to suppressed ion channel activity and in turn influence responses of surviving neurons to stimuli. Some limitations of this study should be considered. First, the analysis extended only to the CA3 subfield of the hippocampus. Regulation of genes in other fields is likely to be important to both seizure-induced neuronal death and post-seizure chronic changes that give rise to epilepsy. Second, only information from a single time point was available. Individual genes may also be present in more than one ontological category. Finally, our investigation highlights how a re-analysis of the same microarray datasets at a later time, even using the same bioinformatics tool, can give rise to subtly different findings. This results from the ontology databases being constantly updated with new information. Accordingly, this should be factored into future analyses and interpretation of microarray results.

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References


Screening for foetal abnormalities in a contemporary Irish practice

Abstract

Background: A number of non-invasive screening tests for foetal chromosomal aneuploidy are available for both the first and second trimester of pregnancy. The RCOG and ACOG advocate national screening; however, there are no national guidelines for chromosomal screening in Ireland.

Methods: The RCSI Foetal Medicine Unit (FMU) at the Rotunda Hospital is a recently opened private clinic that offers these screening tests electively. A retrospective population study was carried out to assess the age distribution of patients presenting for the ‘combined’ first trimester screening test, and the number of women who chose to go on for further invasive testing, as a reflection of Irish interest in prenatal screening.

Results: Of 520 women assessed in a six-month period, 66 women (13%) had at least one abnormal parameter. A total of 320 women (62%) were older than 35 years, a significant risk factor for foetal Down syndrome, and 20 women (30%) opted for diagnostic testing. Based on karyotyping and pregnancy outcomes, the FMU has a detection rate of 100%, with three aneuploid cases detected from three documented.

Conclusions: Low numbers of at-risk women seeking diagnostic testing may indicate that many women are screening to simply assuage anxiety. High numbers of at-risk women presenting suggest a public awareness of the link between maternal age and increased risk for chromosomal aneuploidy, while overall high screening numbers demonstrate a significant interest of Irish women in the accessibility of prenatal screening.

Keywords: Screening, aneuploidy, Down syndrome, Ireland.

Introduction

Down syndrome is the most common chromosomal abnormality among live births, affecting almost 1/700 births without prenatal intervention. A number of safe and non-invasive screening tests are now available in early pregnancy, which can empower parents and healthcare providers to make informed decisions about the pregnancy. Early screening for Down syndrome can take a variety of forms in the first trimester, second trimester, or both. Descriptions of commonly used screening tests are provided in Table 1. Recent population studies in the United Kingdom (UK) and the United States (US) have been conducted to determine the most effective method of early screening for Down syndrome. The Serum, Urine, and Ultrasound Screening Study (SURUSS) conducted in the UK collected data on over 47,000 pregnancies throughout the country, including 101 affected by Down syndrome. The results of this trial, based on the lowest false positive rate, showed that the most effective test was the integrated test, which incorporates values from the first and second trimester. The trial also showed that the results of screening in the first or second trimester alone were virtually the same, and that both were inferior to the results obtained in the integrated test. The First- and Second- Trimester Evaluation of Risk (FASTER) trial conducted in the US described similar findings. Evaluating over 38,000 singleton pregnancies (excluding those with a diagnosis of cystic hygroma), the FASTER trial included 92 affected pregnancies. The FASTER trial showed the integrated test to have the lowest false positive rate (0.8%), followed by the serum integrated test (4.4%). The first trimester combined test had a false positive rate of 4.8%, with the false positive rates of the second trimester tests both rising to well over 7%. The FASTER trial concluded that the optimal time for first trimester screening was at 11 weeks’ gestation. It also indicated that while integrated screening was the most effective, it precluded the
definitive results of chorionic villus sampling (CVS). Women who wait until the second trimester for their results are no longer able to have this definitive test performed, and would instead be considering amniocentesis. However, waiting for the results for amniocentesis could mean that if termination is being considered, the window for legal termination has passed. Thus, a risk–benefit assessment must be made, weighing the advantage of earlier results from the combined test or first trimester screening alone, with the option for further diagnostic testing, against the advantage of a lower false positive rate from integrated testing. A summary of the differences between CVS and amniocentesis is presented in Table 2.

The results of these trials have informed recommendations with regard to screening in both the UK and the US. The Royal College of Obstetricians and Gynaecologists (RCOG) recommended in 2003 that all women should be offered a screening test for Down syndrome with a detection rate of greater than 60% and a false positive rate of less than 5%.5 Projected recommendations for 2007 were that all pregnant women be offered screening for Down syndrome with a test that has a detection rate of greater than 75% and a false positive rate of less than 3%.5 This recommendation anticipated that screening would include the integrated and serum integrated test, the combined test, and the quadruple test, and though more recent evidence shows that these false positive rates are not as low as desired, these tests are currently used. All women who are considered to be at high risk (risk greater than 1/250) for Trisomy 21 should be offered a diagnostic test such as CVS,6 with an option to decline. The American College of Obstetricians and Gynaecologists (ACOG) recommends that all women presenting for prenatal care before 20 weeks’ gestation should be offered aneuploidy screening with a detection rate of greater than 70% and a false positive rate of less than 5%.6 Women who opt for first trimester combined testing should also be offered second trimester testing of maternal α-fetoprotein levels, or ultrasound assessment for neural tube defects (NTDs). All pregnant women should also be offered the option of invasive diagnostic testing. All patients considered to be in a high-risk category for Down syndrome (risk greater than 1/270) should be offered CVS at 11-12 weeks’ gestation.

Currently in the Republic of Ireland, there are no national guidelines for the practice of aneuploidy screening. In a 2003 survey of over 1,000 women at University College Hospital Galway, 75.4% of respondents said that they would like to have a routine foetal anomaly scan if one was available.7 A survey of 371 general practitioners (GPs), specialist registrars (SpRs) in obstetrics, and obstetric consultants, showed that the majority of doctors in all fields agreed that patient demand for, or questions about, screening and diagnosis of foetal abnormalities had increased significantly over the last five years.8 This indicates that knowledge of and interest in prenatal screening has increased in Ireland. Some 68% of consultants, 91% of SpRs, and 57% of GPs surveyed felt that screening should be provided to all patients regardless of risk; however, in all groups, discussion about screening was limited to women with obvious risk factors, or if a patient initiated the discussion. There are a variety of reasons that could contribute to this: when asked, all physicians felt that the reason all women were not offered screening was lack of funding for these services by the government. Some 71% of GPs, as opposed to 38% of consultants, felt

<table>
<thead>
<tr>
<th>Test</th>
<th>Trimester</th>
<th>Maternal age measured?</th>
<th>Nuchal translucency (NT) measured?</th>
<th>Serum markers used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined test</td>
<td>First</td>
<td>Yes</td>
<td>Yes</td>
<td>Maternal free β-human chorionic gonadotrophin (β-hCG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maternal pregnancy-associated plasma protein A (PAPP-A)</td>
</tr>
<tr>
<td>Quadruple test</td>
<td>Second</td>
<td>Yes</td>
<td>No</td>
<td>α-Fetoprotein</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unconjugated oestriol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Free or total β-hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibin-A</td>
</tr>
<tr>
<td>Integrated test</td>
<td>First and second</td>
<td>Yes</td>
<td>Yes</td>
<td>PAPP-A (first trimester)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quadruple test markers (second trimester)</td>
</tr>
<tr>
<td>Serum integrated test</td>
<td>First and second</td>
<td>Yes</td>
<td>No</td>
<td>PAPP-A (first trimester)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quadruple test serum markers (second trimester)</td>
</tr>
</tbody>
</table>
that screening would present ethical problems for their patients. In terms of accessibility, 64% of GPs did not know a local physician who could perform a screening test, indicating that access to services was a limiting factor in screening uptake. Finally, 26% of consultants, 59% of SpRs and 35% of GPs have access to screening tests for women with risk factors but limited access otherwise.

A prospective cohort study conducted in Northern Ireland in 2008 compared surveys of patients at two large maternity hospitals, and found that of the two, only one hospital offered prenatal screening to women at high risk, and even then, only 45% of women reported being offered screening.9 Analysing the responses at the other hospital showed that women with no qualifications had a 73% lower chance of being offered screening than women with degree qualifications or higher, and that women in lower social classes were 60% less likely to be offered screening than women in a higher social class. Analysis also demonstrated that women with less education were less likely to agree to screening. The odds of taking the test were six times higher for women receiving private care. Virtually all of these women were offered and accepted an anomaly scan at 20 weeks’ gestation. Thus, while there are no national guidelines, it is increasingly clear that while Irish patients would like to be offered, and would be likely to accept offers of foetal screening tests in early pregnancy, information and access to screening is not equally or readily available within Ireland.

The RCSI Foetal Medicine Unit (FMU) at the Rotunda Hospital is a private clinic that has offered both screening and diagnostic testing for chromosomal abnormalities in early pregnancy since 2006. Tests are performed on a referral basis from other institutions for women who are interested in screening, as well as being offered to all patients of the clinic itself. The test most commonly offered is the combined test with the option of diagnostic testing. It is routine at the FMU to offer screening to all patients regardless of risk factors. Given the benefits of screening despite the lack of a national Irish screening policy, an audit was performed to assess the age distribution of patients presenting for screening, the resulting abnormal values, and the number of women who chose to go on for further invasive testing, as a reflection of Irish interest in prenatal screening.

Table 2: Summary of differences between CVS and amniocentesis.6

<table>
<thead>
<tr>
<th>VS</th>
<th>Description of procedure</th>
<th>Commonly performed</th>
<th>Risk of pregnancy loss</th>
<th>Other risks</th>
<th>Lowest risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Sample of placental chorionic villus obtained and karyotyping performed</td>
<td>11-13 weeks’ gestation</td>
<td>1.44 relative risk (RR) to second trimester amniocentesis (95% CI; 1.09-1.81)</td>
<td>Risk of spontaneous miscarriage 9.4%; RR 1.50 versus second trimester amniocentesis, (95% CI; 1.07-2.11)</td>
<td>Same risk throughout first trimester</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>A small amount of amniotic fluid containing foetal tissue is obtained from the amniotic sac surrounding the foetus and karyotyping is performed</td>
<td>&gt;15 weeks’ gestation (within the second trimester)</td>
<td>Early amniocentesis (&lt;14 weeks’ gestation) 7.6% versus second trimester amniocentesis 5.9%; RR 1.29 (95% CI; 1.03-1.61)</td>
<td>Incidence of foetal talipes in early amniocentesis versus CVS: RR 4.61 (95% CI; 1.82-11.66)</td>
<td>Amniocentesis performed &gt;15 weeks’ gestation</td>
</tr>
</tbody>
</table>

FIGURE 1: Maternal age distribution of women presenting for combined screening at the FMU, Rotunda Hospital, March to August 2007.
Methods

This retrospective population study was performed at the RCSI FMU at the Rotunda Hospital, Dublin, from April to May 2008. Examining a population of pregnant women presenting for first trimester (combined) screening at the FMU, a consecutive series sample of women presenting from March to August 2007 was chosen. The results of their combined test from the day of screening (maternal age, NT [mm], ß-hCG [MOM [multiples of the mean]], PAPP-A [MOM]), as well as the gestational age of the foetus, were obtained from patient records. Patients who presented for screening whose foetus was diagnosed with cystic hygroma were included in the sample because cystic hygroma has such a strong association with aneuploidy. Patients who presented for other screening tests (such as second trimester screening) were excluded. Patients were separated into five major groups depending on test results: women with no abnormal foetal parameters noted; women with a foetus whose NT measurement was greater than or equal to 2.5mm; women whose ß-hCG levels were greater than 3MOM; women whose PAPP-A levels were less than 0.4MOM; and, women whose total adjusted risk for Trisomy 21 was greater than 1/250. If a patient fell into any of the categories indicating abnormal parameters, results of invasive testing (if any) were noted, as well as the pregnancy outcomes (foetal term at birth, obvious foetal abnormalities, and foetal weight). Because not all women who present for screening at the FMU deliver at the Rotunda Hospital, not all records of pregnancy outcomes were available for analysis. All data was recorded and processed using Microsoft Excel.

Results

A total of 520 patients were analysed at the FMU for first trimester combined screening in the six-month period between March and August 2007. Some 322 (62%) women presenting were over the age of 35, with the majority presenting between the ages of 36 and 40 (Figure 1). Of the 520 patients presenting, 66 women (13%) had an abnormal result either in biometry, biochemistry, or both. Further results are presented in Figure 2. Because not all women presenting at the FMU delivered at the Rotunda Hospital, it was difficult to obtain the pregnancy outcomes of all patients. A total of 36 records were obtained, and pregnancy outcomes of these are shown in Figure 3.

Discussion

The assessment of the FMU yielded some interesting information about patients presenting for early foetal screening. Of all the women presenting, the majority were in an at-risk age group (greater than 35 years of age), including 59 (11%) women over 40 years old. This contrasts significantly with the study carried out at UCHG where only 1.89% of the patients presenting were over 40. This could indicate that public awareness of the link between advanced maternal age and Down syndrome has been heightened, leading to more at-risk women wishing to be screened early.
When examining the women with abnormal values, the majority of women (60%) had a problem with their total adjusted risk; however, adjusted risk is a reflective value of the combined risk of all the other factors. A risk of greater than 1/250 was classified as high risk, although ultimately, patient concerns about a risk value informed the course of action taken. The second highest proportion of abnormal values was with ß-hCG levels (40%). This is difficult to interpret because unaffected pregnancies see ß-hCG levels drop between 11-13 weeks’ gestation, while Down syndrome pregnancies show increased levels within the same time period. Only 20 women went for further invasive testing and, of these, the majority (80%) were normal, indicating that for most women the screening test was used as a means of reassurance about the pregnancy and that definitive answers were not the primary purpose behind seeking the test. The decision not to seek diagnostic testing by the majority of women may have been informed by the lack of availability of pregnancy termination in the Republic of Ireland. The view that the limited provision of prenatal screening and diagnosis is due to the restrictive laws on termination in the Republic of Ireland is not a new perspective. 71% of GPs believe that prenatal screening would cause ethical issues for their patients. This data from the FMU shows that most women simply going for definitive testing seem to be seeking reassurance, but for a smaller group of women, seeking early definitive answers is a way to circumvent the options for termination in the Republic of Ireland. Finally, of 520 women who were assessed at the FMU in a six-month period, two were diagnosed with a Down syndrome pregnancy. This is higher than the accepted risk of Down syndrome occurring spontaneously in 1/700 live births; however, the majority of patients presenting to the FMU were presenting because of risk factors, thus self-selecting the patient population into a higher risk group. Despite this, there were women presenting for screening with no risk factors, both as referral cases and independently.

**Conclusion**

Despite the lack of a national Irish screening strategy for Down syndrome, the FMU assessed 1,000 women for first trimester screening alone in its first year. The rates of detection within a six-month period were excellent: of 66 women with abnormal screening results, three aneuploid cases were diagnosed out of three cases documented. Of those with abnormal screening results, only 20 pursued diagnostic testing, which may indicate that most Irish women undergo screening simply to relieve anxiety and prepare for possible outcomes, although the Irish restriction on pregnancy termination may also influence the decision to undertake early screening. The majority of women presenting were over the age of 35, illustrating the general public’s association of raised maternal age with an increased risk of a Down syndrome pregnancy. However, many women presented independently, confirming documented changes in attitude in favour of prenatal screening in Ireland.

**References**


Introduction
Anti-phospholipid syndrome is an autoimmune condition characterised by antibodies directed against phospholipids. It most commonly manifests with obstetric complications (e.g., recurrent miscarriage) or a predisposition to vascular thromboses. It affects approximately three to four people per 100,000, usually young females.

This case report details a male patient who presented with symptoms suggestive of peripheral vascular disease. During the patient’s operation for a femoral-posterior tibial bypass, the consultant vascular surgeon, Mr Daragh Moneley, Beaumont Hospital, made a surprising discovery. A presentation of this case won the Royal College of Physicians in Ireland Council Medal 2008.

Case presentation
PL, a 55-year-old male from Dublin, presented with a two-week history of constant left-sided rest pain of the leg and a pale, swollen left leg. Of note, he has a diagnosis of anti-phospholipid syndrome, a history of previous vascular surgery and multiple risk factors for peripheral vascular disease.

The patient’s primary complaint was the gradual onset of an ache in his left hallux, heel, calf and popliteal fossa over two weeks. It was present constantly, including at night when it woke him from sleep. Dangling the leg off the side of the bed relieved the pain, but it was not notably relieved by rest. In association with the pain the patient described swelling of his left leg during the past three days and patchy discolouration of his left hallux (Figure 1), in association with paraesthesia and coldness of his left foot. His vascular risk factors include hypercholesterolaemia, hypertension, obesity, an 11-pack-year history of smoking and a strongly positive family history of cardiovascular disease. Mr PL was well until the age of 36, when he had a deep vein thrombosis (DVT) in his right leg. He went on to have multiple DVTs, and a thrombophilia screen revealed a diagnosis of anti-phospholipid antibody syndrome. In 1990, he began suffering from symptoms of peripheral vascular disease, for which he had an aortobifemoral graft inserted. Following this, he had critical ischaemia of his right foot and underwent amputation of his right hallux and second toe. In the interim, before he re-presented to our service, he was diagnosed with anxiety, hypertension and hypercholesterolaemia; however, he did not suffer any cardiovascular or cerebrovascular events during this time, and remained well.

The patient was on the following medication at this presentation:
- warfarin (target INR 2.0-3.0);
- lisinopril 20mg OD; and,
- bendroflumethiazide/potassium 2.5mg OD.
He was not taking any over-the-counter medication or herbal remedies, but was allergic to dairy products and eggs, which precipitated migraines with aura and blurring of vision. Mr PL is a current smoker with an 11-pack-year history, and drinks 40-60 units of alcohol per week. He denies recreational drug abuse. He is currently unemployed but is actively seeking a job. He lives alone, although his children live close by. He is independent in daily living but currently walks with a frame. His family history is significant for death of both parents from cardiovascular disease, both in their early 50s. In addition, his 45-year-old brother has undergone coronary stenting. His three children are well. Systems review was non-contributory to diagnosis. On general inspection, the patient was alert, conscious and responsive, with a pulse of 72 beats per minute, temperature of 37ºC, a respiratory rate of 15 breaths per minute and blood pressure of 138/86. Cardiorespiratory examination was normal. Abdominal examination revealed a median laparotomy scar. On inspection of his legs it was noted that his left lower limb was significantly paler than his right. His right hallux and second toe had been amputated. Palpation of the left lower limb revealed impalpable pulses, delayed capillary refill of 10 seconds, a cold left leg and forefoot, and a positive Buerger’s test at a Buerger’s angle of 35º. Power and sensation were normal.

Based on history and physical exam, the following differential diagnoses were considered:
■ peripheral vascular disease;
■ neuropenic pain;
■ deep vein thrombosis;
■ Raynaud’s phenomenon;
■ musculoskeletal problems; and,
■ gout.

This patient’s work-up started with basic haematological and biochemical investigations. He was found to have a prothrombin time of 24.9 and an INR of 2.21 (within his target range of 2-3). As expected, his anti-cardiolipin antibody was positive with a high titre. Ankle-brachial index was 0.1 on his left lower limb and 0.4 on the right lower limb. Lower limb angiography and a duplex ultrasound were performed. The angiogram (Figure 2) showed no named vessels beyond the common femoral, multiple collateral vessels and no evidence of a thrombus. The ultrasound duplex revealed a patent posterior tibial artery, which was to be instrumental in guiding management.

The following are the treatment options that were considered:

Conservative/medical treatment:
■ lifestyle advice (smoking cessation, exercise);
■ risk factor modification (anti-hypertensives, statins); and,
■ analgesia;

Interventional/surgical treatment:
■ angioplasty;
■ femoral-posterior tibial bypass with long saphenous vein graft; and,
■ below-knee amputation.

With the patient’s informed consent, and given the severity of his symptoms, it was decided to perform a femoral-posterior tibial bypass with a long saphenous vein graft. This procedure was possible due to the presence of the patent posterior tibial artery as identified by ultrasound duplex.
Surgical procedure

Two incisions were made: a femoral incision to locate the femoral artery and a medial leg incision to dissect the long saphenous vein and to identify the posterior tibial artery. On palpation, the superficial femoral artery was noted to be soft and spongy, rather than hard as would be expected with atherosclerosis. The artery was clamped and opened with a longitudinal incision. To the team’s surprise, a large (26cm) clot was located in the artery. It was removed by passing a catheter through the vessel, inflating a balloon at the distal end and pulling out the thrombus, a procedure known as a thrombectomy (Figures 3 and 4). The patient’s lower limb became hyperaemic and it was decided that the bypass procedure was no longer required.

Postoperatively, the patient was stable and comfortable with no pain. Pulses were palpable. Although the limb was re-vascularised, the left hallux may still have to be amputated due to extensive tissue loss preoperatively. Additionally, an extensive cardiovascular work-up is pending to exclude a similar thrombus in the heart and the patient will remain on warfarin for life with a higher target INR than previously set.

Discussion

Anti-phospholipid syndrome is an autoimmune disease with antibodies directed against anionic phospholipids found in cell membranes.1 It can be primary (70% of cases) or secondary (30% of cases). There is a significant occurrence of anti-phospholipid antibodies among systemic lupus erythematosus (SLE) patients (27%).2

The manifestations of anti-phospholipid syndrome can be remembered by using the mnemonic CLOT:3

- Coagulation defects – vascular thromboses (arterial and venous);
- Livido reticularis;
- Obstetric complications (e.g., recurrent miscarriage, pre-eclampsia); and,
- Thrombocytopenia.

Diagnosis is made by detailed clinical history, physical examination and laboratory testing for anti-cardiolipin antibody, lupus anticoagulant and β2-glycoprotein I.1 Anti-phospholipid syndrome is managed by anticoagulation with aspirin and clopidogrel, heparin or warfarin (target INR of 2.0-3.0).4

Conclusion

Anti-phospholipid syndrome is an autoimmune condition that predisposes patients to vascular thrombosis and obstetric complications. It can present in several ways and can be easily confused with peripheral vascular disease. The main lesson learned from this case is that intra-operative decision-making and observation are crucial in ensuring the best outcome for a patient.

Acknowledgements

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References

Introduction

Wilms’ tumour is the most common renal malignancy in children and the fourth most common childhood cancer. In the United States, Wilms’ tumour accounts for 6.6% of childhood malignancies, with 500 new cases presenting each year.1 This condition arises from pluripotent embryonal cells in the developing kidney. Pluripotency is apparent in the pathognomic triphasic histologic appearance, consisting of three components: epithelial, blastemal and stromal cells. The teratoid histological variant of Wilms’ tumour is rare, with only 16 reported cases.2 It is identified histologically by heterologous differentiation in the presence of other mature tissue types within a Wilms’ tumour. These mature tissues may include muscle, squamous, bone, cartilage, glial, adipose and glandular tissues. Fernandes et al3 refined the definition of teratoid Wilms’ tumour by restricting it to tumours with heterologous differentiation accounting for greater than 50% of their volume.

The case

A two-and-a-half-year-old boy weighing 13.5 kilograms was transferred from Iraq to Amman, Jordan, with massive abdominal swelling. He had originally presented at six months of age to an Iraqi facility with abdominal distension and bulging flanks. The mass was associated with constipation, sweating, irritability and malaise. On clinical examination, the patient had severe abdominal distension with overlying distension of superficial veins, compression of the thoracic cage, growth retardation, and underdeveloped motor function (Figure 1). The patient was also unable to walk due to the size of the mass. Computed tomography (CT) scan of the abdomen and pelvis showed a heterogeneous, large mass originating from the left kidney.

FIGURE 1: Patient on admission. Note severe abdominal distension, compression of the thoracic cage, superficial venous distension, and atrophied lower limbs.
The images were highly suspicious for Wilms’ tumour. The patient had no evidence of pulmonary metastasis. The patient received four cycles of chemotherapy (Table 1), but the tumour size did not change. The patient was then admitted for complete surgical resection of the mass with radical left nephrectomy. The excised mass was 5,211.5g and was diagnosed as Wilms’ tumour with mainly necrotic mass and a few foci of viable tumour (Figure 3). The patient was transferred to the paediatric intensive care unit following surgery and was subsequently discharged without complication. The patient was not scheduled for adjuvant chemotherapy. By the time of writing this report, approximately six months after surgery, the patient was well with no evidence of recurrence.

Discussion

The majority of children diagnosed with Wilms’ tumour are treated according to one of two research protocols, which differ in the timing of chemotherapy relative to surgical excision. The National Wilms’ Tumor Study (NWTS) includes most paediatric oncology centres in the United States and Canada. The recommended protocol is immediate surgical resection and staging with adjuvant chemotherapy.4-7 The International Society of Paediatric Oncology (SIOP) includes centres in Europe, Asia and Africa. This protocol recommends four cycles of chemotherapy administered prior to surgical resection and staging.8-11 The NWTS and SIOP protocols show a similar five-year survival rate of 90%.12 The treatment protocol for teratoid Wilms’ tumour has not been fully elucidated due to the rarity of this tumour.

Definitive diagnosis of teratoid or classical Wilms’ tumour can only be made postoperatively. Biopsy is generally not recommended because it may cause tumour spread, and for this reason, a Wilms’ tumour that has been biopsied is necessarily increased to a stage III tumour. Radiology is useful in determining the origin and extent of the tumour but is insufficient to identify teratoid features. Clinically, the teratoid variant should be considered in cases of suspected Wilms’ tumours that do not respond to chemotherapy. Of the 16 reported cases of teratoid Wilms’ tumour, nine received neo-

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Figure 2: A: Pre-operative plain film abdominal x-ray showing mass and compression of viscera. B: Post-operative plain film abdominal x-ray showing deformed thoracic cage and rearrangement of abdominal viscera. C: CT abdomen and pelvis on admission showing a heterogeneous mass originating from the left kidney, displacement of abdominal viscera, compression of the inferior vena cava, and lymph node enlargement. D: Post-chemotherapy and pre-operative CT image showing no change in tumour size. Lung bases appear negative for metastases, calcifications are apparent in the tumour body, and multiple left renal stones are seen with hydronephrotic changes.

Figure 3: A: Macroscopic features of the excised mass include an encapsulated tumour with a homogenous tan-white, trabeculated, and whorly cut surface. Microscopic features include skeletal muscle fibres, squamous cells and multiple areas of haemorrhage. B: Stain for skeletal muscle tissue in tumour. C: Stain for epithelial cells in tumour. D: Positive Desmin stain: Desmin is a 53kD intermediate filament that is present in striated and smooth muscle cells.
adjuvant chemotherapy and only one showed a cytoreductive response. It is thought that resistance to chemotherapy is due to the mature, differentiated, heterologous nature of the tumour elements. Teratoid Wilms’ tumour is not usually aggressive despite the frequent large size, and the prognosis is comparatively good if the tumour is excised. It is thought that metastasis is rare because tumour tissues are solid, mature, differentiated and often encapsulated. In all previously reported cases of teratoid Wilms’, with one exception, postoperative chemotherapy was administered regardless of tumour stage, size, age at diagnosis and histology. A interdisciplinary conference ruled against adjuvant chemotherapy for our patient on the grounds that the risk of further chemotherapy was not justified given the failure of previous treatment. Potential complications of further chemotherapy include secondary malignancy, cardiotoxicity, hepatotoxicity and, in particular, nephrotoxicity, given that this patient has only one remaining kidney.

Future management of this patient will involve monitoring for tumour recurrence and late complications related to chemotherapy. Wilms’ tumours recur most often in the abdominal cavity and in the lungs, so monitoring will consist of abdominal ultrasound and chest x-ray every three months for three to six years. If the patient relapses, possible treatment options include salvage chemotherapy with autologous stem-cell transplantation. However, these treatments are only established for non-teratoid Wilms’ tumour. Late complications of chemotherapy are related to the specific side effects of the chemotherapeutic agents used and should be monitored individually.

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We would like to thank Dr Iyad Sultan and the Department of Pediatrics of the King Hussein Cancer Center (Amman, Jordan) for their enthusiasm in teaching and continued support. We also extend our gratitude to the departments of surgery, critical care, radiology, and pathology.

References
Challenging stigma and discrimination in the mentally ill

Abstract
The aim of this review is to examine strategies for confronting the stigmatisation and discrimination experienced by those with a mental illness. It is first necessary to look at how the current literature defines the concepts of ‘stigma’ and ‘discrimination’, and how these apply to the population in question. The paper then examines ways to challenge these, paying particular attention to current theories of reducing stigma by education, contact and protest. Articles used for this review have been published in the last ten years in medical, nursing and sociological journals. The key theme developed by this study is that stigma and discrimination remain significant problems for those with a psychiatric illness and may act as a barrier to therapy. Stigmatisation occurs in many settings of everyday life for patients with mental health problems. Overcoming this challenge requires a targeted approach, with current research emphasising public education and increased interaction between those with a mental illness and other citizens.

Keywords: Stigma, discrimination, mental illness, mental health, recovery.

Introduction
The World Health Organisation formulated a concept of mental illness in 1980 as encompassing the particular illness itself and its wider repercussions.1 Recovery would not just involve recuperating from a symptomatic disorder, but also from factors such as stigma and lack of opportunities.1 Since then, research has been carried out on the concept of stigma and the effects of stigma and discrimination on psychiatric service users. Current papers strongly emphasise the importance of challenging these effects, as they act as a barrier to recovery.2 This article addresses questions raised by contemporary research in this field. It examines the definitions of stigma and discrimination, how these may affect those with mental illness and, most importantly, how this bias may be addressed.

Defining stigma and discrimination
Numerous articles seeking to define ‘stigma’ have appeared in sociological journals. Medical researchers have attempted to adapt these concepts to the healthcare setting. Public stigma occurs when an individual is perceived as being ‘marked’ by certain attributes and therefore defined in society as different and devalued.3 Corrigan and Watson have proposed a social-cognitive model of stigma in which society holds inaccurate cognitive representations of the stigmatised group, with the result that members of the group are associated with false negative ideas.3 Perceived public stigma may trigger the development of self-stigma and label avoidance.4 In the case of self-stigma, the individual essentially accepts public stigmatising beliefs as being correct.2,4 Consequently, they are affected by negative emotions such as low self-esteem and
reduced motivation. Public stigma, in the context of a health or illness, may discourage undiagnosed individuals from seeking healthcare. This aversion to diagnosis is known as label avoidance. The concept of stigma also helps us to better understand the idea of discrimination. Under the social-cognitive view mentioned previously, when negative stereotypes are accepted, a group of people may be seen as lesser individuals. When stigma affects the behaviour of others towards this group, intentional or unintentional discrimination may occur. This discriminatory behaviour may result in reduced opportunities and rights for the affected group.

How stigma and discrimination affect the psychiatric service user

The social-cognitive model of stigma can be applied to those with mental illness. Studies have looked at stigmatising attitudes from the point of view of both the individual and the public. Research has shown that public opinion is less sympathetic towards mental illness as compared to physical illness. Those with a psychiatric disorder are perceived to be more responsible for their conditions. Mentally ill patients are also more likely to be feared and viewed as violent. Public belief that those with mental illness are irresponsible and need guardianship is also common. From the point of view of the stigmatised individual, an Australian survey noted that a reduction in stigma would be the most crucial factor in improving the lives of those with mental illness and their families. Another study of 46 people with mental illness found that 41 of them experienced feelings of stigma.

Studies have also illustrated discriminatory practices towards those with a psychiatric illness by both individual members of the public and larger social institutions. Examples are encountered in many realms of everyday life. Perhaps unsurprisingly, though no less unfortunately, mentally ill people face difficulties because members of the public are less likely to rent them a property, offer them a job, or grant them entry into college. The Australian survey found that the cumulative effect of stigma and discrimination was to cause “anger, depression, fear, anxiety, feelings of isolation, guilt, embarrassment and prevention from recovery or avoidance of help-seeking”. As is the case with social institutions, the legal system, the health system and the media are commonly implicated. In 1998, 19 out of 50 states in the US had restricted the right to vote for people with mental illness, and in 20 states, these individuals had reduced legal claim in child custody cases. The medical community is not immune from being discriminatory. It has been suggested that complaints of physical illness are more likely to be ignored by doctors if the patient is mentally unwell. Less American research money is spent proportionally on examining psychiatric ailments than physical ones. Furthermore, colloquial use of diagnostic terms that perpetuate stigma persist, for example, the use of the word ‘schizophrenic’ by doctors and medical students, in a negative connotation, to refer to mentally unstable patients. Psychiatrists may be degrading their own patients by asking for higher pay and longer holidays, suggesting that their patients are a source of greater stress and potential danger.

The media also propagates an unbalanced message. For example, as of 2002, one-third of news stories involving the mentally ill focused on violence. Encouragingly, this figure is a significant improvement on a 1991 total of 86%. Unfortunately, when the mentally ill are not portrayed as violent, they are often shown as victims or as pathetic.

Discussion

A model for change mentioned frequently in the literature was devised by Corrigan and Penn in 1999. It is based on the concepts of protest, education and contact (with the stigmatised group). Many, though not all, of the recommendations for modifying attitudes towards those with mental illness are based on these principles.

It is widely argued that education should be the starting point, and this is a commonly employed strategy in real life. For example, the ‘Changing Minds’ campaign provides information to a wide range of people, from health professionals to parents and teachers. Workshops in schools aimed at 14- to 15-year-olds were used in a pilot project to address young people’s understanding of mental health issues. This programme showed an improvement in mean positive attitudes from 1.2 at baseline to 2.3 (range -5 to +5) at six months. Education has also been shown to be potentially effective in addressing a variety of mental health topics, improving knowledge on issues from psychoses to learning difficulties. However, concerns over the efficacy of educational programmes exist. In the schools project, changes were most marked in those who had had previous exposure to mental illness, a fact that is in line with current research. Studies have shown that a broad approach, for example a public service announcement, is strongest in reinforcing the message in those who already have knowledge of mental health issues. Consequently, it appears wise to direct a tailored message towards smaller groups. Along these lines, the ‘Changing Minds’ campaign also tried to reach medical professionals by publishing a series of information leaflets and by encouraging The Lancet’s series of articles on stigma.

It has been argued that informing those working in the media is essential. This strategy makes sense on two fronts, in terms of educating media workers both as individuals and as those who influence the general public. Law and policy makers should also be directly targeted, so that rules are not based on stigma and misrepresentation. For example, the American Disabilities Act stated that one cannot be deemed incompetent if appropriate accommodations are not made. Furthermore, policy makers should be obligated to inform those affected by policy changes. For example, employers should be well informed about the provision of supported employment for those with mental health problems, and of the benefits for themselves in providing such a scheme. Education is often linked with the concept of contact, another method of challenging stigma. Here meetings occur between people with a mental illness and other individuals or groups. Contact has been shown to be most effective when equality exists between both groups and when good interaction is facilitated.
brief discussion about living with mental illness proved successful in one study. However, contact is most useful when it is very specific, both in subject and target audience. This was shown in a study that targeted small groups likely to interact with those with a psychiatric disorder, such as landlords, police officers and employers. On the other hand, contact may also be limited in scope. In another study, it improved attitudes of research participants, but mainly towards people with the particular psychiatric condition encountered in that study. Nevertheless, one major strength of facilitating a contact process is that it has been shown to actually change participants’ thought processes towards those with mental illness. Those who had been involved in contact recalled more positive than negative information about the people they had met.

Of the three facets suggested by Corrigan and Penn, the least evidence exists for protest as a method of challenging stigma and discrimination. This method defines stigmatising behaviour as morally wrong and instructs the public not to act in such a way. Current papers mention anecdotal evidence of the usefulness of protest, such as an organised demonstration against the ABC network over their misrepresentation of mental illness on a television programme. Researchers theorise that the media is one area where protest is effective. However, protest risks antagonising people, with Corrigan himself stating that it “may have little or negative impact on public attitudes about people with mental illness”.

Conclusion
All but one of the papers reviewed for this article were published in the last ten years. These articles share a key theme: stigma and discrimination are real problems for those with a psychiatric disorder. As research has shown, when one feels stigmatised or discriminated against, self-esteem is decreased and feelings of anger, depression and anxiety are increased. Because stigma, or even fear of stigmatisation, may create a barrier to treatment and reduce the quality of life for those with mental illness, it is imperative that the issue is brought to the fore and tackled. Many papers advocate education and contact as a means of doing this, as both help to eradicate false notions that exist among the public about mental illness. It appears that campaigns to reduce stigma would be best organised in a targeted manner rather than using a large-scale blanket approach. It may therefore be necessary to examine the needs of particular groups on an individual basis. Clearly, as social-cognitive models describe, society contributes significantly to stigmatisation. Over the last 30 years, recovery strategies have aimed to integrate many of those with a psychiatric disorder into society, with programmes such as vocational training intending to improve the social abilities of this group. Total integration can only occur when individuals are assisted in the recovery process by their own community. Ongoing efforts to reduce stigma are critical for constructively engaging the community in this process.

References
Surgical management of obesity: is bariatric surgery as good as it’s made out to be?

Abstract

Objectives: Estimates from the WHO indicate that the prevalence of obesity in the developed world is reaching epidemic proportions. In 2005 there were at least 400 million obese adults worldwide and this figure is predicted to rise to 700 million by 2015, with an additional 2.3 billion overweight adults. This review aims to examine evidence for the benefits and risks of bariatric surgery and whether this treatment achieves both long-term weight loss and alleviation of obesity-related diseases.

Methods: An electronic PubMed (1980-2008) search using MeSH database search terms ‘obesity or overweight’ and ‘bariatric surgery’ was performed. The search continued up to August 24, 2008, and yielded 388 papers, of which 62 were considered eligible for inclusion. Manual reference checks of papers cited in recent review articles were examined for suitable studies and the Cochrane Library database was also searched.

Results: Bariatric surgery using restrictive and malabsorptive procedures achieves long-term significant weight loss compared with medical treatment, resulting on average in a 25-44kg weight loss at up to two years, and a 20kg loss up to eight years later. Cardiovascular, respiratory and psychological complications of obesity are also improved after bariatric surgery, with almost complete resolution of type 2 diabetes. Operative death rates are 1% and complication rates are acceptably low.

Conclusions: There is strong evidence supporting a role for bariatric surgery in the management of obesity.

Keywords: Obesity, overweight, bariatric surgery.

Introduction

Overweight and obesity are defined by the World Health Organisation (WHO) as “abnormal or excessive fat accumulation that may impair health”. The pathophysiology of obesity encompasses environmental, psychological, behavioural, genetic, and other factors. Latest estimates from the WHO indicate that the prevalence of obesity is reaching epidemic proportions. In 2005 there were at least 400 million obese adults worldwide and this figure is predicted to rise to 700 million by 2015, with a total of 2.3 billion overweight adults. The increasing prevalence of obesity is associated with a parallel increase in several obesity-related diseases, specifically the diseases of the metabolic syndrome (Figure 1). Epidemiological studies have shown a direct link between obesity and increased mortality. Obesity is associated with poor quality of life, restricted activities of daily living, and increased demand for healthcare services. Obesity costs the United Kingdom’s (UK) economy £3.5bn (£5.1bn, $6.4bn) annually, results in 30,000 deaths and accounts for 18 million days off work for obesity-related illness.

Body mass index (BMI) is an uncomplicated index of weight-for-height that is universally used to classify overweight and obesity in a population. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m²). The WHO defines “overweight” as a BMI equal to or more than 25, and “obesity” as a BMI equal to or more than 30. There are three classes of obesity: class I (BMI 30-34.9); class II (BMI 35-39.9); and, class III (BMI 40 and above).

In morbid obesity, lifestyle and dietary modifications have been shown to be ineffective, with a failure rate approaching 100% at five years.
Medical treatments have been shown to provide only negligible weight loss. Bariatric surgery (from the Greek *baros*, meaning weight, and *iatrikos*, meaning the art of healing) is one of the fastest growing areas of modern surgical practice. A 1991 National Institutes of Health (NIH) consensus conference recommended bariatric surgery as a suitable option for the treatment of morbid obesity and advocated bariatric surgery for well-informed enthused individuals with class III obesity with acceptable operative risks, and for individuals with class II obesity along with more than one high-risk comorbid condition, such as diabetes or poor performance status. The guidelines proposed that surgery would be suitable for patients who had already had intensive management in specialised obesity clinics but who had failed to maintain weight loss after trying appropriate non-surgical measures. It has been calculated that 2.3% of the United States (US) population has a BMI of greater than 40 kg/m², implying that there are more than six million people in the weight range where bariatric surgery is a potential treatment. This review aims to examine the evidence documenting the benefits and risks of bariatric surgery and whether it successfully achieves long-term weight loss and alleviation of obesity-related diseases.

**Methods**

A broad electronic and manual search of the English language literature was conducted. An electronic PubMed (1980-2008) search using MeSH database search terms ‘obesity or overweight’ and ‘bariatric surgery’ was performed. The search continued up to August 24, 2008, and yielded 388 papers, of which 62 were considered eligible for inclusion. Manual reference checks of papers cited in recent review articles were examined for suitable studies and the Cochrane Library database was also searched.

**Bariatric surgical procedures**

The epidemic of obesity in the US and the advent of laparoscopic techniques have led to a dramatic rise in the number of bariatric surgical procedures performed. These increased by more than 400% between 1998 and 2002, and almost 170,000 procedures were carried out in 2005 (Figure 2). This number is expected to rise further, with the number of practising surgeons who are members of the American Society for Bariatric Surgery (ASBS) also on the increase.

Bariatric surgery was first introduced in the 1950s when Mason performed the jejuno-ileal bypass (JIB). Bariatric surgical procedures lessen caloric intake by modifying the anatomy of the gastrointestinal tract and are categorised based on their design as either restrictive or malabsorptive (Figure 3). Both types of surgery have diverse and distinctive long-term effects on eating and are described as “behavioural surgery.”

**Restrictive procedures**

The two most common forms of restrictive surgery are adjustable gastric banding (AGB) and vertical banded gastroplasty (VBG). Restrictive procedures decelerate gastric emptying, thereby inducing early satiety with weight loss, and may also, depending on the type of surgery, reduce the size of the stomach. AGB uses a hollow silicone band to encircle the top 5% of the stomach, creating a small proximal gastric pouch that fills quickly and empties slowly. VBG works in a similar manner, vertically partitioning the stomach via surgical staples to create a small proximal pouch, and also places a synthetic ring around the stoma for reinforcement. Gastric banding procedures are reversible, minimally invasive, do not alter the normal anatomy, require no anastomoses, and allow adjustment of the outlet diameter to suit the particular patient. Major morbidity and mortality associated with gastric banding are five- to ten-fold less than other bariatric procedures. Wittgrove et al first described laparoscopic adjustable gastric banding (LAGB) in 1994, and it is now the most frequently performed bariatric operation in Europe. LAGB has been shown to result in shorter recovery time, smaller wounds and less postoperative pain compared with open gastric banding, but weight loss can sometimes be disappointing.
Beneficial effects of bariatric surgery

Bariatric surgery is the only evidence-based approach shown to achieve sustainable weight loss in morbidly obese adults. In the pivotal Swedish Obese Subjects (SOS) study, treated obese patients were compared with surgically treated obese patients who underwent RYGB (mean age 45 years; 66% women; initial BMI 50kg/m²) with 5,747 controls and found an 82% reduction in cardiovascular morbidity risk and an 89% reduction in overall mortality risk over five years of follow-up. Two recent studies, each using the Framingham Risk Score (FRS), reported a 50% reduction in 10-year coronary heart disease risk assessment and a reduction in obesity-associated left ventricular hypertrophy. In the SOS study, 24 months after surgery, the incidence of hypertension, diabetes and lipid abnormalities was markedly lower in the surgery group (adjusted odds ratio 0.02-0.38) and 11 years after bariatric surgery cardiac deaths from myocardial infarction, heart failure or sudden death were down by 23%. Both gastric bypass and gastric banding have also been shown to induce long-term remission in type 2 diabetes. In a comprehensive meta-analysis, diabetes was shown to completely resolve in 99% of patients who underwent RYGB and biliopancreatic diversion (BPD). Malabsorptive procedures bypass varying portions of the small intestine, decreasing the functional area of mucosa for nutrient absorption, resulting in less caloric absorption, and in weight loss. BPD, first introduced in the late 1970s by Scopinaro, produces early weight loss is greater after RYGB and had decreased by 23.4% in the surgery group (P<0.001) and by ten years, the group treated surgically had lost significantly more weight compared with controls (16.1% decrease vs. 1.6% increase; P<0.001).

A 2005 Cochrane Review concluded that bariatric surgery was more effective than medical treatment, resulting in an average 25-44kg weight loss up to two years after the operation, and a 20kg loss up to eight years later. Success with preoperative weight loss appears to predict long-term postoperative success in patients after bariatric surgery. Mrad et al found that patients who were unsuccessful in achieving a postoperative lifestyle change were at risk for long-term failure. Weight loss is only the first step in long-term obesity management.

Bariatric surgery has been found to positively modify cardiovascular risk factors. Christou et al compared 1,035 patients who underwent RYGB (mean age 45 years; 66% women; initial BMI 50kg/m²) with 5,747 controls and found an 82% reduction in cardiovascular morbidity risk and an 89% reduction in overall mortality risk over five years of follow-up. Two recent studies, each using the Framingham Risk Score (FRS), reported a 50% reduction in 10-year coronary heart disease risk assessment and a reduction in obesity-associated left ventricular hypertrophy. In the SOS study, 24 months after surgery, the incidence of hypertension, diabetes and lipid abnormalities was markedly lower in the surgery group (adjusted odds ratio 0.02-0.38) and 11 years after bariatric surgery cardiac deaths from myocardial infarction, heart failure or sudden death were down by 23%. Both gastric bypass and gastric banding have also been shown to induce long-term remission in type 2 diabetes. In a comprehensive meta-analysis, diabetes was shown to completely resolve in 99% of patients who underwent RYGB and biliopancreatic diversion (BPD). Malabsorptive procedures bypass varying portions of the small intestine, decreasing the functional area of mucosa for nutrient absorption, resulting in less caloric absorption, and in weight loss. BPD, first introduced in the late 1970s by Scopinaro, produces early weight loss is greater after RYGB and had decreased by 23.4% in the surgery group (P<0.001) and by ten years, the group treated surgically had lost significantly more weight compared with controls (16.1% decrease vs. 1.6% increase; P<0.001).

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underwent BPD and duodenal switch, 84% of RYGB patients, 72% of VGB patients, and 48% of AGB patients. Interestingly, reduction in comorbidities has been linked with an increased likelihood of return to work after gastric bypass for medically disabled morbidly obese patients (P=0.001). Respiratory complications of obesity have also been shown to improve after bariatric surgery. In a study of 116 patients with obstructive sleep apnoea (OSA) who underwent RYGB, Haines et al found that 11 months after surgery, parallel with significantly reduced BMI, there was also reduced respiratory disturbance index (P<0.001), a measure of OSA severity, and better sleep quality and sleep efficiency. Psychological disorders are prevalent among bariatric surgical candidates. Extreme obesity is strongly associated with psychosocial problems such as anxiety, depression, low self-esteem, negative body image and discrimination. Dixon et al found that 53% of 487 bariatric surgery candidates had Beck Depression Inventory (BDI) scores of 16 or greater, suggestive of clinical depression. Van Hout et al looked at changes in psychosocial functioning, personality and body image in 104 patients who underwent VBG and found a 58.6% reduction in BMI accompanied by improved body image and self-esteem. Waters et al reported improved mental health outcomes in the first six to 12 months after gastric bypass surgery, and health-related quality of life has also been shown to improve substantially over a five-year period after bariatric surgery.

**Risks and complications of bariatric surgery**

Short- and long-term complications of bariatric surgery are described in Table 1. The major complications of bariatric surgery include pulmonary embolism, respiratory failure, gastrointestinal leaks from the breakdown of staple or suture lines, stomal obstruction or stenosis, and bleeding. Diabetes, open surgery, and surgeon experience are associated with increased risk of complications. In a meta-analysis by Buchwald et al operative mortality rates were found to be 0.5% for gastric bypass, 0.1% for gastric banding, and 1.1% for malabsorptive procedures. Surgeon and hospital case volume influence perioperative safety, with risks lower when surgeons perform more than 100 operations and hospitals host more than 150 operations per year. A recent survey in the US indicated that 95% of bariatric surgeons now use a multidisciplinary team, which is fundamental for high-risk patients with complex comorbidities. The need for postoperative life-long multidisciplinary supervision has been highlighted.

Recent findings question the risk–benefit ratio of bariatric surgery among older patients in terms of increased lifespan. Livingstone analysed the US National Hospital Discharge Survey (NHDS) database from 1996 to 2001, and during this period bariatric surgery increased sevenfold from 19.9 to 125.2 procedures per 100,000 hospital discharges. Complications were recorded using an international classification system and found to be acceptably low. Recent long-term follow-up studies, involving more than 9,000 patients, showed significant reduction in total mortality after gastric bypass surgery, especially deaths from diabetes, heart disease and cancer. Over a mean follow-up of 7.1 years, adjusted long-term mortality from any cause in the surgical group decreased by 40% compared with the control group and the estimated number of lives saved was 136 per 10,000 surgical procedures. Similar results were reported in a recent prospective controlled study involving 4,000 patients.

In an effort to improve the outcome for patients undergoing bariatric surgery, an Obesity Surgery Mortality Risk Score (OS-MRS) has been proposed and tested in a single institution experience of 2,075 patients who underwent gastric bypass surgery for morbid obesity between 1995 and 2004. The OS-MRS is based on analysis of five preoperative factors including BMI ≥50kg/m2, gender, age ≥45 years, hypertension, and known risk factors for pulmonary embolism, including previous thrombosis. Grouping these factors produced three risk classes: A (low); B (intermediate); and, C (high), and the 90-day mortality rate among the three risk classes was significantly different (Class A: 0.21%; Class B: 1.90%; and, Class C: 7.46%). Further testing in a multi-centre setting with 4,431 patients reproduced these results, suggesting that this scoring system might aid surgical decision-making.

**Conclusion**

Obesity is a chronic, progressive disease that requires life-long treatment and is accompanied by substantial comorbidity and mortality. Bariatric surgery achieves superior and long-lasting weight loss when compared with traditional medical approaches in the management of severe obesity, and has an acceptably low morbidity and mortality rate, particularly with the advent of laparoscopic techniques and a multidisciplinary team approach. Associated health benefits of bariatric surgery include substantial reduction in cardiovascular risk, remission of type 2 diabetes, improvement in obstructive sleep apnoea and better health-related quality of life, enabling patients to return to work. Bariatric surgery is now the treatment of choice for morbid obesity.

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References


National alpha-1 antitrypsin deficiency targeted detection programme

Abstract

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder characterised by low serum levels of AAT and is associated with lung and liver disease. In May 2004, a national targeted detection programme for alpha-1 antitrypsin deficiency was established in Beaumont Hospital. So far we have identified 70 severely deficient AATD patients and almost 600 moderately deficient individuals (carriers). A research project recently undertaken in our laboratory screened 1,000 anonymised DNA samples for the presence of the S and Z mutations. This investigation of a sample Irish population revealed a gene frequency of 0.053 for the S mutation and 0.022 for the Z mutation, which is higher than anticipated based on studies in other European populations. The S variant was detected with unusually high frequency in the Irish population. Extrapolating from a population of six million on the island of Ireland suggests that there are approximately 2,900 ZZ and 14,000 SZ AAT-deficient individuals, and over 200,000 MZ carriers. The importance of an early diagnosis of AATD cannot be over-emphasised, as medical follow-up and lifestyle changes can help prevent, or at least postpone, the development of AATD-related lung and liver disease.

Keywords: alpha-1 antitrypsin deficiency, screening, Ireland.

Introduction

Alpha-1 antitrypsin (AAT) is a 52kDa glycosylated protein produced by the liver and secreted into the blood. AAT diffuses into the lungs where it functions as an antiprotease.1 Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder characterised by low serum levels of AAT and is associated with lung and liver disease.2 In May 2004, a national targeted detection programme for AATD was established in Beaumont Hospital. Funded directly by the Department of Health, the programme provides free testing to patients with chronic obstructive pulmonary disease (COPD), non-responsive asthma, and cryptogenic liver disease, and to relatives of AATD patients. A range of methods are used to diagnose AATD, including phenotyping by isoelectric focusing and genotyping by real-time polymerase chain reaction (RT-PCR). If a patient is diagnosed with AATD, the Alpha One Foundation provides a range of ancillary services including counselling, expert advice, information packs and leaflets, and opportunities to enrol in clinical trials and to join the alpha-1 patient support group.

Alpha-1 antitrypsin deficiency

Antiproteases regulate and inactivate proteolytic enzymes such as neutrophil elastase, an enzyme capable of destroying alveolar wall connective tissue. AAT is the most abundant antiprotease in the lung and plays a major role in maintaining lung health and function. AATD is a hereditary autosomal codominant disorder caused by mutations in the AAT gene located on chromosome 14.3 Genetic variants of the AAT gene are characterised by their electrophoretic mobilities as medium (M), slow (S) or very slow (Z). The most common variants associated with disease are the S (Glu264Val) and Z (Glu342Lys) mutations, caused by a single amino acid replacement of glutamic acid at positions 264 and 342 of the polypeptide, respectively. Both mutations result in decreased levels of circulating AAT due to retention of the aberrantly folded protein in the liver,4 and classically result in liver disease in children, and early-onset emphysema or, occasionally, liver disease in adults.5,6 Smoking is the single biggest risk factor for the development of emphysema in AATD patients.
and individuals with AATD who smoke develop severe, early-onset emphysema. This is because the small amount of AAT that reaches the lung in AATD patients is promptly inactivated by cigarette smoke. There are also a number of additional theories emerging in the pathogenesis of AATD-related emphysema, including the fact that the Z AAT protein itself can develop pro-inflammatory properties. The most commonly observed genotypes are MM (normal), MS and MZ (heterozygotes), SZ (compound heterozygote) and SS or ZZ (homozygotes). It remains unclear whether the carrier status (MS or MZ) confers an increased risk of disease, but the MZ phenotype is found in high frequencies in cohorts of COPD patients.

Diagnosis and detection
AATD is an under-diagnosed condition and prolonged delays in diagnosis are common. The majority of AATD individuals with emphysema are misdiagnosed as COPD patients and a recent US study showed that it takes an average of 5.6 years from the time symptoms first appear to an accurate diagnosis. In recognition of this problem, we have launched a national registry of AATD patients and a website (www.alpha1.ie) providing a resource for doctors, patients and the general public. All patients diagnosed through our targeted detection programme are offered a variety of services including counselling, expert advice, information packs and leaflets, and opportunities to enrol in clinical trials and to join the alpha-1 patient support group. Based on studies in other European countries, it is estimated that 1,200 Irish citizens have AATD and up to 200,000 are carriers, yet only 110 individuals with AATD have been identified in Ireland to date. A research project recently undertaken in our laboratory screened 1,000 anonymised DNA samples provided by the Trinity College Biobank for the presence of the S and Z mutations. This investigation of a sample Irish population revealed a gene frequency of 0.053 for the S mutation and 0.022 for the Z mutation, which is higher than anticipated based on studies in other European populations. The World Health Organisation (WHO) guidelines advocate targeted detection programmes for AATD in patients with COPD, non-responsive asthma or cryptogenic liver disease. In May 2004, a national targeted detection programme for AATD was launched by the Alpha One Foundation in Beaumont Hospital. The programme employs a full-time clinical research nurse, who attends respiratory outpatient clinics where patients are targeted for screening. AATD can be diagnosed from venepuncture or a finger-prick test using a dried blood spot (DBS) sample on specially treated filter paper. When a venous sample is obtained, serum can be isolated from blood and used in two different assays. The first assay measures circulating levels of AAT by radial immunodiffusion (RID) and the second provides phenotyping by isoelectric focusing (IEF). IEF separates molecules according to differences in their charge, with each molecule migrating to a point in a pH gradient where it has no net charge (Figure 1). The various phenotypes are identified by comparison with reference standards (for example MM, SZ, ZZ). Standard protein electrophoresis is not precise enough for an accurate analysis of the various forms of AAT, so isoelectric focusing must be performed to correctly diagnose patients. It is also worth considering that determination of AAT levels alone is insufficient evidence of AAT deficiency. AAT is also an acute-phase protein and consequently levels can sometimes be falsely elevated. Therefore, determination of the quantitative level of AAT must be combined with phenotypic or genotypic analysis. In addition, our laboratory has been participating in a pilot United Kingdom NEQAS (National External Quality Assessment Service) Alpha-1 Antitrypsin Phenotyping scheme since July 2007. Every three months the scheme provides two serum samples for inclusion in our screening programme and so far we have achieved 100% compliance with NEQAS.

In the last year, a DNA genotyping system has been developed, which can detect the two mutations (S and Z) responsible for almost 98% of all cases of AATD. A short questionnaire is completed by each patient and DBS sample is obtained. DNA isolated from the treated paper is then genotyped by RT-PCR, using primers and probes specific for each mutation. The major advantage

![Figure 1: Targeted screening in Ireland to date.](image-url)
of implementing the genotyping method is that the ease of sample collection and storage has allowed for self-testing in the home, and the finger-prick kit test is particularly useful for family screening. Information brochures on AATD and a stamped addressed envelope are supplied with each kit and the completed kit can be sent directly to the diagnostic laboratory in the RCSI Education and Research Centre at Beaumont Hospital.

In summary, AATD is more prevalent in Ireland than previously thought, based on the Trinity College Biobank data and the symptomatic population investigated in the targeted detection programme. The advantages of early and accurate diagnosis of AATD are manifold and include: 1. closer observation and management of affected individuals, especially regarding pulmonary and liver health; 2. family member testing, at least some of whom may have lung or liver complications; 3. aggressive smoking cessation efforts, which have been associated with lower rates of smoking among AAT-deficient individuals;17 and, 4. consideration of occupational hazards and environment, as exposures to some occupational dusts and vapours can accelerate pulmonary decline. Once identified, AATD patients have the opportunity to enrol in clinical trials taking place in Beaumont Hospital, such as the AAT augmentation therapy clinical trial for ZZ individuals, and the MZ family study, which is attempting to clarify the risk of COPD in MZ individuals. In conclusion, the importance of an early diagnosis of AATD cannot be over-emphasised, as the resulting appropriate medical follow-up and lifestyle changes can help prevent, or at least postpone, the development of AATD-related lung and liver disease.

Results of the alpha-1 antitrypsin deficiency targeted detection programme

The programme has been running for four years, since May 2004. During this period we have tested 3,000 individuals throughout Ireland. We use a combination of venous blood collection to determine phenotype and DBS samples to determine genotype (confined to Z and S alleles). So far we have identified 70 severely deficient AATD patients and almost 600 moderately deficient individuals (carriers). In a targeted population of 2,600 individuals, over 25% possessed at least one abnormal AAT gene. The full results of the programme as of September 1, 2008, are as follows:

33 ZZ, 37 SZ, 360 MZ, 228 MS, and 12 SS, with six rarer phenotypes also identified, including IZ, IS, and MI individuals.

During the year we have presented to, and met with, various respiratory journal clubs, and biochemistry and immunology laboratories in hospitals throughout Ireland. As a result, we are now receiving samples for measuring AAT levels and for AAT phenotyping from various respiratory consultants and laboratories. During our visits to the hospital labs, it has come to our attention that many biochemistry and immunology laboratories do not have the resources, equipment, or personnel to measure or phenotype for AAT. In many cases, labs send their alpha-1 testing requests to a private company, Claymon Laboratories Limited, who charge €60 for AAT levels and €160 for AAT phenotyping. Alternatively, some other labs send their alpha-1 requests to the Protein Reference Unit in the Northern General Hospital, Sheffield, England, which is also costly. Conversely, we provide AAT measurement and AAT phenotyping for free, which may relieve the financial burden for laboratories outsourcing their AAT testing and may provide an incentive for Irish hospitals to use our services.

Pilot alpha-1 antitrypsin deficiency screening programme to determine the prevalence of alpha-1 antitrypsin deficiency in Ireland

Funding Body: Talecris Biotherapeutics

We recently undertook a research project to identify the incidence of AATD in a representative sample of the general population of Ireland. This involved screening approximately 1,000 anonymised DNA samples for the presence of the S and Z mutations and was undertaken in collaboration with Dr Joe McPartlin of the Trinity College Biobank. The gene frequencies for both the S and Z mutation were higher than anticipated based on studies in other European populations.
The percentage of AAT-deficient alleles detected was higher than that detected, constituting 46 MZ and 98 MS individuals. An S assay carried out on 960 Biobank samples showed 98 MS carriers and one SS (homozygote) individual. The frequency of the S gene in this population was 0.053. In total, between the two assays, three AAT-deficient individuals were identified, constituting two SZ and one SS genotype. A total of 140 AAT-deficient carriers were detected, constituting 46 MZ and 98 MS individuals.

The percentage of AAT-deficient alleles detected was higher than anticipated from studies in other populations. The allele frequencies for S and Z in Ireland were previously estimated as between 0.02-0.04 and 0.005-0.015.11 The S variant, thought to be common to the Iberian Peninsula, was detected with unusually high frequency in the Irish population.10 Our pilot study shows that S and Z alleles occur at frequencies of 0.053 and 0.022, respectively, in the Irish population. Extrapolating from a population of six million on the island of Ireland, this would suggest that there are approximately 2,900 ZZ and 14,000 SZ AAT-deficient individuals, and over 200,000 MZ carriers.

Conclusion

The prospect that AATD is more common in Ireland than previously thought highlights the fact that all COPD, non-responsive asthma and cryptogenic liver disease patients should be tested for AATD. Increased awareness and understanding of AATD is vital to prevent the continuing underdiagnosis of this condition. Early diagnosis of AATD, with appropriate medical follow-up and lifestyle changes, can prevent, or at least postpone, AATD complications.

References


Small bowel obstruction

Small bowel obstruction may develop from a variety of underlying pathologies. In adults, the most common causes include adhesions secondary to abdominal surgery, and hernias. Other causes include malignancy, volvulus, diverticulitis, foreign bodies, intussusception, and inflammatory bowel disease.

A small bowel obstruction may be partial or complete, and simple (non-strangulated) or strangulated. Patients typically present with intermittent crampy abdominal pain. The pain may be associated with vomiting (more common with a proximal obstruction), diarrhoea (in the initial stages), and nausea. Patients who present with a fever or tachycardia may have a strangulated bowel obstruction, which is a surgical emergency.

Imaging studies

Imaging studies play a vital role in the diagnosis and management of patients with a small bowel obstruction. The first study to order is a plain film radiograph of the abdomen with at least two views (supine and upright). This can show dilated loops of small bowel with air-fluid levels and a relative paucity of gas in the colon (Figure 1). The small bowel is often described as ladder-like with loops stacked one over the other (Figure 2). It is always important to look for free intraperitoneal air, which is usually seen as a thin rim under the diaphragm (crescent sign) (Figure 3). This is often best viewed on an upright film, as air will rise in the abdominal cavity. Free air may also manifest as air on both sides of the bowel wall (Rigler’s sign) or outlining of the falciform ligament in the liver (football sign). The next imaging modality that should be used is a computed tomography (CT) scan of the abdomen and pelvis with both oral and intravenous contrast. This allows assessment of the underlying aetiology of the small bowel obstruction, as well as determining the exact transition point. More importantly, it may indicate whether the involved bowel is strangulated. A transition point is often identified by dilated loops of small bowel proximal to the site of obstruction (bowel loops usually measuring 2.5cm or greater in maximal diameter), with collapse of the distal

Figure 1: An upright x-ray with contrast of the abdomen, demonstrating multiple air-fluid levels within the small bowel. There is no free intraperitoneal air. The stomach is distended and filled with oral contrast. There is a paucity of gas in the colon, reinforcing the diagnosis of small bowel obstruction.

Figure 2: A supine x-ray of the abdomen of the patient shown in Figure 1, demonstrating multiple loops of dilated small bowel in a stack, ladder-like appearance. The bowel loops measure 4.8cm at greatest dimension.

Figure 3: Upright plain film x-ray of the chest, demonstrating a thin region of lucency immediately below the right hemidiaphragm, which is consistent with free intraperitoneal air.
loops (usually measuring less than 1cm in maximal diameter) (Figures 4 and 5). Signs of strangulation include bowel wall thickening, portal venous gas, and pneumatosis intestinalis (gas within the bowel wall) (Figure 6, Figure 7).

CT scans may also detect other underlying pathology that may be contributing to the small bowel obstruction. For example, intussusception is the result of telescoping of a segment of bowel (known as the intussusceptum) into the segment immediately distal to it (known as the intussuscipiens). On CT imaging, a bowel-in-bowel appearance with the presence of mesenteric vessels and fat entering the intussusceptum is pathognomonic for this condition (Figure 8). In other cases, small bowel obstruction may occur as the result of other inflammatory or pathological processes in the abdomen, such as appendicitis, diverticulitis or colon cancer (Figure 9).

Management
Immediate treatment of a small bowel obstruction includes aggressive fluid resuscitation, correction of metabolic electrolyte abnormalities and decompression of the gastrointestinal tract (via a nasogastric tube). Intravenous antibiotics may also be necessary. Any evidence of a strangulated small bowel obstruction is an emergency and requires surgical referral. Further management of the bowel obstruction is determined by the underlying aetiology. In some cases, conservative management over the course of a few days is sufficient for resolution. In other cases, patients may require a laparotomy for lysis of adhesions or correction of the underlying abnormality. The majority of cases of small bowel obstruction resolve with non-surgical management.

References
A 44-year-old Traveller woman who has been a ‘street drinker’ for many years. She has seizures and serious injuries from falling out of bed and down stairs. She has suffered brain damage as a result of the falls. This woman is very ill, blood pressure rises dangerously high with vomiting. When dehydration occurs she requires hospitalisation for IV fluids. She is unable to care for herself and is currently living in a hostel with a carer.

‘Homelessness, Health and the Case for an Intermediate Care Centre’

This example is one of 89 open cases that the Multi-Disciplinary Primary Care Team for Homeless People was working on in 2006. This programme was established by the Health Service Executive (HSE) to oversee healthcare for the homeless population in Dublin and throughout Ireland. This woman’s circumstances highlight the complexity of each individual case and convey some of the difficulty in obtaining suitable care and accommodation for such people. An Irish Department of Health strategy document published in 1994 highlighted equity as one of its key goals. It specifically stated that disadvantaged groups should receive special attention. In the context of homelessness, some ground has been made, but equity sometimes seems like an unattainable goal. This article looks at the complex healthcare needs of this marginalised group. It explores their healthcare utilisation patterns, examines the systems that have evolved to address their needs, explores gaps in service provision, and suggests some solutions.

Healthcare needs of homeless people

It is well established that homeless people suffer a higher morbidity from conditions that are both common and uncommon in the general population. It was estimated by Holohan in 2000 that 66% of homeless people in Dublin suffered from at least one physical or psychiatric problem. Chronic diseases such as diabetes, hypertension, arthritis, heart disease and tuberculosis (TB) were reported by 41% of respondents in the same study. Condon et al found that 98% of subjects in their research group required dental treatment. A detailed look at the health status of a group of homeless children and their families revealed that only 44% had completed their primary immunisation programme.

While homeless people have higher morbidity and mortality, and thus higher need, decreased access to primary healthcare services results in poor provision of healthcare to them.

With regard to addiction, a study commissioned by the Merchant’s Quay Project, an organisation established to meet the healthcare needs of drug users, showed that 63% of respondents reported being homeless. The Multi-Disciplinary Primary Care Team for Homeless People also reported that 46% of individuals in their open cases had alcohol addiction.
problems, while 25% reported drug addiction. With regard to mental illness, the psychiatric service in the Mater Hospital in Dublin reported that 13.8% of patients seen over a six-month period were homeless. The homeless cohort presented more commonly in suicidal crisis (26.6%) compared with the non-homeless group (12.5%).

Furthermore, homeless people frequently present to hospital services with more than one of the problems highlighted above. This is referred to as ‘dual diagnosis’ and further complicates their care.

It has been reported that the length of inpatient stays is up to 18% longer for homeless people admitted as medical or surgical patients, and up to 23% longer for psychiatric patients.

Healthcare utilisation and health behaviours

The Tudor Hart Inverse Care Law states that “the provision of services is inversely proportional to the need for services”. While homeless people have higher morbidity and mortality, and thus higher need, decreased access to primary healthcare services results in poor provision of healthcare to them. One of the reasons reported in the Irish context is that some homeless people have difficulty in finding a general practitioner (GP) to sign their medical card applications. Feeney et al reported that a lack of knowledge of the medical card system was a significant barrier to homeless people obtaining and maintaining a medical card.

Several studies have pointed out the inappropriate use of healthcare services by the homeless. Various Irish studies have reported that accident and emergency (A&E) attendance of homeless people was between 22.3% and 37%, compared to 16% of the general population. Holohan states that many A&E visits by homeless people are inappropriate and would be more ideally suited to the GP setting. He further suggests that this is strongly associated with the difficulties in obtaining and maintaining a medical card.

It has also been shown that the homeless have higher admission rates and longer inpatient stays than the general population. O’Carroll et al demonstrated that 19% of a large group of homeless people had inpatient stays in the previous six months compared with 14% of the general population. It has been reported that the length of inpatient stays is up to 18% longer for homeless people admitted as medical or surgical patients, and up to 23% longer for psychiatric patients.

Other factors associated with homelessness affect health service utilisation patterns and health behaviours. For example, difficulties have been encountered in the psychiatric services because of the high mobility of homeless people. Fear of statutory services (for example social services or involvement of the Gardaí) was emphasised as a reason for lack of contact with the public health nurse in a study of the healthcare usage of a group of families. The issue of competing needs has also been explored. This refers to the other needs of homeless people, which may take priority over seeking healthcare, such as finding shelter or satisfying addictions.

Competing needs, along with residential history, mental health, substance abuse and history of victimisation have all been included in the ‘Behavioural Model for Vulnerable Populations’, which aims to understand the healthcare utilisation of homeless people.

Healthcare services for homeless people

In an ideal world, homeless people would have no more difficulty accessing mainstream health services than the non-homeless population. Unfortunately, homeless people have to deal with many barriers to access, and with the burden of their competing needs. This is notwithstanding their tendency to use the system inappropriately when they do access it. As a result, various targeted services have evolved over the years, some of which are outlined here.

Primary care – Safetynet

This programme was developed by a group of GPs in Dublin with practices in various disadvantaged areas. The aim of the service is to provide primary healthcare to homeless people. It provides medical and social support in the agencies where homeless people regularly attend and stay, and co-ordinates the work of organisations and individuals providing healthcare to the homeless population. It aims to create a “critical mass for advocacy” and is involved in the development of treatment protocols and, more recently, in medical outreach. The overarching themes are of communication and co-ordination with health providers, which hopefully can go a long way in closing the gaps in service provision. Despite the short period since its inception, Safetynet is now accepted by policy-makers and homeless organisations alike as the developer of primary care services for the city.

Alcohol and drug addiction services

The Dublin Simon Community has developed an innovative alcohol detox unit for the homeless. This eight-bed unit provides a medical detox service that is staffed by trained professionals 24 hours a day and seven days a week. For those who have completed the programme successfully, there are two comprehensive follow-up services, the Dublin Simon Residential Alcohol Service and the Dublin Simon Alcohol Support and Aftercare Programme.

The National Drug Treatment Centre (NDTC) is the longest established treatment service in the country. It provides assessment and treatment of drug addiction along with monitoring, evaluation and various other services. The Merchants Quay Ireland Drugs Outreach service was developed in response to research that showed an increasing number of ‘hard to reach’ drug users in the city. The ‘hard to reach’ include the homeless, younger chaotic drug users and ethnic minorities. The Outreach service aims to identify and target these groups with education about safer usage and to bring them closer to the centre-based services. It also acts as a bridge between users and the community, working closely with local businesses and groups such as the local policing forum. Safetynet also has an innovative methadone treatment programme based in two inner city Dublin hostels. This was developed in response to the increasing incidence of drug-related medical problems and reports of reduced access to the NDTC due to long waiting lists and intimidation by other clients.
Mental health services

In the past, significant difficulties existed with psychiatric service provision to the homeless population because of the catchment area system, and difficulties in determining exactly what area those of ‘no fixed abode’ would fall into. Today, all homeless psychiatric admissions from Dublin are accepted by St Brendan’s Hospital. They also provide a day centre based in Usher’s Island and three houses in different parts of Dublin, providing various degrees of support within the community.

Gaps in service provision and suggested solutions

Currently there is a major gap in step-down services from the acute hospital setting. Many homeless people occupy beds for much longer than required due to a lack of appropriate accommodation for them when discharged. Sometimes those who are not sick enough to remain in hospital are discharged to hostels with inappropriate facilities. Unfortunately, others may not be provided with hostel services and may not have a suitable place to stay. O’Carroll et al put forward both moral and economic arguments for an intermediate care centre. They propose that a step-down unit would lead to significant savings as a result of reduced hospital stays and prevention of early readmission.

Long waiting lists for access to methadone treatment programmes are a chief complaint of drug users who are fighting to break the cycle. Safetynet has shown significant success in its pilot methadone treatment programme within the hostels. Despite this, only 20 places have been permitted and even though GPs are enthusiastic, they must frequently turn people away despite the dangers addicts will face with continued drug use. Safetynet is currently petitioning the HSE for a further 30 places in the programme.

O’Neill et al reported that 35% of individuals referred from A&E to psychiatry services in the Mater Hospital in Dublin were homeless. While some advances have been made in providing psychiatric care for homeless people, O’Neill et al recommend more targeted approaches to deal with acute presentations to A&E departments. One suggestion is the improvement of the multidisciplinary psychiatric outreach initiatives developed in recent years.

Finally, the lack of communication between various homeless service providers is a recurring theme in the literature as a barrier to full service provision. These shortfalls may also frustrate project workers: “I find, to be honest with you, that other agencies don’t like to help you, which is stupid as we’re all in the same thing…..” (Corr C, ‘Reaching the Hard to Reach’, Conference Paper, Dublin 2008). The Homeless Agency, set up to aid the co-ordination of statutory and voluntary groups, has gone some way towards tackling this problem but it is largely believed that a greater cultural shift is required to achieve real change.

Conclusion

The healthcare needs of homeless people are numerous and complex. Their utilisation of services is affected by many variables including, but not limited to, deficiencies in the system and difficulties resulting from their condition. Mainstream health services have often failed to meet the needs of homeless people and consequently have had to deal with more acute and complicated presentations. As a result various targeted approaches have evolved, which have generally proven to be more successful. Unfortunately, many gaps in service provision and proper communication remain, but it has become clear to this author that many individuals and organisations are still determined to overcome these final barriers.

Acknowledgements

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MOUNTAINS TO CLIMB – healthcare challenges in rural British Columbia

ROBYN JOHNSTON and LIANNE McLEAN describe the challenges involved in providing quality healthcare in rural Canada.

British Columbia (BC) covers a huge geographical area, but has a relatively small population, the majority of which is located in the southwest corner. A major challenge facing the province is the provision of quality healthcare to the many rural areas. The Northern Health Authority is responsible for providing health services to an area that covers 65% of the province. The mountainous geography and often harsh climate provides an added challenge to health service providers. The region covered by the Northern Health Authority has the highest mortality rate and lowest health status in the province, yet in the past 10 years many rural hospitals have been forced to shut down or reduce their services. In rural BC, 17 maternity care services have closed since 2000, forcing women in those communities to travel elsewhere, often months before their due date, to seek maternity care.

Despite provincial guidelines that are designed to guarantee rural residents access to emergency care within specified maximum travel times, almost 11% of the population of northern BC lives outside of a geographical area that allows access within the “golden hour”. Many communities, especially aboriginal communities, have no medical care at all and must either travel for hours, sometimes in severe weather, to get care, or go without. In the communities that do have general practitioner (GP) services, mental health services, social workers, nursing staff and hospital facilities, many challenges still face healthcare providers. For example, they must be willing to practise knowing that they have very little support, such as specialist referral facilities or reasonable staffing levels. There are also issues regarding who runs the clinic when the only doctor or nurse in the area is away.

The thinking behind the additional rural intake and education is based on studies showing that students who are raised and educated in rural communities are more likely to work in rural areas as trained physicians.

Finding solutions
Rural medicine challenges are widespread across Canada and great effort has been put into developing effective training programmes for physicians and medical students to better equip them for the challenges of rural practice. Hutten-Czapski and Thurber demonstrated that there was a strong relationship between the location of medical undergraduate and graduate training and the proportion of graduates in rural practice two years after graduation.
British Columbia has a land area of just over 925,000km², making healthcare provision in rural areas a significant challenge. With increased attention being drawn to failure of infrastructure and to the challenges involved in maintaining rural physician recruitment, rural medicine has come to the forefront of medical policy in recent years. In 2000, the University of British Columbia (UBC) began addressing the increasing challenges of staffing and trying to maintain acceptable levels of rural healthcare in the province. This year saw the first graduates of the Northern Medical Program, which partially trains UBC medical students at a satellite facility in Prince George, BC. This increased focus on rural training is not only demonstrated by the new programme, which takes a small number of UBC students through a complete northern and rural training programme, but also by the broader education goals of the UBC medical undergraduate programme. Specific rural clinical attachments, as well as in-class discussion on rural health objectives and opportunities, help to shape the rural experience of all medical graduates. These clinical and pedagogical components are paired with increased rural selection criteria for programme admission, offering increased opportunities for those students raised in rural areas. The thinking behind the additional rural intake and education is based on studies showing that students who are raised and educated in rural communities are more likely to work in rural areas. With the inaugural cohort of Northern Medical Program graduates starting their residencies this year, an important opportunity arises to gauge the effectiveness of these new protocols in terms of long-term rural retention.

Taking care of the doctors
The challenge with any education initiative is that, while feedback from students is positive in that the clinical learning environment in rural communities allows for more autonomy and breadth of service, the ultimate challenges of rural medical practice remain. Isolation, social wellbeing and family infrastructure have a significant influence on sustaining rural physician practice. Social issues are pervasive across healthcare professions in rural communities. In 1998, a large dispute arose in BC’s northern communities. A group of 22 physicians resigned from their hospital duties, citing unreasonable on-call schedules. At the height of this dispute, a total of 62 physicians withdrew at least some of their services. Thommassen et al distributed a survey to physicians practising in isolated communities. This self-reported survey sought to gauge the effects of practice in these communities on the physicians’ psychological wellbeing. Survey questions asked if physicians suffered from depression currently or in the previous five years, from burnout, or job dissatisfaction, or if they had considered relocation. Some 55% of respondents reported suffering from burnout, with emotional exhaustion (54%), poor sense of personal accomplishment (57%) and depersonalisation (31%) also figuring highly. Self-reported depression was found in 29% of respondents, with 31% suffering from mild to severe depression, as rated by the Beck Depression Inventory. In total, more than half the respondents questioned were considering relocation. Data such as this demonstrates one of the major challenges to rural healthcare – physician satisfaction and retention. Glen Shmidt, a social worker with research interest and practice experience in remote and northern practice issues has addressed some of the challenges facing recruitment and retention of rural physicians. These include on-call rotations, professional fatigue, lack of tertiary centre back-up, and balancing personal requirements.

A reassessment of the current Fee-For-Service structure to include allowances for complex and multidisciplinary care could increase the accessibility of populations to rural and remote healthcare teams.

Helping communities to help themselves
Access to healthcare requires not only the supply of medical professionals in rural and remote communities, but also that we address the challenges that block effective healthcare provision in the communities themselves. The challenges faced by new physicians trying to establish themselves are increased in rural practice and include the issue of cross-cultural practice, the steep learning curve, the psychological impact of colonisation and traditional medicine on rural First Nation populations, and the role of collectivism in these cultures. Buxton et al suggest that increased public health training in rural physician populations can help to decrease patient burden and increase cross-cultural understanding and awareness. These programmes require a long-term commitment to the community and will in turn increase communication, advocacy, and awareness of cultural sensitivities. The challenges to increase physician awareness of the importance of public health training, as outlined by Buxton et al, are mirrored in discussions with many rural physicians. Dr Dan Horvat, the Medical

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In recognition of the challenges implicit in rural practice, a number of incentives are already in place to encourage recruitment and retention of physicians. These include rural retention premiums, isolation and travel allowances, and continuing medical education allowances, all of which are proportionate to the remoteness of the community. There is also a GP locum programme designed to enable rural GPs to take leave from their practices, an advanced skills programme, which funds rural physicians who wish to undertake further training, specialist training bursaries, which fund residents in exchange for a commitment of service in a rural community, and student loan forgiveness programmes, also in return for rural service. In the situation of vacant positions or pending vacancies, there is a recruitment incentive fund of up to $10,000 and also a recruitment contingency fund, which provides funding to assist communities or physician groups experiencing severe difficulty in filling a vacancy. These financial incentives may help to attract physicians to underserved areas and provide some improved quality of life for those that remain, but they do not solve the deeper social and professional challenges of practising in a rural community.

Positive developments
Despite these challenges, the healthcare professionals who do choose to practice in rural regions of BC still manage to provide some excellent services. There are a number of GPs and nurses who provide monthly or bi-monthly fly-in medical care to communities with no health services, and many communities have a full-time nurse who, despite the lack of supportive services, provides dedicated medical care to an otherwise unserviced community. In 19 communities, GP surgeons and GP anaesthetists provide care, often allowing patients to undergo elective procedures with a shorter wait time than if they were referred to an urban centre. Nurse practitioners are now being trained to provide care in many rural areas and the development of a health sciences campus at the University of Northern British Columbia has allowed doctors, nurses and nurse practitioners training in the province to have earlier and increased exposure to healthcare in rural and remote settings. Additionally, resources such as video conferencing are increasingly being used to connect remote communities to specialist services.

More to do
With increased attention being paid to gaps in rural care, as well as increased training for medical students, BC has begun to address the challenges of rural and remote healthcare. Greater work must be done, however, to allow for a successful cultural interface, increased infrastructure support, and greater collaboration between members of multidisciplinary teams.

References
Introduction
Medical tourism is the practice of travelling abroad to receive healthcare, be it reproductive medicine, cardiac surgery, joint replacement surgery, or even cosmetic surgery. Medical tourism today has reversed the traditional model of international medical travel, where wealthier patients journeyed from their home nations to highly developed countries for more advanced treatment. Medical tourism is now driven by a diverse demographic and involves both public and private services. Between 2000 and 2005, the medical travel industry generated a whopping US$513 billion and is growing at an annual rate of about 3.9%. Healthcare, which is traditionally seen as a domestic market, is becoming increasingly global. Perhaps because of the lack of laws regulating international healthcare, countries around the world are marketing and utilising the medical tourism industry in different ways, creating niche markets. As a result, governments around the world have had to change policies and strategies to adapt to this increasingly profitable market.

North America
Medical tourism in America has undergone a reversal in the past few decades. While the United States (US) was once a prime destination for wealthier international patients, US citizens are now the largest group of medical tourists seeking healthcare abroad. The increasing affordability of international travel, the worldwide availability of technology, and the increasing prevalence of American- and United Kingdom- (UK) trained doctors abroad are the likely catalysts for Americans seeking healthcare overseas.

Perhaps because of the lack of laws regulating international healthcare, countries around the world are marketing and utilising the medical tourism industry in different ways, creating niche markets.
While insurance isn’t a problem north of the border, increasing numbers of Canadians are turning to medical tourism for their healthcare needs. This is primarily due to the long waiting times encountered by patients, which is a common shortfall in countries with public healthcare systems. For instance, non-essential surgeries such as knee reconstruction may come with waiting times of up to eight months, whereas in India the entire procedure can be done in less than a week, plus ten days of post-op recovery. Other reasons for this trend may include access to procedures not available at home and anonymity in elective procedures (e.g., cosmetic surgery).

North American patients aren’t the only ones benefiting from the lower prices abroad. Many Fortune 500 companies are now looking to outsource medical care for their employees as it may earn the firm substantial savings while offering the employee a mini-medical holiday. For example, the United Group Programs of Boca Raton, Florida, have started promoting ‘mini-medical plans’, giving their customers access to optional heart, lung, liver, and kidney transplants at Bumrungrad Hospital in Thailand. The premiums range from approximately $50 to $150 per month per employee, as opposed to $308, the average national monthly premium for employer-sponsored coverage in 2006.

The American public sector is beginning to echo these trends, with several US states submitting healthcare tourism proposals for public employees. West Virginia is a prime example, where House Bill 4359 would give public employees the option to travel overseas for fully paid medical treatment, airfare, and lodging, plus a 20% rebate of the cost savings paid back to the employee.

As more companies seek alternatives to high healthcare costs, and more patients are informed about their medical choices abroad, an exodus of US patients abroad may be imminent. The global competition is only going to heat up, with “the potential of doing to the US healthcare system what the Japanese auto industry did to American carmakers,” according to Uwe Reinhardt, a Princeton University healthcare economist.

Global destinations

The efflux of patients from the American healthcare system is having collateral effects on other countries. To Vishal Bali, head of India’s Wockhardt Hospitals, medical travel is now “truly reaching an inflection point”. India’s National Health Policy legally considers foreign patients “exports” and they are deemed “eligible for all fiscal incentives extended to export earnings”. It is forecast that medical tourism could bring between US$1 billion and US$2 billion into the country by 2012 and the industry is expected to grow by 30% per year. This robust growth is supported primarily by the increasing numbers of Americans seeking treatment in India, spurred on by the increasing popularity of ‘middlemen’ in the US. IndUShealth, a medical tourism start-up in Raleigh, North Carolina, makes logistical arrangements and co-ordinates care between the US and Indian providers, saving patients many potential headaches. Many such companies offer package deals that couple the medical procedures with exclusive hotels, airfare, and even local sightseeing options.

India is also no stranger to the business of outsourcing. By sending radiological images, MRIs, and ultrasounds to India, where the labour costs are much lower, US healthcare providers are seeing huge savings. This sector in India has shown a compound annual growth rate of 150% within the last two years.

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India is not the only country that recognises the potential of this industry. In the Gulf, the United Arab Emirates (UAE) boasts a jewel, the Dubai Healthcare City, one of the world’s largest medical complexes specialising in medical tourism. This medical complex includes five-star hotels, a host of medical services, and even a graduate school affiliated with Harvard. In Malaysia, medical visa regulations have changed, increasing the length of stay for up to six months from the current 30 days. In Singapore, the multi-agency group Singapore Medicine, composed of government and industry representatives, has been created to promote Singapore as a medical hub. Curtis Schroeder, boss of Bumrungrad Hospitals Thailand, beams: “After all, we’re selling Cadillacs at Chevy prices”.

Medical tourism has also evolved in other continents into a collection of niche markets, with specialised services marketed towards a specific demographic. Patients have travelled to South America for years for healthcare and in the past several decades many of these countries have undergone significant restructuring of their healthcare options to cater to the growing demands of medical tourists. A good example is Colombia, which has previously been offering cosmetic surgery to foreign patients and is now also known for its organ donor and donor banking system.

Argentina aggressively markets to foreigners interested in cosmetic surgery, with detailed websites advertising their trendy new “boutique clinics”. Following the devaluation of the currency in 2002, boutique clinics saw a major boom. US residents flocked for treatments in
Buenos Aires, paying about a quarter of what they would have back home.7 One such clinic that has been riding this wave is Plenitas. Plenitas employs not only a dozen plastic surgeons to work exclusively on foreign clients, but also a marketing co-ordinator who liaises with local hotels, spas, and the tourism bureau. By its third year in business, the clinic had catered to over 500 international patients whose flights, hotel stay, translators, and leisure activities were included in the cost of their treatment.7 Many other South American countries are also involved in cosmetic surgery, and are actively seeking accreditation to compete on an international level. Brazil has been a recognised destination for cosmetic surgery, and is gaining recognition as a leader in eye surgery. For example, the Albert Einstein Jewish Hospital is the first facility outside the US to receive Joint Commission International (JCI) accreditation, the gold standard for healthcare safety and quality.8

More recently, the niche market of ‘reproductive tourism’ is expanding across the globe. This is especially true in Europe, where medical regulation is particularly tight, and increasing numbers of couples are travelling to other jurisdictions for assisted reproductive technology (ART) unavailable at home. Other reasons for this trend include long waiting lists, high fees, safety regulations, prohibitive legislature, monetary incentives for donors and even, in some cases, where the candidate is considered unfit for the treatment in their own country due to their sexual orientation.9 For couples who have the means to go abroad for ART, they are spoiled for choice. Available treatments run the gamut from pre-implantation genetic diagnosis, oocyte donation and assisted zona hatching, to artificial insemination. While the practice of seeking reproductive technologies in more legally lenient countries has its critics, proponents of reproductive tourism have lauded the new autonomy of individuals over their reproductive health. Guido Pennings, Professor of Ethics and Bioethics at the University of Ghent, Belgium, argues that there is no monolithic European culture and it would be unfair to place unified restrictive laws regarding reproductive health on such a diverse demographic: “The main reason for leaving these decisions to national states is that reproductive matters should be decided by the people concerned … the main argument is that legislation should not try to express the moral convictions of only one group in society”.10

Discussion
Cost is likely to be the main factor that drives people to seek treatment outside traditional ‘first world healthcare centres of excellence’. In the US, the majority of patients seeking treatment overseas are uninsured or underinsured.12 Arnold Milstein of Mercer Consultancy calls them America’s medical refugees. Some 18% of Americans are uninsured, which means that, potentially, 47 million people11 might be unable to bear the tremendous costs of healthcare in the US. The cost of elective surgeries outside the US is remarkably lower for a variety of services and this often includes airfare and a stay in a resort hotel. Knee surgeries abroad can cost as little as 10% of the cost in the US and last year US patients who had surgeries overseas saved an average of 87%.12 Thanks to these low-cost ‘mini-vacations’, acceptance of medical travel is stronger than ever. In 2007, one million Americans travelled abroad for care and the numbers are expected to grow to 10 million by 2012.13,14 It is possible that the pressure exerted by foreign markets may eventually force US policymakers to lower healthcare costs as more patients travel overseas. For example, the pressure may come because elective surgeries are key cash cows for most US hospitals and every patient lost represents a significant loss to their revenue. Another driving force for medical tourism is the increasing cost of healthcare in general. In the US, the cost of healthcare is increasing by 6-8% per year.16 This is much higher than the Consumer Price Index, which effectively means that healthcare costs will reduce corporate profits and household disposable incomes.17

Patients have travelled to South America for years for healthcare and in the past several decades many of these countries have undergone significant restructuring of their healthcare options to cater to the growing demands of medical tourists.

Safety issues
The quality and safety of overseas medical institutions has always been a major concern to patients contemplating overseas care, but there has been a paradigm shift in recent years. Many overseas hospitals are now accredited or are seeking accreditation under the Joint Commission International (JCI) or the Trent Accreditation, mentioned previously as the gold standard for safety and quality for hospitals around the world. Furthermore, increasing numbers of institutions outside the US are affiliated with top-tier US hospitals. For example, the Dubai Healthcare City has a Harvard teaching hospital, Cornell Medical School has an advisory unit in Seoul and a medical school in Qatar, and Memorial Sloan-Kettering Cancer Center has partnerships in nine countries. In addition to the actual accreditation, these well known names provide psychological reassurance that standards of overseas hospitals may even rival or surpass their US counterparts. With such a high level of quality assurance, the ‘dangerous’ stereotype often associated with ‘third world’ healthcare is unlikely to persist for long.
Pitfalls

There are still some hurdles for medical tourism to overcome before it can be widely accepted. Very often, the issue of loss of continuity of care arises if the patient’s surgical notes are not transferred with them when they return to their home country. Follow-up treatment carried out by the original surgeon is ideal and complications may arise where any information gap occurs. Attempts to retrieve information may also be difficult because documents may be in a different language or because a streamlined administrative process has not yet been established.

Some of the countries that offer medical tourism have inadequate and ineffective malpractice laws, so patients have little recourse in local courts or medical boards if something goes wrong. The difficulty in obtaining legal redress may be one of the reasons why insurance companies are reluctant to offer overseas treatment plans. Furthermore, government and basic medical insurance often does not pay for medical procedures, meaning that the patient has to pay in cash. Opposition to medical tourism also arises when it is seen to have a negative impact on the local community. For example, medical tourism may drain expertise, money, and resources away from locally run public health systems. This brain drain to the private sector is seen to compromise the standard of care for locals.

Another problem arises when individuals in the local community are paid or coerced into donating organs to patients from wealthier countries. This compensation is often given as a financial ‘incentive’ to donate their organs, which raises a lot of ethical issues, notwithstanding the issue of encouraging the illegal practice of organ trafficking. Despite this, the medical travel boom may create jobs, bring home emigrated doctors and nurses, and stimulate the local economy. Financial gains may also be used to serve the more underprivileged members of these societies. If governments fully tap the potential of this unique industry, it has the potential to improve the health of rich and poor alike.

Conclusion

Medical tourism is still in its infancy as an international industry, and as such is imperfect. Although many countries are altering legislation and resources to accommodate this growing business, the discrepancies in legal, ethical, and economic issues remain unresolved. However, the rapid growth of this industry has caught the attention of patients, companies and governments across the world. Many overseas hospitals are interested in acquiring international accreditation, and many organisations have formed to assist patients in the process of seeking healthcare abroad. As more individuals, families and companies seek international healthcare, there are more opportunities to fix the industry and make it a safer, more accessible, and more affordable alternative to healthcare at home. Hopefully, robust growth in medical tourism will democratise access to healthcare, and give us the chance to make more educated and fully autonomous decisions about our own healthcare.

References

Is stimulation a good thing? 
An overview of sacral nerve stimulation in faecal incontinence

Abstract
Sacral nerve stimulation (SNS) is a new technique used in the treatment of faecal incontinence. It refers to chronic low frequency electrical pulse stimulation of the sacral nerves at their spinal origin. SNS was first used in the treatment of urinary retention and detrusor instability, but has since been used in the treatment of faecal incontinence in patients with a functionally deficient but morphologically intact anal sphincter. Although the exact neuroanatomical mechanism is unclear, both motor and sensory components are believed to be involved. The greater than 75% reduction in the frequency of incontinent episodes and an almost complete resolution of symptoms (75-100%) may make SNS one of the most revolutionary treatments in this field.

Keywords: Sacral nerve stimulation, sacral neuromodulation, faecal incontinence, anal sphincter.

Faecal incontinence
Faecal incontinence is the involuntary loss of gas or liquid stool (minor incontinence) or the involuntary loss of solid stool (major incontinence). It affects 10% of the population but may be under-reported because of the embarrassing nature of the illness. The psychosocial issues caused by incontinence include anxiety and social isolation. Many patients are also unaware that it is a treatable condition.

Causes
Since continence requires the normal function of both the lower digestive tract and the nervous system, any dysfunction of these can lead to faecal incontinence. There are many possible causes of faecal incontinence and any combination of the following may lead to anal incontinence:
- damage to the anal sphincters;
- decreased distensibility of the rectum, especially due to inflammatory bowel disease and radiation-induced inflammation of the rectum;
- faecal impaction, especially due to immobility, loss of rectal sensation, and poor oral intake of fibre and liquids; and,
- idiopathic causes.

The internal and external anal sphincters are muscles located in the distal rectum. These sphincters, along with the levator ani muscle group in the pelvic floor, aid in preventing faecal leak. Damage to the sphincters or loss of neurological control can lead to incontinence. Trauma to the sphincters usually results from vaginal childbirth or rectal surgery. Since the rectum lies posterior to the vaginal canal, the anal sphincters may be damaged during traumatic birth. Scleroderma, multiple sclerosis, spinal cord injury and diabetes may all decrease sensation and neural control over the colon, which can also lead to incontinence. Figure 1 shows the basic anatomy of the rectum.
Diagnosis and treatment

An evaluation of the patient’s symptoms is needed to determine the underlying cause of faecal incontinence. A full history, physical examination and diagnostic investigations are all used to obtain a complete clinical picture. Common tests include colonoscopy, anorectal manometry (measurement of internal pressure) and ultrasound. Once a diagnosis is made, treatment for faecal incontinence can be divided into non-surgical and surgical options.

Non-surgical options include medical therapy and biofeedback exercises. Medications aimed at reducing the frequency of incontinent episodes and altering stool consistency are the cornerstones of therapy. The goal is to improve overall bowel control. These options are often effective for patients with minor incontinence. Common treatments used include bulking substances, increased dietary fibre and anti-diarrhoeal medications.

Biofeedback is a method of re-training muscles in the pelvis and abdominal wall. It is both safe and non-invasive. During biofeedback training, the feedback from sensors placed on the abdominal wall and on an anal plug aid in identifying and contracting the muscles used to maintain continence. This treatment may initially be successful but the beneficial effects may begin to decline six months after initial training. Some studies show that re-training may be helpful in maintaining efficacy.

Surgical options include direct repair of damaged sphincters, implantation of artificial sphincters, colostomy, graciloplasty (both dynamic and non-dynamic), and sacral nerve stimulation (SNS). Surgery cures incontinence in 80% of women with childbirth-related sphincter tears. Graciloplasty involves the surgical transfer of the gracilis muscle from the thigh to the rectum to act as a sphincter. The patient controls the muscle via electrical stimulation to maintain continence in dynamic graciloplasty. SNS is a relatively new technique. This paper aims to provide an overview of SNS.

Sacral nerve stimulation

SNS, also known as sacral neuromodulation, refers to low frequency electrical pulse stimulation of the sacral nerves at their spinal origin. SNS was first performed in 1982 in California by Dr Tanagho and Dr Schmidt for the treatment of detrusor instability and urinary retention. During treatment, an improvement in bowel symptoms was observed prompting investigation into the role of SNS as a treatment for faecal incontinence. Results showed that treatment was beneficial in those with a morphologically intact anal sphincter. Indications for SNS are continuing to broaden with time. A good example is the current investigation of SNS as a treatment for idiopathic constipation.

Mechanism of action

Theories on the mechanism of action of SNS are speculative and based on indirect evidence from studies done on patients with faecal incontinence. Current evidence suggests an effect on multiple nerves in the sacral plexus, including voluntary somatic, afferent sensory and efferent motor nerves. Recent studies have shown that there is increased rectal sensitivity to balloon distention, which implies that SNS has an effect on sensory nerves. In addition to the increased sensitivity, the mean duration of voluntary contraction of the levator ani and external anal sphincter increased from 19.6 seconds before temporary stimulation to 25 seconds post implantation of a permanent implantable pulse generator (IPG). This effect on the levator ani muscle can contribute to an increase in the rectal angle, thereby increasing continence.

Currently, no neuroanatomical basis has been found for SNS. The difficulty in correlating the human urge to defecate with that of animal models may represent the greatest barrier to understanding. However, both afferent and efferent nerve pathways are implicated in incontinent patients, though the effect of stimulation on these components may vary. In some patients, the efferent pathways are significant, while the afferent pathway is the primary mechanism in others. Fowler et al reported that anal sphincter contraction during peripheral nerve evaluation (PNE) was the result of an afferent-mediated response due to S3 stimulation during the procedure. Although the mechanism of action and the exact neuroanatomical pathway is unclear, current evidence implies that SNS may promote sensory nerve function and may improve the ability to use a functionally deficient but morphologically intact anal sphincter.
Sacral Nerve Stimulation Therapy

Selection criteria
Currently, both a functionally deficient but morphologically intact external anal sphincter (EAS) and an intact neuromuscular pathway are essential criteria for consideration for SNS. Magnetic resonance imaging (MRI) or endo-anal ultrasound should be used to determine whether the EAS is intact. A successful PNE is required to demonstrate an intact neuromuscular pathway that shows at least some response to therapy. Patients must have a 50% decrease in incontinent episodes or in the number of incontinent days with no severe complications during the two-week procedure, or implantation of an IPG is not possible.

Contraindications
- Congenital anorectal malformation (anorectal malformations can limit access to the anal sphincter);
- previous rectal surgery or prolapse;
- chronic diarrhoea, bowel disease, pain;
- neuropathy, multiple sclerosis, Parkinson’s disease;
- some types of spinal cord injury;
- bleeding complications, pyoderma, pilonidal sinus (pilonidal sinuses are located in the area of battery placement); and,
- pregnancy.

Current research is aimed at reducing the contraindications for SNS therapy. Recent evidence from Melenhorst et al. has suggested that there is no difference in SNS outcome if the defect in the anal sphincter is less than or equal to 33% of the circumference. Baten et al. have also performed SNS on patients with a partial sphincter injury (less than one quadrant defect).

Inclusion criteria included failure of conservative treatment, an intact EAS and greater than or equal to four days with faecal incontinence per 21-day period more than one year after surgery. Three of the patients had multiple surgeries for recurrent rectal prolapse, one of whom underwent prolapse repair following stimulation. A reduction in the frequency of faecal incontinent episodes from 5-24.7 per week to 0.5 per 21-day period more than one year after surgery. Three of the patients had multiple surgeries for recurrent rectal prolapse, one of whom underwent prolapse repair following stimulation. A reduction in the frequency of faecal incontinent episodes from 5-24.7 per week to 0-5.5 per week was observed.

A study carried out by Vitton et al. has indicated that SNS can be successful in treating faecal incontinence secondary to disruption of the anal sphincters in Crohn’s disease. Crohn’s disease is an inflammatory bowel disorder causing anoperineal lesions, which may lead to disruption of both the internal and external anal sphincters. Patients were treated with temporary stimulation for three weeks followed by permanent implantation, and continence was improved in all patients.

Procedure
SNS involves a two-step procedure. The first stage involves temporary stimulation or PNE. The electrodes are placed in the sacral area through a skin incision. The S2, S3 and S4 nerves are stimulated and the patient’s response is monitored. The pudendal nerve (S2-S4) supplies the anal canal; thus, stimulation of these nerves should increase the activity of the anal sphincters and reduce the number of incontinent episodes. Once a response to stimulation is detected, a wire is tunneled into either the right or left buttock, where a small pocket is created. This pouch is where the battery for the permanent pulse generator will be placed. The lead extension is then tunneled to the opposite buttock and brought to the surface of the skin. An external stimulator will be connected to the lead wire. This can be performed under local or general anesthetic. The effect of the device is then monitored for two weeks. If, at the end of this period, the patient has a more than or equal to 50% reduction in the number of incontinent episodes, or in the number of days without serious complications, then stage two is initiated.

In stage two, an IPG is inserted under general anaesthesia. A programmer (a programming device) is used to set stimulation settings and to check neurostimulator information. A handheld programmer is used postoperatively to control the IPG, providing the patient with control over the output amplitude. The neurostimulator device typically lasts for five to ten years and the battery can be replaced as an outpatient procedure.

FIGURE 2: To place the electrodes and pulse generator, a wire is tunneled into either the right or left buttock where a small pocket is created. This pocket is where the battery for the permanent pulse generator will be placed. Electrodes are placed in the sacral area through skin incisions. Source: Dartmouth-Hitchcock Medical Center. Sacral Nerve Stimulation Therapy (document on the Internet). Dartmouth-Hitchcock Medical Center, 2008 (cited March 2008). Available from: http://www.dhmc.org/webpage.cfm?site_id=2&org_id=843&gsec_id=43187&sec_id=43187&item_id=43677.
Efficacy of SNS

According to the National Institute for Clinical Excellence (NICE), SNS therapy in the United Kingdom (UK) achieved a 41-75% complete continence rate, while 75-100% of patients experienced a decrease of 50% or more in the number of episodes of incontinence. There was also an increase in the ability to defer defecation with permanent implantation in the studies used by NICE. Additionally, improvements in both general and disease-specific quality of life scores were noted after the procedure.

Complications

Though generally well tolerated, SNS is associated with a few complications. Some 4% of patients with temporary stimulation have reported adverse effects, whereas 13% of patients with permanent IPGs had adverse events.

The main complication reported is pain, generally in the buttocks area (associated with the IPG implantation site), but also in the leg, perineum, or associated with infection. Analgesia is typically a sufficient treatment for non-infective pain. In cases where it is ineffective, adjustment of the parameters of the IPG device may be indicated. Medtronic® has indicated that only a single parameter (frequency, pulse duration, voltage) should be adjusted at any one time.

Infection affects 10% of patients with IPGs and often requires device removal for a two-week period. The leads are more commonly infected than the IPG device itself. An increased risk of infection has been noted if the same tined leads are used for both temporary and permanent SNS.

As a result, many centres prefer to use the older, untined wires for temporary stimulation. The two-week removal of the implanted device allows the skin to heal and the infection to clear. The device is usually re-implanted at a later date. Patients should also receive antibiotics perioperatively during the temporary SNS procedure. Minor trauma is the most common cause of lead dislodgement. It is also a problem with the older temporary wires and manifests as a return of symptoms. It is recommended that postoperative investigations should include x-ray of the sacrum to document the position of the leads for future reference. This problem has been largely eliminated by the use of new tined leads, as the tines anchor the wire within the tissue.

Conclusion

SNS is a relatively new procedure but the expanding list of indications has made it one of the more promising techniques available for the treatment of faecal incontinence. Although the exact mechanism of action is unclear, evidence has shown that both efferent motor and sensory afferent pathways play a role. Studies report a greater than 75% reduction in the frequency of incontinent episodes and an almost complete resolution of symptoms (75-100%). The success of SNS may make this procedure one of the most revolutionary treatments in this field.

Acknowledgements

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References

Introduction

The neurological examination often falls short as a definitive test of central nervous system (CNS) integrity in newborn infants. In addition, neonatal brain injury often eludes diagnosis, especially in preterm infants, because obvious signs are not apparent or may be attributed to immaturity. However, the likelihood of CNS compromise increases dramatically with signs of perinatal distress such as low umbilical cord blood pH, low Apgar score, and seizures. The importance of early diagnosis becomes apparent in studies showing the efficacy of treating brain injury with pharmacologic and head- or body-cooling therapies. These treatments may support the maturing brain in its early self-repair mechanisms and rescue neurons after the initial perinatal insult. The treatment’s success, however, hinges on early diagnosis. Magnetic resonance imaging (MRI) techniques are far superior to ultrasonography (US) or computed tomography (CT) in detecting early perinatal brain injury. MRI provides more specific anatomical localisation and more often reveals the underlying cause and timing of the initial insult. In addition, MRI is the only technique that can distinguish the presence or absence of myelin. Information such as the timing of the insult, its location, and myelination are crucial for assessing neurodevelopmental outcome. This paper reviews the basic principles of MRI as well as the benefits of imaging the neonatal brain. It also examines two pathological patterns of neonatal brain injury on MRI: intraventricular haemorrhage (IVH) and hypoxic-ischaemic encephalopathy (HIE).

Abstract

The purpose of this paper is to provide the most current information on the patterns of neonatal brain injury and its presentation on MR imaging. Magnetic resonance imaging (MRI) has become the investigation of choice for suspected neonatal brain injury and is the most sensitive imaging technique available. In addition, with the advent of new therapeutic techniques for perinatal and neonatal brain injuries, such as head cooling, MRI may provide early information on whether intervention is needed or not.

This paper describes many aspects of neonatal brain injury in regards to MRI, including its safety in the neonate. Also of importance is the normal appearance of the neonatal brain where abnormal patterns of myelination can be one of the first indications of injury. Finally, the two most common patterns of neonatal injury, intraventricular haemorrhage (IVH) and hypoxic-ischaemic encephalopathy (HIE), are discussed.

Keyword: Magnetic resonance imaging, neonates, myelination, hypoxic-ischaemic encephalopathy, intraventricular haemorrhage.
rays and CT scans do. This technique places the patient within the bore of a powerful magnet and passes radio waves through the body in a particular sequence of very short pulses. The power of MR magnets ranges in field strength from 0.3 to 1.5 Tesla. For comparison, 1 Tesla is equal to approximately 10,000 gauss, where the earth's magnetic field is only 0.5 gauss.12 Scanning derives information from the hydrogen atoms in fat and water molecules. When placed in a magnetic field, the hydrogen atoms (which are essentially magnets themselves) align similarly to the way a compass aligns with the earth's magnetic field. Pulsed radio waves of a particular radiofrequency (RF) are then directed at the patient, causing the hydrogen atoms to be knocked out of alignment.1 After a pulse, the atoms re-establish their previous alignment in the magnet's field and emit absorbed RF waves. The distribution of the waves is plotted by a computer to produce an image. The time required by the hydrogen atoms to regain the equilibrium state is referred to as the relaxation time. Two relaxation times are recognised with MR scanning: the T1, or longitudinal scanning time: and, the T2, or transverse relaxation time. Different body tissues emit characteristic signals, which determine whether they will appear gray white, or black on the final scans. Tissues that emit strong signals appear white in MR scans, whereas those emitting little or no signal appear black.1 In comparison with CT, MR scans of the brain allow a greater differentiation between gray and white matter. In addition, MRI provides superior anatomical resolution of the brain, and is the only technique that can distinguish the presence or absence of myelin in the neonatal brain. Currently, with the development of MR-compatible incubators and neonatal coils, there is improved patient safety and image quality. Neonatal MRI is becoming important in predicting neurodevelopmental outcomes and the future of MRI is compatible incubators and neonatal coils, there is improved patient safety and image quality. Neonatal MRI is becoming important in predicting neurodevelopmental outcomes and the future of MRI.

MRI safety
Sedation is usually unnecessary for neonatal MRI and neonates are customarily imaged during natural sleep,14 although chloral hydrate may be used.15 All neonates, sedated or otherwise, should be monitored during scanning with MR-compatible pulse oximetry and ECG. A qualified member of the paediatric staff should be present at all times throughout the scan.

The RF pulses used during imaging deposit energy in the form of heat into the tissues.2 The rate at which RF energy is deposited is defined as the specific absorption rate, which is measured in watts per kilogram (W/kg). The current FDA parameters for brain imaging, 3W/kg for any 10-minute period, become especially crucial in neonates because of their limited thermoregulation capabilities.16 In effect, all MR magnets, RF pulses and MR coil combinations should have the exact absorption rates recommended above to prevent excess deposition of RF energy and inadvertent rise in patient temperature. Despite this, there are no current indications for monitoring patient temperature. Furthermore, it is advised that ear protection be used with fast sequence imaging as this produces excessive noise that may be harmful to the neonatal auditory system.17

Normal MR appearance of the neonatal brain
The most distinctive finding in the neonatal brain is the almost complete lack of myelin.18 MRI is extremely sensitive for detecting myelination. The posterior limb of the internal capsule is the first area to myelinate in the immature brain and provides an indicator of early pathology if myelination does not occur (Figure 1).19 Unmyelinated brain is hyperintense on T2-weighted (T2) images and hypointense on T1-weighted (T1) images. Although most neonatal brain is unmyelinated, term neonates typically demonstrate myelination of the primary motor and sensory cortices, along with the thalamus and gracile and cuneate nuclei.8

Routine sequence
In a neonate with suspected brain injury, the majority of neonatal studies would include a sequence described by Rutherford et al.17

1. T1 sequence acquired in the transverse plane. This is ideal for assessing the basal ganglia and thalami, and provides the best views of the posterior limb of the internal capsule (Figure 1).
2. T2 sequence acquired in the transverse plane. This is better than T1 for identifying early ischaemic change and provides excellent gray/white matter contrast in the immature brain.
3. T1 sequence in the sagittal plane.

Table 1: Encephalopathy score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score = 0</th>
<th>Score = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td>Normal</td>
<td>Gavage, gastrostomy tube, or does not tolerate oral feeding</td>
</tr>
<tr>
<td>Alertness</td>
<td>Alert</td>
<td>Irritable, poorly responsive, or comatose</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Hypotonia or hypertonia</td>
</tr>
<tr>
<td>Respiratory status</td>
<td>Normal</td>
<td>Respiratory distress (need for continuous positive airway pressure or mechanical ventilation)</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
<td>Hyperreflexia, hyporeflexia, or absent reflexes</td>
</tr>
<tr>
<td>Seizure</td>
<td>None</td>
<td>Suspected or confirmed clinical seizure</td>
</tr>
</tbody>
</table>

FIGURE 1: T1-weighted MRI of a one-week-old neonatal brain. Arrows show hyperintensity in the region of the corticospinal tracts, specifically the posterior limb of the internal capsule, indicating normal myelination.20
In addition, certain studies may include: a venogram to exclude the presence of sinus thrombosis; intravenous contrast medium (gadolinium) for cases of suspected infection (such as herpes encephalitis); and/or, angiography to examine cerebral and neck vessels in cases of stroke.\textsuperscript{17}

**Clinical presentation**

Symptoms of neonatal brain injury usually evolve quickly over a period of days and serial neurological examinations are essential for diagnosis.\textsuperscript{21} Classically, in the first hours after the insult, the neonate will present with decreased consciousness along with apnoea and bradycardia.\textsuperscript{18} Cranial nerve function is usually preserved at this point, along with pupillary responses and spontaneous eye movements. However, if the injury is severe enough, these may also be compromised. In addition, seizures often manifest in severe injuries to the neonatal brain and occur very soon after the insult. Hypotonia can also be seen when injury occurs to the cortical regions of the brain.\textsuperscript{18}

One week post insult, a noticeable improvement in levels of consciousness is often noted. Yet this improvement does not coincide with other signs of improvement in neurological function. This period in neonatal brain injury is characterised by jitteriness, refractory seizures accompanied by apnoeic episodes, and/or shrill cry. The symptoms of hypotonia, generalised limb and bulbar weakness, and exaggeration of the Moro and muscle-stretch reflexes are also often seen, and may persist for months after the injury. Subsequently, if the injury is severe, respiratory arrest and other signs of brainstem dysfunction (pupillary dilatation, absent gag reflexes, etc.) may precede a decline in consciousness. Ferriero recommends scoring the clinical signs of encephalopathy (Table 1) to standardise the approach to neonatal brain injury.\textsuperscript{22}

**Patterns of pathological injury**

**Intraventricular haemorrhage**

IVH encompasses a range of pathological processes that result from blood filling around the ventricles. The occurrence of IVH is directly related to prematurity and occurs infrequently in term infants.\textsuperscript{7} A subtype of IVH is germinal matrix haemorrhage (GMH), which is the most common form of IVH and the one correlated with the best prognosis. IVH, if severe enough, can cause mass effects and subsequent obstruction of venous outflow from periventricular brain parenchyma. This may culminate in periventricular haemorrhagic venous infarction (PVHI), and is secondary to venous hypertension in about 15\% of neonates with an initial diagnosis of IVH.\textsuperscript{23} Most cases of PVHI occur 96 hours after birth and with varied clinical symptoms, ranging from apnoea and bradycardia to seizures or loss of consciousness.

While both IVH and PVHI are detectable by cranial ultrasonography, conventional MR scanning has demonstrated increased sensitivity and specificity, especially in the acute setting, where MRI exhibits superior capacity to differentiate blood from other lesions\textsuperscript{24} (Figure 2). Acute haemorrhagic foci on T1 images appear as small areas of normal to increased signal and can be confirmed on T2 images as ovoid regions of hypointensity. Gradient echo (GRE) sequences, which are essentially fast MR pulse sequences, are extremely sensitive to haemosiderin deposits, which may be missed on other MR sequences and neurosonography.\textsuperscript{2} In effect, very small haemorrhages can be detected that would be missed otherwise. Regarding PVHI, where ultrasound again demonstrates the ability to detect the lesion, MR scanning is more specific and thus can differentiate between haemorrhagic and necrotic areas, in addition to quantifying the amount of haemorrhage present. Additionally, MR scanning and GRE can differentiate between white and gray matter, providing a more specific location and size of the infarct. This is clinically significant because the occurrence of cerebral palsy is related to the anatomical location of brain lesion. For instance, injury to the cortex/pyramidal tract will cause a spastic cerebral palsy characterised by hypereflexia and clonus.\textsuperscript{25}

**Hypoxic-ischaemic encephalopathy**

Neonates who have not received adequate brain oxygenation, either in the prenatal or perinatal state, may incur significant parenchymal brain injury known as hypoxic-ischaemic encephalopathy (HIE). HIE is a major recognised cause of neonatal morbidity and mortality.\textsuperscript{26} Processes by which HIE occur include birth injury, haematologic abnormalities, and hypovolaemia. Clinical risk factors associated with HIE are: foetal heart rate; abnormalities directly preceding birth; low Apgar scores; acidosis; and, major resuscitation during delivery.\textsuperscript{11}

Imaging features of HIE vary in preterm infants versus term infants. HIE in preterm infants exhibits predominantly white matter injury.
whereas term infants typically show necrosis in both the white and gray matter. Mild to moderate hypotension in a term neonate usually causes injury to the parasagittal region (Figure 3), whereas severe hypotension has the tendency to injure the basal ganglia, the thalamus and the corticospinal tracts. Specific abnormal signal intensity in posterior limb of internal capsule (PLIC) is an excellent predictor of abnormal outcome in term infants with HIE. In addition, basal ganglia and thalamic (BGT) lesions give rise to motor impairment in the form of cerebral palsy. The severity of BGT lesions dictates the severity and nature of the cerebral palsy (Figure 4). BGT lesions are often accompanied by injury to the white matter and are most easily seen after the first week. The motor outcome for infants with a BGT lesion depends on the severity of the lesion and is not dictated by additional lesions in the white matter. However, white matter involvement may exacerbate any cognitive deficit. This is significant because previous studies have shown that matter lesions can actually deteriorate over time, and thus early recognition and intervention can be beneficial in preventing further insult. For example, in patients with spastic quadriplegia, a less favourable prognosis is correlated with a longer delay in the resolution of extensor tone, and thus early intervention with physical therapy is favourable.

Conclusion

MRI has contributed significantly to the early diagnosis of neonatal disease. It is superior to CT and US in its ability to attribute a lesion to a specific anatomical location, discern the timing of an injury, and assess the degree of myelination. Specific patterns of brain injury are now being diagnosed with MR scans, as specific regional changes are indicative of particular pathological processes. For instance, MR images showing low signal in the posterior limb of the internal capsule on T1 imaging are indicative of hypoxic damage and insult to the upper motor neurons. This information in the early stages of injury can provide paediatric teams with the necessary information to plan a fitting treatment and accurately establish a long-term neurodevelopmental prognosis. In the case of HIE, lesions involving the white matter can deteriorate over time, making early recognition essential. In addition, the ability of MR to differentiate the exact location of haemorrhage in the brain permits not only early recognition of cerebral palsy but also better characterisation of its anatomical cause and likely sequelae. Because the signs and symptoms of early neonatal brain injury may be subtle and nonspecific, MR is essential for differentiating early brain lesions in order to prevent a delay in the diagnosis of cerebral palsy, learning disabilities, and complex behavioural disorders.
References


This year, over 5% of global trade will transit the Panama Canal and in 2010 it is projected that the canal will celebrate its millionth transit.1 It has now been 94 years since the first steamship began its journey through the 50-mile long canal. The building of the canal, while a technical and mechanical marvel, was also a seminal public health experience. The theory attributing the transmission of yellow fever to the mosquito *Aedes aegypti*, first proposed by the Cuban physician Carlos J. Finlay decades earlier, was recognised for its accuracy and significance. My summer vacation of 2008 allowed me the opportunity to visit both the birthplace of Carlos J. Finlay and the Miraflores Locks of the Panama Canal.

The Cuban connection
Stepping off the air-conditioned bus in Camaguey, the humidity of the Cuban summer was striking. As the city awakened to the smell of small cups of Cuban coffee, I walked to a monument that displays the face of Carlos J. Finlay next to other famous personalities, Che Guevara and Fidel Castro among them. With the sun rising quickly, small corners of shade provided by the colourful houses in the city centre were welcome. A short walk from the main square led me to the house where Dr Finlay was born. It was humbling to stand in the birthplace of a man who made a scientific discovery that saved so many lives. Outside his home daily life continued, with people heading to work on bikes and buses, and most likely not thinking twice about the effects of his discovery – a discovery that reshaped both the global transit of goods and the health of millions.

The dream of building the Panama Canal was one that would eventually claim thousands of lives. The deadly duo of malaria and yellow fever is thought to have caused the death of over 30,000 canal builders. The French were the first to attempt to link the Atlantic and Pacific oceans. Ferdinand de Lesseps, who had just completed the Suez Canal, led the efforts; however, he was thwarted not only by the difficult environmental factors in Panama, but also by the deaths of many of the workers. It is estimated that over 3,500 workers died in each one of the eight years during the first failed French attempt to build the canal.2

Like many scientific theories that challenge the status quo, Dr Finlay’s theory was initially not given much credence. It was in 1881 that he first proposed the idea that the humble mosquito should be “hypothetically considered as the agent of transmission of yellow fever”.3 It would be many years and many deaths later before his theory would be proven correct. This eventually led to mosquito control and prevention methods that allowed the completion of the canal.

Primara Havana
Today, walking the colourful streets of Old Havana is like stepping back 50 years in time. The old Chevrolet cars zipping along the Malecon and the smell of the salty sea air makes it a very unique city. Years ago it was the United States Army Yellow Fever Commission, led by William C. Gorgas, that was given the task of eliminating the scourge of yellow fever in Havana. Members of the Commission initially did not place much credence in Finlay’s theory and proceeded with a large-scale clean-up of Havana. The belief was that contamination and grime were somehow
the reservoirs of the disease. It was only the lack of success in eliminating the disease through this approach that eventually led them to test Finlay’s theories. 

It was in a specially constructed camp in Cuba, Camp Lazzar, that Finlay’s theory would finally be proven. Dr Walter Reed, a member of the Commission, constructed two buildings where volunteers were exposed to bloodstained bed sheets and clothing from patients confirmed to have yellow fever. In a second building, volunteers slept separated from each other by screens with mosquitoes carrying the yellow fever virus. After one volunteer was exposed to the infected mosquitoes for three nights, he developed yellow fever, confirming the idea that the disease was in fact transmitted by the lowly Aedes aegypti. This success led Dr Reed to write in a letter to his wife that: “the case is a beautiful one, and will be seen by the Board of Havana experts today, all of whom, except Finlay, consider the theory a wild one!”

Even with the results of the study, many remained unconvinced. However, Gorgas and the Commission began a programme to eliminate mosquito breeding grounds and placed patients with yellow fever in quarantine. It was a resounding success, and within a year yellow fever was virtually eliminated from Havana. Dr Reed wrote to his wife after the success of the campaign, recognising that “It was Finlay’s theory, and he deserves much for having suggested it.”

With this initial success, the Commission began eliminating the breeding grounds for Anopheles mosquitoes. Again, this was a dramatic success and was considered “the first large-scale systematic public health effort of its kind anywhere in the world.”

Havana to Panama
As I boarded the flight from Havana to Panama City, I was off to the country where the public health successes in Cuba would eventually lead to the successful completion of the Canal on August 15, 1914. Panama City today is a bustling international metropolis with sparkling skyscrapers biting into the city sky. It is a vastly different cityscape than Panama City today is a bustling international metropolis with sparkling skyscrapers biting into the city sky. It is a vastly different cityscape than even individual apartments for any standing water, which could be a breeding ground for mosquitoes.

Today, finding swampland in the city itself is impossible, but gazing beyond the wet streets after a tropical rainstorm, I recognised a mosquito heaven in the lush, thick green foliage surrounding the city. The knowledge gained in Cuba about controlling yellow fever and malaria through eradication of the mosquito populations would be used in Panama to great effect. Gorgas and his colleagues began an extensive campaign to eradicate mosquitoes and their breeding grounds. The plan consisted of several steps that were strictly implemented across the isthmus. The steps included: drainage of all pools of standing water within 200 yards of all villages and 100 yards of all individual houses; brush and grass cutting; the addition of oil to ponds and swamps to kill mosquito larvae; the use of larvaecide; prophylactic quinine administration for workers; and, the screening of windows. The results of this campaign were impressive, with the number of cases of workers contracting malaria decreasing dramatically, and yellow fever becoming completely eliminated. The mortality rates due to malarial infection in employees decreased from 11.59 per 1,000 in November 1906 to 1.23 per 1,000 in December 1909. The total number of deaths from malaria in the Panamanian population decreased from a high of 16.21 per 1,000 in July 1906 to a low of 2.58 per 1,000 in December 1909. With this decrease in the mortality and morbidity of the workers, completion of the canal fast became a reality.

Standing on the lookout over the Miraflores Locks, watching giant ships loaded with containers raised up in the Locks is an amazing sight. That the implementation of a theory from a Cuban doctor about a tiny mosquito would lead to such a momentous movement of goods around the world is tremendously impressive. Gorgas recognised this in a letter to Walter Reed and wrote that: “his reasoning for selecting the Stegomyia [Aedes aegypti] as the bearer of yellow fever is the best piece of logical reasoning that can be found in medicine anywhere”.

When the campaigns against malaria that began over 100 years ago continue to this day. The campaign block where I stayed in Panama was visited by public health officials, who examined the building’s grounds and even individual apartments for any standing water, which could be a breeding ground for mosquitoes.

The gains achieved by the application of Dr Finlay’s theory in Cuba, and put into practice in the building of the Panama Canal, are truly remarkable and serve to remind us that simple measures can make a huge impact on public health.

References


Meet ‘The Todd’

I wasn’t sure quite what to expect when I asked Rob Maschio for an interview. Most people are familiar with his television persona, ‘The Todd’, the archetypal misogynistic, lecherous, and yet hilariously loveable jock surgeon on the TV sitcom *Scrubs*. So when we sat down for a late breakfast at one of the local cafés, I came prepared for just about anything. I’m embarrassed that we haven’t ordered before my mobile buzzes and I remember to turn it off.

Rob: Hope that’s not important.

Liz: Not at all. Just about the meeting later today.

Rob: So what’s your meeting about?

Liz: We’re having a committee meeting for Surg Soc. We have to do a debriefing for the event.

Rob: De-briefing?

With mischief in his eyes it becomes apparent that Rob and his character share a similar sense of humour. We talk shop until our food arrives: when he’d have to leave for the airport on Monday, the best way to get there, why Dublin Airport may not be fully functioning at five in the morning. But once the coffee reaches the table, our conversation turns to medicine, surgery, the presentation he gave in the RCSI the previous Wednesday, and *Scrubs*.

Rob: Personally, I would have stood in the centre of the stage and not even worried about the podium. I wouldn’t have held the script either. I wrote all that stuff. I knew it. I didn’t need the script, but I kind of just held it. But that space was awesome. If you have another speaker again, just tell them they can stand centre stage.

Liz: I think it was great. But what do we do differently?

Rob: Personally, I would have stood in the centre of the stage and not even worried about the podium. I wouldn’t have held the script either. I wrote all that stuff. I knew it. I didn’t need the script, but I kind of just held it. But that space was awesome. If you have another speaker again, just tell them they can stand centre stage.

Rob is an inquisitive guy, and I am, admittedly, not a practised interviewer. It takes a concerted effort, but eventually we fall into a rhythm where I am asking more questions than answering.

Liz: Do people ever assume you know more than you do about medicine?

Rob: Yeah, sure. I wouldn’t know how to do stuff, but I can talk the talk. I feel like I do kind of know a little bit. Maybe that has to do with my real life experiences and having been in the doctor’s office so many times.

Liz: And you were pre-med.

Rob: I was pre-med. And I read a bunch of books. I do think I have an understanding of the life of doctors, interns and residents.

Liz: Have you ever thought about going back and doing medicine now?

Rob: I think I’m too old at this point. It’s too late for me. In high school I was a straight-A student. Then when I went to college, in my first year I took chemistry. I worked my ass off and I got a C. I was stunned. I thought, wow, this is going to be really hard. It overwhelmed me. In retrospect, it would have gotten easier. I would have gotten more comfortable. The Cs would have become Bs and eventually I would have had my pre-med qualification. But as a

Meet ‘The Todd’

LIZ LARKIN meets Rob Maschio, star of the TV show *Scrubs*, for a chat about medicine, television, and making people laugh.
Rob: Never with a group like this. med students before?
Liz: Had you ever been asked to speak to a room full of

home. But I had a really good time while I was here. around with scripts in my bag. I have a bunch of interviews when I get

night to catch up for the week. I have work to get back to. I'm walking

night, but I'm on a different schedule than you guys are. This is my
day jobs. In truth, I have a lot of homework. And I know it's a Saturday

He explains the process he goes through to pull off even the simplest jokes. Writing, speech
rehearsal, memorisation so it sounds natural; multiple steps are
required to create an organic impression. And the common
assumption is that he can just stand there and be funny. If it looks
effortless, it's successful.

Liz: When you take out a part of the small intestine.
Rob: Yes, yes, that's a good term. Or if there's a term for how you have
to hold back fat flaps so the big boys can get in there and do their
thing. The bowel disimpactments. All the grunt work. It's like you're
mechanics – mechanics of the body. It's barbaric almost. It's amazing.
Totally amazing.

Liz: You've recently had a few surgeries yourself. Were you ever afraid of
having a Todd as a surgeon?
Rob: I have a great orthopaedic surgeon. He's really thorough and on
the cutting edge. We look at the MRIs together. He discloses
everything I need to know. I imagine there are cases where you don't
want to disclose everything. But I've had an elbow, a shoulder, and a
knee done in the last three years. Every year I get a surgery.

Liz: What's up next then?
Rob: Penis reduction. No, hopefully that's it. I don't want to get on a
surgery craze.

Rob has strong opinions about cosmetic surgery and the
overabundance of needless surgery in Los Angeles. He would like to
avoid it himself, taking a more natural route to keep in shape. He does
admit that people who pursue repeated, elective cosmetic surgeries
fascinate him, but it's not his cup of tea.
Rob's a natural speaker and charismatic, so it's easy to forget how
much work goes into being funny for a living. He explains the process
he goes through to pull off even the simplest jokes. Writing, speech
rehearsal, memorisation so it sounds natural; multiple steps are
required to create an organic impression. And the common
assumption is that he can just stand there and be funny. If it looks
effortless, it's successful.

Liz: You'd be more successful picking up women claiming
to be an actor or a doctor?
Rob: I never say I'm a doctor. But I'm sure that doctors get more
chicks. Most actors are out of work. Tell your friends not to quit their
day jobs. In truth, I have a lot of homework. And I know it's a Saturday
night, but I'm on a different schedule than you guys are. This is my
night to catch up for the week. I have work to get back to. I'm walking
around with scripts in my bag. I have a bunch of interviews when I get
home. But I had a really good time while I was here.

Liz: Had you ever been asked to speak to a room full of
med students before?
Rob: Never with a group like this.

Liz: What's your overall impression of Dublin?
Rob: I'm very impressed that medical students get any work done,
because it seems like the party atmosphere in this town, on a scale of
one-to-ten, comes in at 11. I mean, I don't know that I could put in the
hours that you guys do, and then drink around the clock. Though I'm
sure you guys don't all do that. But Dublin is a really nice town, an
interesting town, very fine and generous people. I've always wanted to
come to Dublin and I'm really glad I did. And I know there's so much
more of Ireland to see. This is just the tip of the iceberg.

Liz: Any impressions of the RCSI as a school?
Rob: It seems like you have a really good programme here, but it seems
very old-school. And I wonder is it as technologically friendly to practise
medicine here as it is in the States?

I assure him that not only is RCSI technologically on the cutting edge of
research and medicine, but our professors are the best and brightest in
their fields.

On our walk from the café to the RCSI main building, we are stopped
and Rob is politely asked for an autograph. He graciously complies and
struggles to understand the Irish spelling of what sounds like Evan
(Eibhan) and a girl's name he has never heard of (Naoise), before giving
the two kids a high-five. Once they've left, he sheepishly admits he was
worried about spelling the names wrong. How horrible it would be to
have your name spelled incorrectly on an autograph!

Liz: You seem to have made the decision to be very available to your fans.
Does that ever cause problems?
Rob: I think people like that I make myself available. People can get my
email through my website and they can actually send me a message. I
think the website was one of the smarter things I've ever done. It gives
me a chance to promote myself. Does that make sense?

Liz: It certainly worked well for us. Now that you've met a bunch of us,
how does it feel knowing we're the future of the healthcare system?
Rob: Terrifying. Absolutely terrifying. Bunch of nerds. I can't believe
you're the next generation of doctors.

Liz: You'll wind up in the emergency room one day, and you'll recognise
one of us.
Rob: Well I have learned never to go to an emergency room in July. I just
find it amazing that you throw up and you're like, ugh, I'll just call a
doctor. The doctor is a larger than life person, a god, someone who
knows the answers to everything. And then you realise what
knuckleheads go into medicine... Lord help us all. But having said that,
seeing what you have to go through, how many hoops you have to
jump through to become a doctor, there is some saving grace in that.
So, I'm ok with you guys being my doctors.

Since it's such a lovely day, I convince him to read his scripts and
do his homework in one of the local parks rather than staying
inside for the day. I give him directions to the DART and send
him off to Howth.
Running interference: an overview of therapeutic RNAi

Abstract
RNA interference (RNAi) is a powerful, naturally occurring gene-silencing phenomenon. Our understanding of the mechanism has evolved rapidly, resulting in significant interest in its therapeutic potential. The power to specifically and efficiently silence any gene of interest hints at the power to approach clinically difficult problems in new and exciting ways. As examples, Huntington’s disease, prostate cancer, and HIV infection are examined briefly. Several key challenges currently face successful translation of RNAi into viable therapeutics. These involve the human miRNA system, the chemistry of small interfering RNA (siRNA), and the development of suitable delivery strategies. Given the potential of the mechanism, and the impressive interest in RNAi for so many applications, it appears likely that RNAi will make a name for itself as a whole new therapeutic modality.

Keywords: RNAi, siRNA, miRNA.

Introduction
Shortly after its discovery in the early 1990s, the power of RNA interference (RNAi) became apparent. Science called the discovery of RNAi the “scientific breakthrough of the year” in 2002. Andrew Fire and Craig Mello, credited with characterising the phenomenon,1 won the 2006 Nobel Prize in Physiology or Medicine for their work on RNAi. While still in its early stages, the translation of RNAi into viable therapeutics is being tenaciously pursued.2–5 Because RNAi can be programmed to silence any gene, the scope of its potential clinical applications is truly impressive.

RNAi
RNAi is a ubiquitous, naturally occurring gene-silencing phenomenon found in fungi, plants and animals. In fungi, plants and some animals, it begins with the presence of long double-stranded RNA (dsRNA) in the cell. Long dsRNA is a common intermediate in the replication of viruses and some transposons, and the RNAi system appears to have provided an important, evolutionarily conserved defence against these agents.7

FIGURE 1: The structure of a prototypical siRNA, 23nt long, with 2nt overhangs at each 3’ end, and free phosphate groups at each 5’ end. The ribonuclease Dicer generates these fragments from longer dsRNA. Alternatively, they can be synthesised in this form.
subsequent rounds of cleavage.\cite{11}

The guide strand is retained by the RISC for encoded protein. After cleavage, the target fragments are released in a sequence-specific fashion. Cleavage of mRNA by AGO2 prevents expression of the strand that directs the ribonuclease activity of AGO2 in a sequence-specific manner.

When these are met, synthetic siRNAs can escape immune detection easily for a siRNA to successfully activate RNAi: the absence of a long dsRNA (greater than 30nt in length) in the mammalian cell activates protein kinase R (PKR) and leads to global gene silencing via translation inhibition.\cite{12} Compounding this, certain GU-rich sequence motifs may activate TLR7 and the interferon-linked inflammatory response,\cite{13} leading to further non-specific silencing. The machinery necessary for RNAi is, however, conserved in mammals.\cite{14} In fact, it is functional and routinely engaged in the processing of endogenous micro-RNAs (miRNAs).\cite{15} Thus, in mammals there are two requisites for a siRNA to successfully activate RNAi: the absence of a long precursor, and an appropriately non-inflammatory sequence. When these are met, synthetic siRNAs can escape immune detection easily to take advantage of the highly specific gene silencing mechanism outlined above.

**The promise of interference**
The therapeutic potential of the RNAi mechanism is truly impressive for its all-encompassing breadth. Furthermore, diseases for which current treatment is unsatisfactory have shown promising responses to RNAi-based approaches. This review aims to provide a glimpse of this potential with the following select examples of in vivo success with siRNAs. Table 1 and Table 2 provide longer, but by no means exhaustive, lists of some of the most exciting experimental and clinical applications for RNAi.

Dominant disease genes, where the expression of a single mutant gene product is responsible for the disease state, are some of the most obvious candidates for therapeutic gene knockdown. As an example, a number of studies have demonstrated in vivo efficacy in mouse models of Huntington’s disease (HD), where an expanded trinucleotide repeat in the huntingtin gene causes disease. Franich et al.\cite{16} recently demonstrated that siRNA delivered by a neurotropic adeno-associated virus (AAV) protected mice from neurodegeneration and motor behavioural impairment. Rodriguez-Lebron et al.\cite{17} have even demonstrated a partial resolution of cellular pathology along with delayed behavioural deterioration using a similar approach in a separate mouse model. Other groups using varied RNAi approaches have shown success in multiple mouse models of HD, further reinforcing interest in an RNAi approach to HD.\cite{18, 19}

Many of the hundreds of cancer-associated genes involved in growth dysregulation, oncogenesis, invasion and metastasis are prime candidates for silencing. In this vein, mouse models of prostatic adenocarcinoma illustrate the possibilities for a combinatorial RNAi approach to cancer inhibition. For example, McNamara et al.\cite{20} were able to selectively deliver two siRNAs targeting the survival genes PLK-1 and BCL-2 to cells expressing a prostate cancer-specific antigen, PMSA. In their prostate tumour xenograft model, intratumoural injection of these siRNAs effectively inhibited tumour growth and spread of prostate tumours.

Silencing genes involved in pathogenicity should prove useful in battling viral infections. A phase II clinical trial of siRNA directed against respiratory syncytial virus (RSV) should help to better define this role in the near future.\cite{6} For viruses with a high propensity for mutation, siRNAs that target highly conserved sections of a viral genome offer the most promise.\cite{23} This is a strategy that is often not achievable by small molecule drugs, which are limited to molecularly accessible epitopes, encoded by potentially mutable sequences. RNAi, on the other hand, is quite flexible in terms of the sequence targeted. Tacere Therapeutics’ product TT-033 targets conserved regions of the hepatitis C virus (HCV) genome using three separate siRNAs delivered in an AAV shell.\cite{24} Animal studies have demonstrated inhibition of replication for up to two months after a single injection. Combinatorial approaches will most likely be necessary in many cases. For example, Benitec Limited is running a

**FIGURE 2** The RNAi pathway, beginning with a long dsRNA, which is processed into a siRNA by Dicer. siRNA is incorporated into the RISC, where one of its strands will direct the degradation of complementary RNA (the guide strand), and the other is discarded (the passenger strand). Certain characteristics of the individual strands have been shown to favour one over the other for incorporation into the RISC (discussed below). The RISC contains the ribonuclease Argonaute 2 (AGO2).\cite{10} The guide strand associates itself with AGO2 such that any strand of RNA that binds the guide strand with perfect complementarity becomes ideally positioned to be cleaved by AGO2 (Figure 2). In this way, the guide strand directs the ribonuclease activity of AGO2 in a sequence-specific fashion. Cleavage of mRNA by AGO2 prevents expression of the encoded protein. After cleavage, the target fragments are released and degraded. The guide strand is retained by the RISC for subsequent rounds of cleavage.\cite{11} In mammals, including humans, the RNAi mechanism is primed differently. This is because the presence of long dsRNAs (greater than 30nt in length) in the mammalian cell activates protein kinase R (PKR) and leads to global gene silencing via translation inhibition.\cite{12} Compounding this, certain GU-rich sequence motifs may activate TLR7 and the interferon-linked inflammatory response,\cite{13} leading to further non-specific silencing. The machinery necessary for RNAi is, however, conserved in mammals.\cite{14} In fact, it is functional and routinely engaged in the processing of endogenous micro-RNAs (miRNAs).\cite{15} Thus, in mammals there are two requisites for a siRNA to successfully activate RNAi: the absence of a long precursor, and an appropriately non-inflammatory sequence. When these are met, synthetic siRNAs can escape immune detection easily to take advantage of the highly specific gene silencing mechanism outlined above.
Table 1: Selected examples of in vivo efficacy with RNAi-based approaches. α1-AT = alpha-1 antitrypsin; AAV = adeno-associated virus; ApoB = apolipoprotein B; BACE = β-secretase; CCR5 = chemokine receptor 5; CSF = cerebrospinal fluid; D5W = dextrose 5% in water; EWS-FLI1 = Ewing’s sarcoma fusion protein; HBsAg = hepatitis B surface antigen; HER2 = human epidermal growth factor receptor 2; i.t. = intratumoural; IV = intravenous; PEI = polyethylenimine; PLK-1 = polo-like kinase 1; PrP = protease-resistant (prion) protein; PSMA = prostate-specific membrane antigen; siRNA = small-interfering RNA; SOD1 = superoxide dismutase 1; TAR = transactivation response element; TNF-α = tumour necrosis factor α; UTR = untranslated region; VEGF = vascular endothelial growth factor.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target (or disease model)</th>
<th>Delivery, route of administration</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Genetic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1-AT liver disease</td>
<td>α1-AT Z allele</td>
<td>Viral: AAV8</td>
<td>48</td>
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<tr>
<td>Familial ALS</td>
<td>SOD1</td>
<td>Viral: lentivirus</td>
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<tr>
<td>Huntington’s disease</td>
<td>i. (HD70)</td>
<td>Viral: AAV1</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>ii. (R6/1 mice)</td>
<td>Viral: AAV5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>iii. (R6/2)</td>
<td>Synthetic: liposome (CSF infusion)</td>
<td>19</td>
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<td>Spinocerebellar ataxia type 1</td>
<td>Ataxin-1</td>
<td>Viral: AAV1</td>
<td>50</td>
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<tr>
<td>Sporadic disease</td>
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<td></td>
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<tr>
<td>Alzheimer’s disease</td>
<td>BACE1</td>
<td>Viral: lentivirus</td>
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<td>Arthritis</td>
<td>TNF</td>
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<td>Creutzfeldt-Jakob disease</td>
<td>PrP</td>
<td>Viral: lentivirus</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>ApoB</td>
<td>Synthetic: cholesterol conjugate; IV</td>
<td>54</td>
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<tr>
<td>Hypertension</td>
<td>β1-adrenoreceptor</td>
<td>Synthetic: liposomal; IV</td>
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<td>Parkinson’s disease</td>
<td>α-synuclein</td>
<td>Viral: lentivirus</td>
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<tr>
<td>Wet AMD</td>
<td>VEGF</td>
<td>Naked siRNA: direct intravitreal injection</td>
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<td>Cancer</td>
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<tr>
<td>Breast adenocarcinoma</td>
<td>C-raf</td>
<td>Synthetic: cardiolipin lipoplex; IV</td>
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<tr>
<td>Cervical carcinoma</td>
<td>E6, E7</td>
<td>Synthetic: atelocollagen complex; i.t.</td>
<td>58</td>
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<tr>
<td>Colon adenocarcinoma</td>
<td>VEGF</td>
<td>Synthetic: oligoarginine cholesterol polymer; i.t.</td>
<td>59</td>
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<tr>
<td>Ewing’s sarcoma</td>
<td>EWS-FL1</td>
<td>Synthetic: cyclodextrin nanoparticle; IV</td>
<td>60</td>
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<tr>
<td>Melanoma metastases</td>
<td>C-Myc, MDM2, VEGF</td>
<td>Synthetic: liposome/peptide nanoparticles; IV</td>
<td>34</td>
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<tr>
<td>Pancreatic adenocarcinoma</td>
<td>HER2</td>
<td>Synthetic: antibody-targeted liposomes; IV</td>
<td>61</td>
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<tr>
<td>Prostate adenocarcinoma</td>
<td>i. PLK1, BCL2 (xenograft)</td>
<td>Synthetic: PSMA</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>ii. EZH2, P110α (bone metastases)</td>
<td>aptamer; i.t.</td>
<td>22</td>
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<tr>
<td></td>
<td></td>
<td>Synthetic: atelocollagen complex; IV</td>
<td></td>
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<tr>
<td>Viral</td>
<td></td>
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<tr>
<td>Ebola</td>
<td>Ebola L</td>
<td>Synthetic: PEI (polymer); intraperitoneal injection</td>
<td>62</td>
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<tr>
<td>HBV</td>
<td>HBsAg</td>
<td>Viral: AAV8</td>
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<tr>
<td>HCV</td>
<td>NS5, 5’ UTR</td>
<td>Viral: AAV</td>
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</tr>
<tr>
<td>HIV</td>
<td>Tat/rev, TAR, CCR5</td>
<td>Viral: lentivirus</td>
<td>25</td>
</tr>
<tr>
<td>HSV2</td>
<td>UL27, UL29</td>
<td>Synthetic: lipoplex; intravaginal</td>
<td>63</td>
</tr>
<tr>
<td>SARS</td>
<td>Spike, Nsp12</td>
<td>Synthetic: surfactant or D5W; intranasal</td>
<td>64</td>
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phase I trial to test HIV-resistant leukocytes created from patients’ own autologously harvested stem cells. The aim is to transduce the stem cells with a lentivirus encoding three unique elements: a siRNA targeting an exon in the tat/rev gene; an RNA decoy mimicking the HIV Tat-reactive element; and, a ribozyme targeting the host cell viral co-receptor CCR5. These HIV-resistant leukocytes can then be reinfused into patients by bone marrow transplant. Targeting the HIV genome as well as the host cell co-receptor (which is not under any selective pressure) prevents the establishment of infection at multiple points in the pathway.

### Key challenges
Research into successful bench-to-bedside translation of the powerful RNAi mechanism is grappling with three key challenges today: the miRNA system in humans; siRNA chemistry; and, siRNA delivery.

#### Interfering with miRNA
miRNAs are endogenously produced, non-translated RNAs involved in a myriad of critical cellular functions, such as apoptosis and differentiation. miRNAs are very similar in size

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**Table 2:** Summary of current pharmaceutical development of siRNA by company, including products, indications and stages of development. AMD = age-related macular degeneration; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RSV = respiratory syncytial virus.

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Disease</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alnylam</td>
<td>ALN-RSV01</td>
<td>RSV</td>
<td>Phase II</td>
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<tr>
<td></td>
<td>ALN-VSP01</td>
<td>HCC</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>ALN-HTT</td>
<td>Huntington’s disease</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Benitec</td>
<td>(unknown)</td>
<td>HIV lymphoma</td>
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<td>OKTO</td>
<td>Bevasiranib</td>
<td>Wet AMD</td>
<td>Phase III</td>
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<td></td>
<td>Bevasiranib</td>
<td>Diabetic macular oedema</td>
<td>Phase II</td>
</tr>
<tr>
<td>Silence</td>
<td>RTP801i</td>
<td>AMD</td>
<td>Phase II</td>
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<tr>
<td></td>
<td>AKli-5</td>
<td>Acute kidney injury</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>DGFi</td>
<td>Kidney transplantation</td>
<td>Phase I</td>
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<tr>
<td></td>
<td>Atu027/</td>
<td>GI, lung, other cancer</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Atu093</td>
<td>Diabetic retinopathy</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>RTP801i</td>
<td>Chemo-induced hearing loss</td>
<td>Preclinical</td>
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<td>ALHi-11</td>
<td>Prostate cancer</td>
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<td></td>
<td>Atu111</td>
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<td>Atu150</td>
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<tr>
<td>Sirna/Merck</td>
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<td>Phase I</td>
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<td>Sirna-034</td>
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<tr>
<td>Tacere</td>
<td>TT-033</td>
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</tr>
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</table>
and structure to siRNAs, and share the same ultimate function: gene silencing. In fact, miRNAs utilise most of the steps in the RNAi pathway, with two key differences. The first difference lies in the fact that miRNAs are genetically encoded, and thus must be exported from the nucleus after transcription to reach the cytoplasmic RISC. Unprocessed miRNA is exported from the nucleus via the saturable transport protein exportin-5. This is relevant when viral vectors are used to deliver siRNA. Vector-expressed siRNA is derived from an intermediate type of RNA called short hairpin RNA (shRNA), which can compete with miRNAs for access to exportin-5 (Figure 3). Interfering with intracellular miRNA handling may disrupt normal miRNA-regulated functions, leading to adverse effects. In support of this notion, recent evidence from Grimm et al demonstrated that vector-derived shRNA could indeed cause hepatotoxicity in mice. They subsequently showed that this toxicity could be ameliorated by transgenic overexpression of exportin-5, thus confirming its role in miRNA transport. There is also the suggestion that siRNAs may compete for the RISC machinery in tissues where its expression is low, which would be a concern for the use of any siRNA, vector-derived or not.4

The second difference involves guide strands derived from miRNAs. They are typically incompletely complementary to their targets, usually only requiring complementarity of six or seven nucleotides in their 5′ region (the ‘seed’ region). This second difference highlights an important variation in the gene silencing mechanism of the RISC. Where base mispairing is present, bulges in the dsRNA helix prevent the conformational changes in AGO2 necessary for target cleavage to occur. The RISC will, however, remain bound to the target mRNA, thereby preventing its translation. This dual silencing mechanism has an important implication in the design of therapeutic siRNAs, in that the sequence of the guide strand must have minimal sequence redundancy with other miRNAs likely to be present in the cell. Even where the guide strand has perfect complementarity with the intended target only, seed-region homology to unintended targets can result in off-target silencing via translation repression.

The chemistry of interference
RNA is notoriously unstable in vivo due to the abundance of nucleases. Because both strands of a siRNA travel together prior to encountering the RISC, both can be usefully modified to improve their in vivo behaviour. For example, the addition of fluorine at the 2′ position of riboses throughout both strands has been shown to reduce susceptibility to endonuclease digestion. Similarly, replacing the phosphodiester linkages at the 3′ end of each strand with sulphur-containing phosphorothioate linkages reduces their susceptibility to exonuclease digestion.2 The strands can also be individually modified. For example, modifying the second nucleotide of the guide strand (part of the 5′ seed region) by 2′-O-methylation of ribose has been shown to significantly reduce off-target silencing, without disturbing on-target efficacy.31 Interestingly, 2′-O-methylation is also useful in abolishing the immunostimulatory effects of siRNA mediated through TLR7.32 In general, modifications of the guide strand are more likely to interfere with siRNA function. However, altering the nucleotide sequence in the 5′ region of the intended guide strand to reduce thermodynamic stability of the helix in this region favours its incorporation into the RISC.10 This reduces the chance of forming a passenger strand-programmed RISC that will silence unintended targets. Alterations to the passenger strand are generally well tolerated, since the passenger strand...
plays no role in guide:target interactions. Perhaps the most interesting passenger strand modification is the recent creation of so-called small internally segmented interfering RNA (sisiRNA).\(^{33}\) sisiRNAs are composed of an intact guide strand and a nicked passenger strand, which is essentially two separate short (10-12nt) strands (Figure 4). Nicking of the passenger strand absolutely ensures that no RISC can incorporate it, which removes the possibility of off-target silencing mediated by the passenger sequence.

**Delivering interference**

There are three basic approaches to delivering siRNAs to the cell: synthetic siRNA preparations; expression vectors; and, direct injection of naked siRNA. Synthetic preparations package siRNAs created \(\text{\textit{ex vivo}}\) into particle formulations that can be systemically administered. They typically consist of siRNA and a cationic excipient consisting of lipid, peptide, or polymer.\(^{10}\) These particles are often further modified to improve stability, tissue targeting or cellular penetration. For example, cholesterol conjugation promotes association with the cell membrane, while the incorporation of fusogenic lipids facilitates endosomal escape after uptake.\(^{2}\) Covalent addition of polyethylene glycol (PEGylation) improves particle half-life in serum. The addition of specific ligands into the particle promotes localisation to tissues expressing the cognate receptor.\(^{20,34,35}\)

This strategy is probably the most likely to succeed clinically in the short term, but it is not without disadvantages. siRNAs have been shown to be capable of activating inflammation via TLR7, particularly when complexed with certain lipid-based vehicles.\(^{36}\) This highlights the need for chemical modification and careful sequence selection. Systemic delivery often results in siRNA accumulation in particular organs, especially the liver, lung, spleen and kidneys, which may be toxic.\(^{10}\) There is particular evidence that high doses of certain lipid-based particles can cause liver toxicity,\(^{37}\) thus necessitating the optimisation of siRNA potency to minimise dosing requirements.

Double-stranded siRNA can be virally delivered by encoding both strands in a single-stranded transcript in an orientation that promotes hairpin formation. Dicer readily processes this hairpin RNA (shRNA) into active siRNA. Viral vectors under investigation for the delivery of siRNA include lentivirus,\(^{38}\) adenovirus,\(^{39}\) and adeno-associated virus (AAV).\(^{17,28}\) A particularly good example is AAV, which has proven useful in its ability to stably transduce cells in a non-mutagenic fashion (through episome formation rather than genome integration), thus offering the promise of safe, single-injection therapies. AAV is also non-pathogenic and weakly immunogenic, which limits its side effect profile even at high doses. Moreover, AAV has hundreds of serotypes with specific tropisms for a variety of tissues.\(^{40}\) For example, Fechner \textit{et al}\(^{41}\) recently demonstrated the use of a cardiotropic AAV vector encoding a shRNA targeting cocksackie virus B3 in a mouse model of cocksackie myocarditis. Vector-treated mice showed significant attenuation of their cardiac dysfunction after 10 days of treatment. In addition to highly specific tissue transduction, viral vectors offer the advantage of promoter-mediated temporal regulation of silencing.\(^{42}\)

Unfortunately, viral vectors have several disadvantages. Immunogenicity, especially in the case of adenovirus, poses the risk of severe side effects including death.\(^{43}\) Lentiviral transduction may result in insertional mutagenesis.\(^{44}\) Both of these issues are significant impediments to clinical use. Direct application of naked siRNA is sometimes feasible. In fact, this is the most clinically advanced strategy at present and the first to provide proof-of-principle for RNAi therapeutics in human disease. As the name suggests, siRNAs are administered directly to the target organ without the need for vectors or special formulations. Generally, this is accomplished via direct injection (e.g., the eye), or in the lungs by inhalation. Nebulised solutions for inhalation have proven effective in delivering naked siRNA to the lungs. Alnylam Pharmaceuticals is using this approach for their phase II product ALN-RSV01, which targets RSV infection.\(^6\) The OPKO Health product bevasiranib, a siRNA targeting the expression of vascular endothelial growth factor (VEGF), has been shown to be efficacious in phase II trials for wet age-related macular degeneration (AMD) and has now entered phase III.\(^{45}\) VEGF targeting siRNA is delivered by direct intraocular injection,\(^{46}\) as is Sirna Therapeutics’ phase II AMD compound sirna-027.\(^{47}\)

There are several advantages to naked injection. First, by avoiding systemic delivery, dosing requirements should be lower, and off-target delivery less likely. Second, chemical modification to achieve serum stability is unnecessary (and probably undesirable), as it is preferable for any escaped drug to be degraded rapidly. Third, avoiding the use of viruses or lipid formulations reduces the risk of vehicle-related toxicity. Unfortunately, direct administration at many sites is not feasible.

**Conclusion**

The powerful silencing mechanism of RNAi is most impressive in light of its programmability. Genetic defects, cancers and viruses are now being targeted or retargeted in the crosshairs of RNAi. Clinical trials have begun to provide reassurance of the safety of siRNA therapeutics. Our understanding of miRNA processing, siRNA chemistry and siRNA delivery strategies continues to evolve, as siRNAs move ever closer to clinical applicability. The astounding scope of possible applications, bolstered by clinical successes, should ensure an enduring interest in RNAi and will likely define it as an entirely new therapeutic modality.
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Xenotransplantation in 2008

Abstract
Transplantation is the gold standard of care for end-stage organ failure. For example, two-year mortality in patients with advanced class III or IV heart failure exceeds 50%, compared to five- and ten-year survival rates of 82% and 62.5%, respectively, for heart transplant recipients. A major donor shortage has resulted in 95,000 registered patients waiting for an organ transplant in the US. At this time, xenotransplantation is a promising potential solution to this donor shortage. Xenotransplantation is defined as any procedure that involves transplantation, implantation, or infusion into a human recipient of live cells, tissues, or organs from a non-human animal source. Most recent research efforts use the pig as a solid organ donor for heart, kidney and liver transplantation, and as a source of pancreatic islets. The barriers to successful xenotransplantation include the immunology of xenograft rejection, physiological differences between the pig and the human, and the possibility of cross species infectious disease transmission. The field of xenotransplantation has come a long way, with survival of xenograft organs having been extended from minutes to months at the present time. The FDA and ISHLT have recommended that a median orthotopic xenograft survival of 90 days could result in initiation of clinical trials. This goal may be achievable within the next few years. Successful clinical xenotransplantation would change the face of modern medicine.

Keywords: xenotransplantation, organ transplantation, pigs, graft rejection.

The need for transplantation
Transplantation is the gold standard of care for end stage organ failure.1 Two-year mortality in patients with advanced class III or IV heart failure exceeds 50%2,3 compared to five- and 10-year survival rates of 82% and 62.5%, respectively, for heart transplant recipients. Similarly, the one- and five-year survival rates for kidney and liver transplants are 96% and 88%, and 80% and 75%, respectively. In addition, these survival statistics do not capture quality of life improvements with transplantation. For example, 79.1% of kidney transplant recipients are able to function at normal levels, compared to 59.1% and 47.5% of patients on peritoneal dialysis and haemodialysis, respectively.4 Donor shortage has resulted in 95,000 registered patients waiting for organ transplant in the United States (US),5 with comparable numbers existing in Europe. However, this number does not reflect the true need, as the scarcity of donor organs necessitates strict recipient selection criteria. Over five million people currently suffer from heart failure in the US, and it is the underlying cause of death in 57,000 patients per year.6 Despite these numbers, the current donor shortage limits the number of heart transplants to just over 2,200 per year.7 At this time, xenotransplantation is a promising solution to the organ donor shortage. Furthermore, xenogeneic cellular materials may be used in cellular transplantation, as the supply of human donor cells is unlikely to fill the demand. This is especially true for treating diabetes with transplanted pancreatic islet cells. Recent progress in xenogeneic islet transplantation is promising and clinical trials are now being proposed.8,9

Xenotransplantation
Xenotransplantation is defined as any procedure that involves transplantation, implantation, or infusion into a human recipient of either live cells, tissues, or organs from a non-human animal source, or human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues, or organs.10 Most recent research efforts use
pigs as a solid organ donor for heart, kidney and liver transplantation, and as a source of pancreatic islets. As well as solving the donor shortage, xenotransplantation has a number of further advantages over conventional (allo) transplantation.

As xenotransplantation could provide an unlimited supply of donor organs, ideal size matching of the donor and recipient would be possible. Also, unlimited donor supply would enable patients to undergo elective surgery. Procedurally, as donor organs would not have to be transported, ischaemic times would be minimised, reducing ischaemic reperfusion injury and early organ dysfunction. Similarly, organ damage from donor brain death would be avoided. By using pigs as donors, xenotransplantation leaves the door open for ongoing genetic modification to create a better donor. In the case of xenogenic hearts, they have advantages over mechanical devices; no extrinsic power source is required, and complications such as bleeding and thrombosis would be avoided, as there is no need for anticoagulation therapy.

**History**

Xenotransplantation is not a new concept. Early attempts include transplantation of ape testicles for treatment of sexual dysfunction, sheep to human blood transfusions, and bone and skin grafts.11 The most notable clinical attempts are those of Reemtsma, Bailey and Starzl. During the 1960s at Tulane University in New Orleans, Louisiana, US, Reemtsma performed 13 kidney transplants using chimpanzee donors. The majority of the patients died within 60 days, but one patient survived for nine months and resumed work as a schoolteacher post transplant.12 In 1984, at Loma Linda University in California, Bailey transplanted a baboon heart into a newborn baby with a lethal congenital heart defect. The patient, known throughout the world as “Baby Fae,” survived for 20 days before the heart was rejected.13 Starzl performed two baboon-to-human liver xenotransplants at the University of Pittsburgh in 1992/93. The outcome of the first case was encouraging, with the patient surviving for 70 days. The second case was less successful as the patient never regained consciousness after the transplant and died 27 days later.14 These clinical experiences led to a return to the laboratory for further research in animal models.

**The ideal donor**

Early in xenotransplantation, there was much debate over the most appropriate donor species. The closest donors to humans are non-human primates, but their use is problematic. The great apes (chimpanzees, gorillas, bonobos, orangutans, gibbons) are endangered and so could not provide enough donor materials. The most common non-endangered, non-human primate, the baboon, is too small for adults but, as mentioned, has been used as a donor for children. Furthermore, potential pathogenic virus transmission between primates and humans is of particular concern. Of the non-primate animals, pigs are considered the most suitable organ donor on anatomical and physiological grounds. Their breeding characteristics are also favourable because large litter sizes, short gestation period (four months) and early age of sexual maturity (five to six months) guarantee adequate supply and is conducive to genetic modification.15 In fact, genetic modification through the addition of human transgenes or gene deletion has already been achieved in the pig using cloning technology.16 Pigs are also commercially available with established husbandry techniques, are inexpensive to maintain, and are more socially acceptable than other species as potential donors. Over 80 million pigs are slaughtered annually for food purposes in the United States.17

**Barriers to successful xenotransplantation**

**Immunological**

Most available resources have been devoted to understanding and managing the immune barriers to xenotransplantation. Initially, the apparently impenetrable barrier was hyperacute rejection (HAR), in which rejection of the xenograft occurs within minutes to hours. HAR is caused by activation of the classical complement pathway when it is triggered by recipient anti-pig antibody (Ab) deposition on donor organ endothelium. The recipient anti-pig Ab, which is pre-existing only in old world primates and humans, targets the ubiquitous carbohydrate epitope Galβ1-3Galβ1-4GlcNAc (α1,3Gal), present on all porcine vascular endothelium.18 Histologically, the hallmark of HAR is vascular deposition of Ab with associated interstitial haemorrhage, oedema, and vascular thrombosis (Figure 1).19 HAR does not occur in complement-deficient and complement-depleted recipients.20 The human body has multiple
mechanisms to control complement so as to avoid autoimmune tissue destruction during local inflammatory responses. This regulation is achieved through several plasma and membrane proteins, such as C1-inhibitor and decay-accelerating factor (DAF), respectively. 

Unfortunately, recipient susceptibility to infection limited the effectiveness of initial complement depletion efforts. Subsequently, methods to regulate complement activation intrinsic to the graft were explored. The introduction of genes for DAF and other human complement regulatory proteins (CRPs) into the porcine genome was achieved by nuclear injection techniques. The use of these transgenic pigs resulted in the abrogation of HAR and prolonged xenograft organ survival time from minutes and hours to days and weeks. 

The next immunological obstacle was delayed xenograft rejection (DXR), also known as vascular or humoral rejection. Histology of rejected xenografts showed no evidence of complement deposition, thus rejection must have been caused by complement-independent mechanisms. The mechanism of DXR is believed to be consistent and widespread deposition of anti-α1,3Gal antibody on porcine endothelium, leading to endothelial cell activation and dysfunction. Local inter-species incompatibility of coagulation factors may also play a role. Initial research into DXR focused on control of recipient anti-α1,3Gal Ab by either physical removal of Ab in the recipient or by immunoabsorption of circulating anti-α1,3Gal Ab by pharmacological means. Such therapies led to xenograft organ function for weeks to months. A more elegant solution was the development of α1,3Gal-deficient donor pigs, which became possible with the advent of successful cloning. Such pig donors can also express human CRPs on their cell membrane.

Investigation is currently ongoing into the use of these donor animals.

Physiological

Physiological differences exist between pigs and humans. For example, pigs function at 39°C compared to 37°C in humans. This temperature change could alter metabolic activity or efficiency of certain enzymes necessary for normal function. There are, however, greater similarities between pig and human physiology. Similarities include size, digestive physiology, dietary habits, kidney structure and function, pulmonary vascular bed structure, coronary artery distribution, respiratory rates, and cardiovascular anatomy and physiology. The functional parameters of the cardiovascular, hepatic, and renal systems are effectively equal. For example, human cardiac output ranges from 2.5-3.5L/min/m², while the pig’s ranges from 2.0-2.5L/min/m². Also, human left ventricular systolic pressure ranges from 100-140mmHg and pigs average 116mmHg. Renal functional parameters between the species are also very similar, for example human glomerular filtration rate (GFR) averages 130ml/min⁻¹ per 70kg, and total renal blood flow is approximately 4ml/min⁻¹/g⁻¹, while pig GFR ranges from 126-175ml/min⁻¹ per 70kg and total renal blood flow ranges from 3.0-4.4ml/min⁻¹/g⁻¹. Experimental data indicates normal, life-sustaining function of pig organs in non-human primates for up to two months, the cause of failure being rejection. 

Thus far, it seems that physiological differences do not pose a significant problem in xenotransplantation.

Infectious disease

The term xenozoonosis has been coined to describe infection acquired from xenogeneic cells, tissues, and organs. Infections from xenografts can be exogenous or endogenous. Good manufacturing practice and designated pathogen free pig facilities have been operated successfully for a number of years, largely dealing with the exogenous infectious risk of porcine donors. Cross-species infection became a key issue after demonstration that porcine endogenous retroviruses (PERVs) can infect human cells in vitro. Xenotransplantation presents a unique opportunity for cross species infection. The infective risk may be increased in xenotransplantation for a number of reasons. First, the xenograft may act as an infective reservoir, allowing donor microorganisms to bypass host defenses. Second, the risk is compounded by the fact that the human recipient must be immunosuppressed. The lack of laboratory tests to screen for PERVs has largely been resolved in recent years. Thus far, no evidence has been found that PERVs can be spread in vivo. Genetic selection may lower this risk: certain lines of pigs have been reared that are not able to transmit PERVs in vitro. Selective use of these animals may minimise the possibility of cross-species viral transmission. Although extensive investigations offer no evidence of in vivo viral transmission, the danger may never be completely eliminated. Diligent human recipient surveillance will be required.
Current status and future prospects

The field of xenotransplantation has come a long way, with survival of xenograft organs having been extended from minutes to months. A greater understanding of the mechanisms of the various forms of xenograft rejection has been achieved. Xenotransplantation researchers have overcome HAR and various forms of xenograft rejection has been achieved. To months. A greater understanding of the mechanisms of the survival of xenograft organs having been extended from minutes with promising results. The FDA and ISHLT have recommended, at least for the heart, that median orthotopic xenograft survival of 90 days could indicate “a reasonable expectation for success” and may sufficiently warrant the initiation of clinical trials. With individual non-human primate recipients surviving for months with xenotransplant organs, this goal may be achievable within the next few years. Successful clinical xenotransplantation would change the face of modern medicine.

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For three and a half months I exchanged the Dutch student life in Nijmegen for a research elective in the Department of General Practice at the Royal College of Surgeons in Ireland – Guinness instead of Heineken and porridge instead of Dutch bread for breakfast!

I lived in a student home in Rathmines with one English and four Irish housemates, and spent the weekdays working on a systematic review. This systematic review is contributing to the Cochrane Primary Health Care Field (www.cochraneprimarycare.org), which is seeking to develop a register of clinical prediction rules in primary care. My area of research was the diagnostic accuracy of symptoms, signs and diagnostic tests in relation to rectal bleeding and the risk of colorectal cancer.

Besides my research activities I took part in a student-selected component, went to a conference on academic primary care, and joined several different general practices around Dublin where I practiced taking a history in English. Moreover, I had fun with fellow students and colleagues going out for lunch, listening to Irish music in Temple bar and going to clubs and pubs. I also visited tourist attractions and travelled to Cork and Galway.

At the end of my research fellowship I presented my results to the RCSI Department of General Practice.

Back in the Netherlands, I am finishing the article and will give a final presentation to our own General Practice Department. My time in Dublin was a great experience.

Curious about the Dutch health system?
The Dutch Department of General Practice is setting up a network in collaboration with the Department of General Practice at the RCSI. The Radboud University in Nijmegen has arranged many research electives for students coming from various countries all over Europe. Some of these electives have even led to co-authorship of publications.

The research electives can be recognised by the RCSI medical school and will be carried out within the Cochrane Primary Health Care field for a period of three months or more. The exchange is facilitated by the international Erasmus exchange programme. This programme can provide financial support if required. English speaking is sufficient; however, you can improve your Dutch language skills by participating in one of the Erasmus Intensive Language Courses (EILCs) offered at the Radboud University.

During the research fellowship you will be supervised by both a host supervisor in Nijmegen and by a supervisor from RCSI. Nijmegen is a great student city with many pubs, cinemas, shopping centres and a modern university sports centre. The Erasmus programme has set up a varied social programme for international students who study in Nijmegen. Dutch students can guide you and organise dinners, movie nights, sports, parties and more.

If you are at least a third-year medical student who would like to gain research experience and have a great time abroad, I encourage you to apply. Please contact Ms Caroline van de Ven at the Radboud University Nijmegen Medical Centre (intoffice@owi.umcn.nl). Limited places are available, so don’t delay!

I hope to see you in the Netherlands!
Once third Med comes around the word ‘elective’ seems to be included more and more in conversation. Everyone is talking about going to Africa, heading to Australia or simply popping over to New York. Very few discussions look at what is available at home.

Having started medicine with a view to entering primary care after completing my internship, heading half way around the world to experience emergency medicine at its best didn’t appeal to me. What interested me was the thought of finding an elective in the primary care field with a twist. Driving up the North Circular Road one evening a thought came to mind: ‘Would it be possible to do an elective in Mountjoy Prison?’ I quickly found out who to contact and, low and behold, one email and one phone call later, my elective was sorted.

To be honest, I didn’t really think about my elective until my first morning when I was strolling down the North Circular with the Dochas Centre on my left (female prison in Mountjoy). On entering the prison my mobile phone was locked away and naturally I had to be signed in. Apprehension hadn’t crept into my psyche but I was beginning to think about what my first morning would unveil.

What was revealed to me in the following few hours was a health centre with a difference. Obviously, its clients were all female but, more surprisingly, so was the multidisciplinary team working together to provide quality female healthcare to their patients. Heading home I was smiling at the thought of spending three more weeks in the Dochas Centre.

The majority of my time in Dochas was spent shadowing Dr Therese Boyle, the Centre’s general practitioner. Daily clinics were held in the morning and consisted of reviewing any new prisoners who had been committed within the last 24 hours. A medical history was obtained, concentrating on areas of women’s health, substance abuse and vaccination history. Strict guidelines exist in the area of substance abuse and it was pleasing to see how respectful prisoners were in relation to such things as valium detox, methadone dosage, night sedation, etc.

Discrimination is rampant in our health service, and by choosing the Dochas Centre I wanted to see if this discrimination stretched to an area of our community that is all but ignored. How wrong I was. The level of primary care provided in the Dochas Centre was superlative and I would be absolutely delighted to end up working there in 2015 when I eventually qualify as a primary care physician.

I feel strongly that this quote from Mountjoy Prison’s Mission Statement reflects what I experienced:

*The Irish Prison Service seeks to provide clinical services for the assessment, treatment, and care of patients comparable to those available in the community, and which are appropriate to the prison setting.*
Ring! Ring!

It is early morning and a final year medical student rushes over to the nurses’ station to answer the phone. Yes. Immediately. Bed four? Reaching the bed, she sees her patient, Stan. Respiratory distress. 25 breaths per minute. A cursory glance at the ECG – Narrow QRS complex. Tachycardia. Supraventricular tachycardia? – and the stethoscope is whisked off its position around the neck. Crackles. With no nurses to help her she rushes off to the treatment room to get supplies to give her patient a dose of adenosine. After finally finding a sharps container, the distraught medical student quickly swipes the antecubital fossa and searches for a vein. Found it! Needle in, push the drug and a wave of relief floods through the medical student. The patient seems to be quieter and sleeping now. Only then does the medical student look at the ECG again: oddly, it’s a flat line.

Thankfully, episodes such as this are not common, but fears of making a fatal mistake as a young intern are commonplace. This entire scenario, however, is false. False, in that it took place in a clinical skills laboratory with no risk to any real patients: ‘Stan’ is a patient simulator.

Medical skills laboratory
During the 2008 Association for the Study of Medical Education (ASME) conference in Leicester, United Kingdom, we had the opportunity to visit the state-of-the-art medical skills laboratory at the University of Leicester. The lab consists of a dedicated floor in a hospital building solely for the purposes of medical education. This area is open from 9am to 5pm, Monday to Friday, with full-time nursing staff available as tutors. The long opening times...
allow both for structured learning times and for independent or group study where students can hone or remediate skills where they feel they are lacking.

In terms of physical space, it truly impresses. Four simulated wards, with four beds each, comprise the bulk of the training space. This allows for different groups to work on different tasks. However, the walls are movable, allowing for a variety of configurations. In addition to the ward space, a fully stocked sluice room, working sinks, and a functioning nurses’ station allow for a realistic simulation of an actual ward.

Essential to complete the realism of the lab are the training tools available. During the time we spent in the lab we were able to see and use ‘strap-on’ suturing kits, realistic venepuncture sets, ECG machines, male and female catheterisation models and gluteal muscle injection models. Key to these training tools was the ability for them to be used in conjunction with live actors during OSCEs. This creates a much more realistic training and evaluation environment where students would have to interact with a patient, consent them and then perform a procedure with real time feedback.

Importantly, it is an area not only for medical students but also for nurses and doctors, allowing for a truly interdisciplinary learning environment. This allows students in different training courses to interact with each other before they begin work on the wards – a true innovation in medical education.

The ultimate patient simulator
Another impressive aspect of the skills laboratory is the three patient simulators available: two iStans and one SimMan. iStan, an evolution and step above the SimMan, was developed in conjunction with the United States Army and provides the most realistic patient simulation in the world today. iStan has the ability to cry, sweat and bleed, all in response to the trainer’s computerised commands. Watching iStan lying in bed is disconcertingly, as he blinks and his chest rises and falls with respiration. The pathology that iStan can be programmed to exhibit is truly impressive, and ranges from murmurs to a pneumothorax to a flail chest. The additional capacity of being able to wirelessly speak through his mouth raises the realism to an entirely different plane.

In addition to physical examination, the variety of procedures that can be performed on iStan include:

- intubation;
- venepuncture;
- urinary catheterisation;
- all pulses are palpable and touch sensitive;
- capillary refill;
- pneumothorax needle decompression;
- chest drain placement;
- blood pressure;
- five-lead ECG monitoring; and,
- sternal and tibial inter-osseous access.

For the first time this year, the RCSI is letting Senior Cycle 1 students train using a METI human patient simulator very similar to iStan at Beaumont Hospital. Students will have a chance, during a one-week rotation, to put all their skills on the line and try to manage this almost-real patient during simulated emergency situations. Feedback so far has been very positive and the College hopes to expand the programme to Senior Cycle 2 students next year. The Emergency Medicine Society at the College is hoping to purchase a SimMan simulator within the next year for student use.

Experiencing older age
Another interesting learning tool available in the clinical skills laboratory at the University of Leicester is a patient age simulator suit. Originally purchased from Japan, this suit allows for a realistic simulation of old age. The young 24-year-old medical student transforms within minutes into an elderly gentleman with difficulty walking due to stiff joints, difficulty sitting and standing due to spinal curvature, and special glasses that cause the loss of peripheral vision. This allows students to understand why elderly patients have such difficulty with movement and tasks that may seem simple to a younger generation.

In the current learning environment, a dedicated clinical skills laboratory is an excellent way to address many educational issues, such as time demands placed on clinical teaching staff, limitations in patient numbers, increasing student numbers and worries about litigation. Built at a cost of approximately £1.3 million, and with staffing and supply costs, it is a significant investment. However, it also greatly improves learning opportunities for students and goes a long way towards addressing the intrinsic conflict of healthcare education – between the need to educate junior healthcare staff and the need to provide the best patient care.
Traditional black and white darkroom printing is almost a lost art these days. Despite the undeniable appeal of real photographic black and white prints there are few photographers who continue to master both the art of taking photographs and the craft of printing their work very well.

Philip Pankov recognizes that both elements are key to the black and white art form and continues to print his black and white images by hand. For images that are too large to print in the darkroom he offers black and white canvas prints – an option which adds texture and depth to the image while enabling Philip to offer much larger pieces.

25% of proceeds for all Royal College of Surgeons Ireland photographs sold are donated to the RSCI Student Medical Journal
Every current or aspiring medical student should read The House of God. This satirical novel follows a group of interns as they discover the hypocrisy of modern medical training. While outrageously funny, realistic and frightening, this book is not for the faint of heart. It begins after the intern year has ended. Dr Roy Basch and his girlfriend Berry (a clinical psychologist) are sojourning in France. The first chapter introduces the mood and progression of the story. If you are uncomfortable with the level of eroticism found in chapter one, you may want to stop reading – it only gets raunchier. While some may find this shallow, superficial and possibly inappropriate, I would encourage the reader to look past it as Shem is using this to reveal a stark reality: doctors focus on examining the human body. His suggestion is that enhanced sexual activity is natural given doctors’ acute appreciation of healthy human bodies. Subsequently, the story centres around Basch, a Rhode’s Scholar from the Best Medical School (BMS) during his intern year at the hospital, the House of God. Samuel Shem is a pseudonym for Stephen Joseph Bergman, a Harvard graduate and, coincidentally, a Rhodes Scholar. Basch travels through five rotations: internal medicine, accident and emergency, gastroenterology, the intensive care unit and, finally, more internal medicine, and a familiarity with medical terms is very useful for relating to his experiences. Throughout the story, Basch’s girlfriend Berry provides a psychoanalytical voice of reason, unsurprising given Bergman’s own personal interest in psychiatry. The story takes place at the same time as the Watergate Scandal, which was to change the face of American politics. The scandal is used by Shem to mirror his own theme of changing perspectives. The public shock at the downfall of an admired institution mirrors the shock felt by Basch when he sees the true face of the medical establishment. Shem uses a series of letters from Basch’s father, a dentist, to make his point. The letters portray the idyllic picture of doctors embraced by society at that time: noble, caring, and almost superhuman. It shows medicine as clean, stable and respectable. This picture is directly contrasted by Basch’s experience, where doctors and interns alike all suffer from chronic stress, fatigue, addiction and instability. To this end, the book reveals the humanity and hypocrisy in modern medicine. Despite the “Laws”, emotional and psychological support from Berry, and the Fat Man, Basch and his fellow interns are physically, psychologically and professionally crushed. They face death, relationship problems, and the incompetence of senior staff, private doctors and medical students. Coping strategies come in many forms: lust, infidelity, addiction, self-medication, aggression and, for some, internalisation. Shem’s depiction of internship is disturbing in its realism, yet he leads you with warmth and humour. The House of God is certainly a must-read for all medical students.
Background
Intravenous drug users (IVDUs) are at high risk of infection with the human immunodeficiency virus (HIV). In 2007, 14.9% of newly diagnosed HIV infections in Ireland were in IVDUs. Many HIV positive IVDUs receive both antiretroviral treatment for HIV and methadone therapy to manage narcotic dependence and withdrawal symptoms. Methadone has been shown to inhibit cardiac human ether-a-go-go-related gene (hERG), which codes for potassium channel proteins. This is thought to lead to a prolonged QTc syndrome and ventricular tachycardia. Asymptomatic QTc prolongation was observed in HIV positive individuals and healthy volunteers receiving ritonavir-boosted atazanavir (ATVr) in a clinical trial.

Methods
Gallagher et al. reported on two cases of symptomatic ventricular tachycardia associated with QTc prolongation in two HIV-1 infected individuals who were receiving both methadone and antiretroviral therapy. The first patient was receiving an antiretroviral regime of ATVr, tenofovir, and emtricitabine. The second was receiving ATVr, lamivudine, and abacavir.

Results
The QTc of both patients decreased substantially after ATVr was removed from the regimen. ATVr was reintroduced in one of the patients whose QTc had returned to normal. The result was a mean prolonged QTc of 431ms (range: 421-441ms) in the six days following.

Conclusions
The health of HIV positive IVDUs is already compromised by immunodeficiency, risky lifestyle and the adverse effects of polypharmacy. This study highlights the increased importance of recognising signs of syncope, symptomatic torsade de pointes ventricular tachycardias and ECG changes consistent with QTc prolongation in this patient group. It is hoped that methadone administration and antiretroviral therapy can now be tailored to protect against QTc-associated sudden cardiac death in these patients.

References
Assessing genetic risk in children with congenital heart disease in the current era

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Background
Congenital heart disease (CHD) affects one in 100 newborns. The cause is known in less than 20% of patients. We assessed environmental versus genetic risk factors in children with CHD participating in a biorepository for genomics research.

Methods
Children less than 18 years old with structural heart defects were prospectively enrolled. A detailed questionnaire including prenatal, birth, medical and family history was administered to each family. Questionnaire data was compared to demographic data from public sources including Statistics Canada, the Canadian Community Health survey and the Public Health Agency of Canada.

Results
Of the 398 patients enrolled since February 2008, 211 questionnaires and 201 family trees were analysed. Some 77% of participants were Caucasian and 56% were male. Prenatal history revealed maternal exposure to smoking during pregnancy in 25% and alcohol ingestion in 10.4% (versus 34% and 14%, respectively, in women of childbearing age in the general population) (p<0.0001). Eight mothers were on fertility drugs. Some 31% of women suffered miscarriages versus 2% in the general population (p<0.0001). Some 40% had a positive family history for heart defects, and 33% had other extra-cardiac birth defects, including 24% with learning difficulties and/or delayed developmental milestones. Only 14 out of 200 (7%) children had an identifiable genetic mutation.

Conclusion
Despite a strong genetic basis for CHD highlighted by the high incidence of positive family history, spontaneous miscarriages, and extra-cardiac anomalies, a genetic aetiology was identified in only 7% of patients. This underscores the need for large population-based studies using genome-wide approaches to identify new genetic defects that cause CHD. The DNA biobank will serve as a valuable resource to accomplish this goal.
Upjohn Prize

The next generation of cancer therapeutics: Ehrlich’s magic bullets realised

David Rajaratnam

As pharmacological science and medicine evolve together it is clear that a common theme defines their progression. This growth demands innovation imbued with precision and efficiency. This notion resonates with the advancement of cancer therapeutics embodied by the development of monoclonal antibody (mAb), small molecule, and apoptosis-inducing anti-cancer agents. These drugs herald the commencement of the twilight of the age of imprecise cancer therapy. The crux of these revolutionary drugs is their ability to target cancer cells while sparing healthy cells thus minimising the systemic effects traditional cancer therapy typically generates. mAbs, like other antibodies, bind to highly specific targets. Once bound, mAbs exert their effects via immune-mediated destruction of cancer cells, as with alemtuzumab (Campath) or toxin delivery (via toxins bound to mAbs), as with ibritumomab (Zevalin). Small molecule therapeutics act by targeting specific receptors that are mutated in cancer cells. For example, erlotinib, used for the treatment of non-small cell lung cancer, acts by reversibly inhibiting autophosphorylation of EGFR and thereby “inhibits the downstream signalling pathways that lead to angiogenesis, cell propagation, and cell survival”.1 Apoptosis-inducing agents act by either promoting pro-apoptotic pathways or disabling anti-apoptotic mechanisms unique to cancer cells. Bortezomib, used in the treatment of haematological malignancies, inhibits proteasome 26S, thus eliminating the cancer cell’s means of anti-apoptosis.2 While mAb, small molecule, and apoptosis-inducing drug therapy are relatively new additions to cancer treatment options, they are still in their infancy. However, as time progresses, they will undoubtedly mature and become far more sophisticated in both function and target specificity as well as become more cost effective.

Kane Medal

Are new neurons good for the adult brain?

Atish Chopra

The burgeoning field of regenerative medicine promises significant progress in the treatment of cognitive degenerative conditions as well as other neural injuries. Fundamental to its success is the ability of new neurons to integrate into pre-existing circuitry of already established cells in order to be functional.1 Characterisation and an enhanced understanding of the neural stem cells in the brain is required to further understand the intrinsic properties, nature of the signals, and mechanisms involved in neoneurogenesis in the adult brain. Transcriptional studies need to be conducted to elucidate factors involved in gene expression of the progenitor cells. Adult neurogenesis may be advantageous for adult brain functioning, however, only within a restrictive physiological adaptive range.2 Consequently, further research is needed on the contribution of neurogenesis to hippocampal functioning.3 It is not known clearly whether a modification in neurogenesis is the reason or result of psychiatric illness, yet studies suggest that affective or cognitive disorders are characterised by altered rates of neurogenesis.4 Although these suggestions are based on conjectures, it is evident that research in this field is still in its infancy. Though studies emphasise treatments that increase neurogenesis with the intention of curing or preventing the development of affective and/or cognitive disorders, the reality remains that a much greater exploration is needed to expose this promise. Nevertheless, neurogenesis is a groundbreaking new field of research and one that has the hopes of many within for a healthier and brighter neurological future.

References

Abstract
Throughout the years, medicine has revolutionised patterns of illness found globally, achieving the eradication of once widespread and fatal infectious diseases, and greatly increasing the survival and quality of life of millions of people. However, with the rise of the ‘modern’, consumerist lifestyles, rates of non-communicable disease have risen dramatically, and it is even feared that by the year 2020, 60% of deaths in developing countries will be due to diseases caused by unhealthy behaviours. To tackle this, a large variety of theories, models and suppositions have been proposed aiming to induce change, some focusing their efforts upon the individual, others upon society as a whole. So, which is more effective? Targeting individuals using theories such as the Health Belief Model, the Theory of Planned Behaviour and the Transtheoretical Model provides a personalised plan for change, psychologically instilling healthy behaviours that can successfully be maintained; however, while these methods are highly effective, they lack the widespread effect needed to significantly reduce disease rates worldwide. To achieve this, lifestyle advice must be disseminated across the population, by means such as community-based groups and helplines, nationwide campaigns, and new political laws so that enough people around the world are exposed to the idea of lifestyle change for better health. Thus, only by a combination of both methods will populations be provided with an entirely health-conscious environment at all levels; subsequently producing tangible reductions in diseases caused by the people themselves.

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