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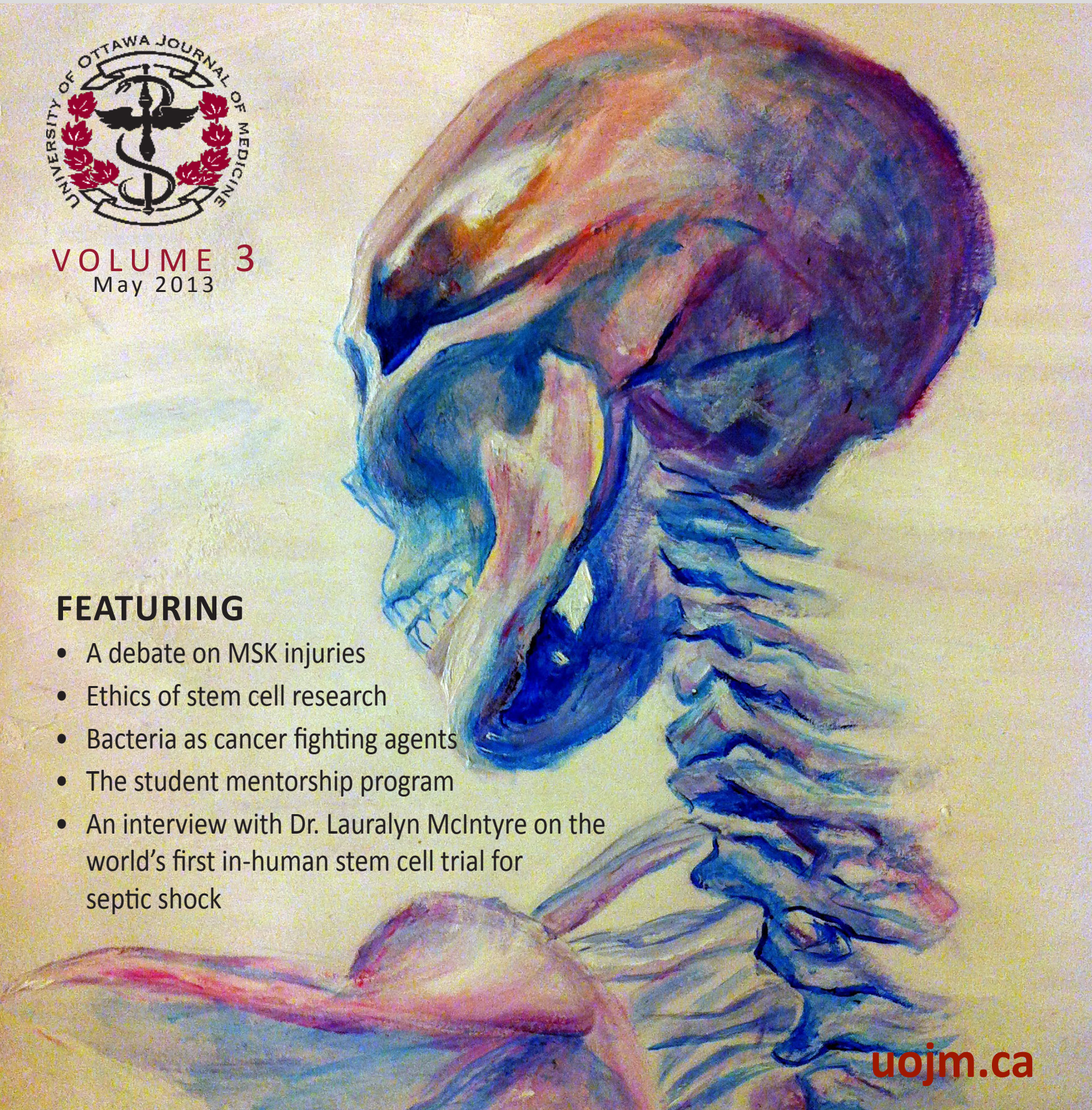

VOLUME 3
May 2013

FEATURING

- A debate on MSK injuries
- Ethics of stem cell research
- Bacteria as cancer fighting agents
- The student mentorship program
- An interview with Dr. Lauralyn McIntyre on the world's first in-human stem cell trial for septic shock

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REVIEW

ORIGINAL RESEARCH

GLOBAL HEALTH

UOJM: Preface

On behalf of the entire editorial team, we are extremely excited to present you with the third issue of the University of Ottawa Journal of Medicine (UOJM). Since its re-launch in 2011, two very impressive issues have been published. The UOJM is a student-run, peer-reviewed journal that is dedicated to showcasing the opinions and scholarly accomplishments of the Faculty of Medicine students, with both scientific and non-scientific pieces. Not only are we the only bilingual student-run medical journal in Canada, but we are also the only journal to actively integrate graduate students within the editorial team. Furthering last year's efforts to unite graduate and medical students, this year's editorial team is composed of 37 editors – with equal representation of medical and graduate students.

This year, we implemented changes to not only ensure sustainability of the journal in the years to come, but also to maximize every editor's experience. The first goal was to re-structure the editorial team to increase efficiency and workflow. Many new positions have been created, such as VP Promotion, VP Technology, VP Education, Treasurer, and more. Implementing this new structure increased the efficiency of various key aspects, including budget planning, networking, website maintenance, and promoting the journal throughout the faculty. The second important goal was to modify the training of editors. Since first-line editing is such an essential part of the journal, we decided to create editing training workshops, where editors received more exposure to the peer-review process and practiced how to critically appraise articles.

It is important to note that all this work would not have been possible without the help and collaboration of many people. We would like to recognize and thank the managing editors, Colin Suen and Loretta Cheung, for their tireless efforts and dedication to managing the review process and helping with the editing training workshops. We would also like to thank the entire peer-review team, which was comprised of 24 sectional editors and 6 associate editors. They have all shown continuous enthusiasm throughout the year-long review process.

Implemented this year, the UOJM has created the Outstanding Editor Award to recognize a member of the review team who demonstrated commitment to their role as editor. Selecting the recipient of the award was extremely difficult, as many editors have shown a very high level of dedication. The UOJM is proud to present the Outstanding Editor Award to Ellen Snyder, sectional editor, who distinguished herself with active participation at the training workshops, always giving high-quality constructive feedback, assisting with copy editing and volunteering to help promote the journal to students and faculty members. We would also like to congratulate Bhavika Patel for winning the cover contest. We received many impressive submissions this year and we are very happy to showcase her beautiful artwork on the cover of the third issue.

We are very grateful to Dr. Melissa Forgie and Dr. Phil Wells, who continuously supported us through their roles as mentors. We would like to thank our wonderful sponsors for their generous funding – without them this issue would not be possible. We would also like to thank the Bureau of Francophone Affairs for their efforts translating all the abstracts, and fulfilling our commitment to being a bilingual journal.

We are very impressed with the high quality and variety of submissions this year. This issue contains 12 exciting articles, covering a wide range of subjects from bacteria as cancer fighting agents, to fasciotomy wound closures, to a mentee versus mentor debate on musculoskeletal injuries. Also featured in this issue is an interview with Dr. Lauralyn McIntyre, a clinician scientist in critical care medicine at the Ottawa Hospital. We were fortunate enough to have a chat with her about her career as an intensivist and, more recently, her involvement in starting up the first in-human stem cell clinical trial for septic shock (CISS Trial). Her work serves as a great example of how innovations at the bench can be translated to the bedside, and should serve as inspiration to all trainees – whether they are involved in basic science, translational research or clinical practice.

The editorial team has worked very hard all year to make this issue a success and I feel very fortunate to have worked with such a dedicated group of individuals. We hope you enjoy the May 2013 issue as much as we enjoyed putting it together!

André B. Martel
Editor-in-Chief

JMUO: Préface

Toute l'équipe de rédaction est très excitée de présenter la troisième édition du Journal médical de l'Université d'Ottawa (JMUO). Depuis que la publication a été relancée en 2011, deux numéros exceptionnels ont été publiés. Le JMUO est une publication avec comité de révision qui est dirigée par les étudiants et qui a pour but de servir de vitrine aux points de vue et perspectives des étudiants de la Faculté de médecine tant sur des sujets scientifiques que non scientifiques. Non seulement produisons-nous la seule publication médicale canadienne bilingue qui soit gérée par des étudiants, mais nous sommes également la seule qui invite les étudiants gradués à participer activement dans l'équipe de rédaction. Afin de continuer les efforts déployés l'année dernière pour réunir les étudiants gradués et les étudiants en médecine, cette année, l'équipe de rédaction est composée de 37 rédacteurs répartis également entre les étudiants de premier cycle en médecine et les étudiants gradués.

Cette année, nous avons apporté de nombreux changements, non seulement dans le but d'assurer la viabilité de la publication, mais aussi pour optimiser l'expérience de chacun des rédacteurs. Le premier objectif était de réorganiser l'équipe de rédaction pour augmenter l'efficacité et le flux de travail. De nombreux nouveaux postes ont été créés, tels que vice-présidence promotion, vice-présidence technologie, vice-présidence pédagogie, trésorier et bien d'autres. La solidification de la structure a permis d'améliorer l'efficacité de bien d'autres aspects importants tels comme la planification budgétaire, le réseautage, le maintien du site internet et la promotion de la publication dans l'ensemble de la faculté. Le deuxième objectif important a été de modifier la formation en rédaction. Comme la rédaction de première ligne joue un rôle tellement important dans la publication de notre revue, nous avons décidé de créer des ateliers de formation où les rédacteurs ont été exposés au processus de rédaction et se sont pratiqués à faire l'évaluation critique d'articles.

Il est important à noter que tout ce travail n'aurait pas été possible sans l'aide et la collaboration de plusieurs gens. Nous aimerions plus particulièrement remercier les gestionnaires éditoriaux, Colin Suen et Loretta Cheung, pour leurs efforts inlassables et leur dévouement dans la gestion du processus de révision, et pour avoir donné un coup de pouce avec les ateliers de formation à la rédaction. Nous aimerions également remercier tous les membres du comité de révision qui est formé de 24 rédacteurs de section et de 6 rédacteurs adjoints. Ils ont tous fait preuve d'un grand dévouement et ont travaillé inlassablement tout au long du processus de rédaction.

Cette année, le JMUO a créé le prix du Rédacteur exceptionnel afin de saluer le travail d'un membre de l'équipe de rédaction ayant démontré un engagement à leur rôle de rédacteur. Il a été très difficile de choisir le récipiendaire, car de nombreux candidats ont fait preuve d'un niveau très élevé de dévouement et d'engagement. Le JMUO est fier de présenter le prix du Rédacteur exceptionnel à Ellen Snyder, rédactrice de section qui s'est démarquée en participant activement aux ateliers de formation, en donnant de la rétroaction constructive de haute qualité, en aidant avec le stade de publication et en se portant volontaire lors des activités pour faire la promotion du JMUO. Nous aimerions également féliciter Bhavika Patel qui a remporté le concours de la page couverture. Nous avons reçu plusieurs très belles soumissions cette année. Nous sommes fiers de montrer l'œuvre exceptionnelle de cette étudiante en page couverture de la troisième édition.

Nous sommes reconnaissants envers Dre Melissa Forgie et Dr Phil Wells qui nous ont toujours soutenus en endossant le rôle de mentors. Nous aimerions remercier nos merveilleux commanditaires pour leur soutien généreux. Sans eux, il aurait été impossible de publier ce numéro. Nous aimerions aussi remercier le Bureau des affaires francophones pour les efforts déployés pour traduire tous les résumés, accomplissant notre engagement à être un journal bilingue.

Nous sommes très impressionnés de la grande qualité et de la variété des articles soumis cette année. Ce numéro contient 12 articles intéressants, couvrant toute une gamme de sujets, allant de l'utilisation des bactéries dans la lutte contre le cancer, à la fermeture de plaie suite à une fasciotomie, ainsi qu'un débat entre un mentor et un mentoré sur les blessures musculosquelettiques. Dans ce numéro, vous pourrez aussi lire une entrevue avec Dre Lauralyn McIntyre, chercheure clinique en soins aux malades en phase critique à l'Hôpital d'Ottawa. Nous avons eu le privilège de pouvoir discuter avec elle de sa carrière d'intensiviste et, plus récemment, de sa participation au lancement de la toute première étude clinique sur l'utilisation de cellules souches pour traiter le choc septique chez les humains (essai CISS). Son travail est un merveilleux exemple de la façon que les innovations en laboratoire peuvent être appliquées au chevet des patients. Il devrait inspirer tous les stagiaires, qu'ils soient du milieu des sciences fondamentales, de la recherche translationnelle ou de la pratique clinique.

L'équipe de rédaction a travaillé très fort tout au long de l'année pour assurer le succès de ce numéro. Je me sens très privilégié d'avoir pu travailler avec un groupe aussi dévoué. Nous espérons que vous aimerez l'édition de mai 2013 autant que nous avons pris plaisir à la créer!

André B. Martel
Rédacteur en chef

The world's first in-human stem cell trial for septic shock: A bench-to-bedside journey in critical care from the perspective of Dr. Lauralyn McIntyre

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In this issue of the UOJM, we sit down with Dr. Lauralyn McIntyre who is a critical care physician, professor at the University of Ottawa, and scientist at the Ottawa Hospital Research Institute (OHRI). Dr. McIntyre has impressed us with her research on fluid resuscitation in the critically ill and, more specifically, in septic shock. Recently, she has taken on the role as the lead investigator on the CISS trial (Cellular Immunotherapy for Septic Shock) at the OHRI. This is the first in-human clinical trial evaluating the safety and efficacy of mesenchymal stem cell therapy for septic shock patients. We had the incredible opportunity of speaking with Dr. McIntyre about her exciting career as a clinician-scientist, the CISS trial and the importance of collaboration in clinical and translational research. The following are excerpts from this interview.

Dans cette édition du JMUO, nous faisons une entrevue approfondie avec Dre Lauralyn McIntyre. Elle est intensiviste, professeure à l'Université d'Ottawa et une scientifique affiliée à l'Institut de recherche de l'Hôpital d'Ottawa (IRHO). Nous avons été impressionnés par la recherche du Dre McIntyre en soins aux malades en phase critique, et plus particulièrement dans le traitement du choc septique. Récemment, elle a endossé le rôle de chercheure principale dans l'essai clinique CISS (Cellular Immunotherapy for Septic Schock) à l'IRHO. Il s'agit de la toute première étude chez des humains pour évaluer la sécurité et l'efficacité du traitement du choc septique à l'aide de cellules souches mésenchymateuses. Nous avons été très chanceux de pouvoir parler avec Dre McIntyre de sa stimulante carrière de clinicienne-scientifique. Vous pourrez lire ci-après des extraits de l'entrevue.

How did you become interested in medicine?

Ever since I was young, I always wanted to help people. In grade 7 I did a lot of volunteering with spinal cord injury patients. In grade 8, I did a lot of volunteer work with kids who had troubles with their speech, so I worked with an audiologist to help the kids get rid of their lisps.

Can you tell us about your education background and how you started working on your research?

I did an Honours Bachelor of Science Degree with a Biomedical Science Minor at the University of Guelph. I actually wasn't ready to go into medicine after my undergrad so I took a break and was a ski instructor in Whistler for a year. Then I moved down to Vancouver and worked for a couple of years. Afterwards, I went to McMaster University for medical school and then I came to Ottawa for my residency in Internal Medicine. I went back out to Vancouver for my critical care training and that's where my research interest started to kick in. When I did my Internal Medicine training in Ottawa, I did an elective with Dr. Hebert and he got me started in my research interest. Then I continued this out west in Vancouver and worked in a lab for 6 months with Dr. Keith Walley and I guess I had a lot of mentorship. The more I did research, the more I wanted to do it because it was really fun. So when I finished my clinical fellowship I came back here to work with Dr. Paul Hebert and Dr. Dean Ferguson. And the two of them mentored me for my Master's in Epidemiology in Ottawa. Then I started working clinically as an intensivist and developed a program of research in resuscitation and that's where it really got started for me and it still is one of my main interests: fluid resuscitation and septic shock.

All along the way, I've been blessed with incredible people around me. When doing research, it is so important to have that infrastructure and people to care for and help you. It's always important to have idea generation and to be challenged in research. In critical care, we have a national research network called the Canadian Critical Care Trials group and the Canadian Critical Care Translational Biology group. This group of investigators from across Canada is incredible. We come together and talk about research protocols, how to get that research funded, and we meet 3 or 4 times a year. So we all do multi-center clinical research together. A few years ago, Dr. Duncan Stewart approached me and asked me if I wanted to be involved with septic shock research.

How did you become interested in this field?

Well, it's a dynamic environment. Things change really quickly in the ICU. People get really sick really quickly, but they can also get better really quickly. We're talking about weeks rather than years kind of thing. I love human physiology. I'll never forget [my professor], he was a major mentor in university for me. His name is Dr Berkeley from Guelph. Another big thing is the teamwork; [working in the ICU] is very collaborative and very multidisciplinary. You have your ICU staff and then you have the residents, fellows, a medical student, and then you've got your nurses, research coordinators, nutritionists, physiotherapists, occupational therapists, respiratory therapists, the social worker,

the spiritual care worker and our ward clerks. And most of us are rounding. The army is going through the ICU, rounding to try and help patients. So I absolutely adore working with everybody. It's just so great. That's why I work in the ICU.

Can you tell us more about septic shock?

Septic shock is sneaky and unpredictable. It is a syndrome from a [pathogen] that enters your body and you respond to that [pathogen] and try to eradicate it. The inflammation and coagulation responses get ramped up, but the way septic shock happens is that the inflammation response gets out of control and we think it's those processes that lead to the development of organ failure and the high death rate that we see in septic shock. The average baseline death rate for septic shock is 30-40% and the more organs that fail, the higher the death rate.

It is not selective; young people and old people are all affected. Patients with comorbidities and those who are immunosuppressed are more predisposed to it, but we see people at a young age coming to the ICU with septic shock. We can often get rid of the infection, but it is the inflammatory response that causes the problem. It is one of the most common reasons that people come to the ICU; about 20% of cases are septic shock related. When someone comes in with septic shock, the whole team is included: doctors, nurses, social workers, pharmacists – it is very multidisciplinary.

Tell us about the management of septic shock.

Septic shock is very perplexing; we've have decades of research to explore the treatment and medical therapies for it and we've truly made little headway for medical therapies in terms of them helping reduce the death rate. The mainstay of therapy is to make the diagnosis as it is very sneaky and unpredictable. If we can make the diagnosis, we can treat the patient earlier, resuscitate them with enough fluids, give them antibiotics as quick as we can, and monitor them so they do not deteriorate. We also help with their breathing, treat their comas, take away their pain, use intravenous medication to support their blood pressure, and put them on the kidney machine if their kidneys are failing. We really need a lot of supportive measures to help patients not only survive but survive well. Leaving the ICU is just the first step; this condition is associated with immense long-term morbidity, so we are talking about weeks to months of rehabilitation. Even when they go home, studies have shown that patients are physically deconditioned and are left with emotional issues and post-traumatic stress and that can impact the way they integrate their life back into society.

What do you think needs to be changed in the management?

The primary prevention part is that everybody gets vaccinated so that you do not get infected. Other than that, most are secondary prevention meaning that you already have sepsis and you need to prevent it from getting worse. We need to diagnosis [patients] early enough because if we diagnose it too late, it is hard to control. We are talking about hours to diagnose and control their condition.

Where do you think stem cells fit in?

Stem cells have a profound effect on the inflammatory response and coagulation cascade. We know that sepsis' initial phase is entirely pro-inflammatory and we know that stem cells seem to modulate many processes in inflammation. It was demonstrated that over 3000 genes are modulated by these [stem] cells in an experiment with sepsis [1]. That's what's really exciting; it's not just modulating one small process because sepsis is very complicated. These cells seem to go in and calm the "house" down and put it back in order. There is also data to suggest that they enhance the clearance of bugs and enhance repair of injured organs through messaging with other cells. It is particularly interesting for sepsis because it happens in such a short timeframe, so you want something that acts quickly – in and out – as you don't want long-term effects from the cells. They seem to have an impact on cell leak. The lining of the blood vessels have endothelial cells and in the setting of sepsis you get profound leak of proteins and white blood cells to the interstitium and that draws fluid with it. So whenever you resuscitate these patients, the following day they are like pincushions because you have given them 10-14L of fluid as it doesn't stay in the intravascular space. The stem cells seem to restore the endothelial function, which is very cool [2]. I truly think that these cells have a strong potential to help these patients.

What about safety?

Our team did a safety systematic review to tally all adverse events in human clinical trials with MSCs [3]. We tried to find all of those trials and then we grouped the adverse events in different categories and we looked for signals. Overall, it seems that the cells are very safe in different patient populations and there were few adverse events, so that gave us more credibility to move forward with our clinical trial.

When evaluating the evidence, why is a systematic review so important?

A systematic review is really critical because it is a transparent and unbiased systematic search of the literature that provides you with the totality of evidence, both good and bad. You synthesize it and describe it in such as way that you understand the strength of the evidence-base that's out there. It's a critical piece for all researchers to be a part of: both clinical and preclinical researchers. Now, preclinical researchers are starting to do the same are starting to do this more. Here, in Ottawa, this is the fourth or fifth one [systematic review]… because if you don't do it, how do you really know everything that's out there? As a researcher, you want to know the good, and the bad.

So can you briefly describe the CISS trial?

The CISS trial is the first in-human [septic shock trial] with stem cells. The main objective of the trial is to establish safety and patient-tolerability of the cells. The other objective is to find the best dose of cells to give. [If in the] Phase I trial, we deem that the cells appear safe and we find out what the best dose is, the aim will be to go to a Phase II trial that will be aimed

at looking at loose surrogates of efficacy for patients with septic shock. Right now, there are two arms of the trial. The first arm is an observational arm, so these patients meet all CISS eligibility criteria but they don't receive the cells. We just follow them forward and we do serial blood and urine measurements of acute inflammatory markers and acute phase proteins to compare that to the group of patients who receive the cells. The other purpose of this observational arm is to document frequency and severity of adverse events that occur in this patient population. Adverse events related to the disease occur every day, much more frequently than you would see in chronic disease. That's why it's really important that we understand and document the frequency and severity of these adverse events before we go to what we call the "dose escalation" intervention arm of the trial.

We've recruited 4 patients into the observational arm and we hope to have the intervention arm of the trial up and running before the end of 2013. For the intervention arm, there are three different doses planned for the stem cells. For each dose, we will enroll three patients. We start with the low dose and after the 3 patients are enrolled, we have a safety and data monitoring board that will be looking [to assess] the occurrence of the adverse events, how the protocol was adhered to, and how the patients tolerated the cells. If they deem that everything went well, we go to the mid dose arm and then we look at the high dose arm until it's finished. And if the patients develop – in any one of those arms – a serious adverse event that's definitely thought to be related to the cells, then the trial's over.

If we deem this trial to be safe, then we will be moving to a Phase II trial very quickly. We want to enroll a lot more patients and it will probably be a trial that's not just conducted at one site or center, but at multiple centers in Canada. (see news article: Ottawa researchers to lead world-first clinical trial of stem cell therapy for septic shock. http://www.ohri.ca/newsroom/newsstory.asp?ID=306 [4])

What advice would you give to students who want to pursue this kind of career?

The advice is to keep your mind open, pursue the opportunities, and explore the potential to do research. Just because you take on a research project as a student doesn't mean you are committed to becoming a big researcher. It could just be scientific exploration and learning how to think in different ways that you can benefit from. Or having the opportunity to work with someone you respect that could be a major mentor in your life. Even if you don't become a researcher, they can still help guide you. So I just think [it's important] to try and pursue the opportunities. Keep your mind open and don't get too overwhelmed. It's easy to say because I was there too – I remember that! I still wish that I could have gotten involved earlier. I just think it enriches your life to be a part of it early in your medical career.

Can you just describe what your weekly schedule is like?

Clinically I work 12-14 weeks in the ICU. All of the other weeks are research. And the research is anywhere from my program to other people's programs locally, nationally and internationally. Another fun thing about research when you're doing it at this level is that you get to collaborate with incredible people around Canada and the world on their projects; you get to learn much more. Also, I chair research committees and there's a lot of administrative research duties built-in. And then, mentoring the young, that's the other thing.

It's very fulfilling. Sometimes it's so busy. You're always trying to manage your time and being realistic about it. That's always a challenge because I've got a daughter. I've got a six-year old behind my door and she's my priority. Nothing comes above her, doesn't matter what it is. But balancing everything can be challenging.

How do you balance family life and work life?

Reevaluate. Reevaluate regularly where you're at. Try to be organized. Just making sure that you carve out time for yourself. And then the last thing is to not constantly say "yes", although, we're all kind of bad for that. Being able to say "no" to some stuff [is important] because it can become overwhelming. So, know what your limitations are. Reach out and have good mentors around you that can help you keep yourself in mind. Because if you say yes to 25 different things, there's no way you can get good research done. So it's got to be a balance.

It's good to hear that from you. It sounds like you really like what you do and that's really inspiring.

That's the other thing. How do you manage your time? You love what you do. Whatever you choose to do, have a passion about it. Don't just do it because you're supposed to or because you think your academic department wants you to. Take something on because you love it. Because you are going to be really busy whatever it is you take on, be it education, research, administration, quality of care initiatives. Take it on with a passion and then you will be so fulfilled by what you do.

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Examining the usefulness of the evidence-based medicine model for decision-making in clinical and research settings

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Evidence-based medicine (EBM), one of several disciplines that have evolved from clinical epidemiology, entails using the best current evidence in making decisions related to patient care [1]. The practice of this discipline involves the integration of: (i) best available evidence from research, (ii) clinicians' expertise, and (iii) patients' beliefs and values (Figure 1). The best available evidence refers to clinically relevant research that must be considered when examining the accuracy of diagnostic tests, the power of prognostic markers, and the effectiveness of therapeutic regimens. Expertise refers to the proficiency and judgement that clinicians acquire through medical practice. Patients' beliefs and values refer to the unique concerns and expectations of each patient that must be integrated into clinical decisions.

Figure 1: Evidence-Based Medicine Triad [2]

When making a clinical decision, health care teams should consider all three components. Using two recent controversial news articles, the objective of this commentary is to examine the usefulness of EBM in decision-making related to: (i) individual-level patient care and (ii) population-level medical care. The first article examines Hassan Rasouli's case to assess the evidence used to determine end-of-life decisions. The second article assesses the evidence used in obtaining approval to conduct a clinical trial of Multiple Sclerosis Liberation Therapy.

ARTICLE 1: MR. RASOULI

Hassan Rasouli, a recently immigrated 60-year-old retired engineer, underwent surgery at Toronto's Sunnybrook Health Sciences Centre to remove a benign brain tumour. Mr. Rasouli suffered post-operative brain damage that left him in a vegetative state [3,4]. This state is defined by an absence of patient awareness due to widespread brain damage. These patients are able to maintain blood pressure and cardiopulmonary function, but lack cognitive awareness. When this condition lasts longer than one month, the patient is considered to be in a persistent vegetative state (PVS) [5].

Recently, Mr. Rasouli's physicians have updated his status to a minimally conscious state (MCS). Patients in a MCS are known to preserve some awareness of themselves and their surroundings [5]. Although there appears to be an improvement in Mr. Rasouli's state, his condition still requires him to be on a ventilator, as well as feeding and hydration treatment [3,4].

Clinical Evidence

Current evidence indicates that most patients in a PVS die within six months. However, patients in MCS may recover some limited awareness and tend to have a better prognosis compared to patients in PVS [5]. The treatment for PVS and MCS patients is similar and is mainly supportive. Unfortunately, the chance of significant functional recovery diminishes over time [6].

Measuring quality of life (QOL) for these patients is challenging due to the lack of reliable communication. This difficulty is substantiated by a lack of evidence on studies that measure QOL in this patient population. Several studies have used functional imaging modalities to assess subjective phenomena such as pain perception [7]. These studies are valuable; however, current scientific understanding of areas associated with pain processing in the brain has yet to be fully realized. It is argued that although functional imaging is insightful, it cannot substitute behavioural or clinical assessment [8].

Clinicians' expertise

Although the evidence is clear on prognosis, there is diagnostic uncertainty. Diagnosis is typically a clinical process to distinguish between PVS, MCS, and other severe conditions. In addition to meeting clinical criteria, functional imaging modalities such as Positron Emission Tomography have been used [5]. The misdiagnosis in this patient population is highlighted by a study that demonstrated 19% of patients who were believed

to be vegetative showed signs of awareness through Electroencephalography [9].

In fact, Mr. Rasouli was first diagnosed as persistently vegetative for a year. Following further testing, his clinical status was updated to be in a MCS [3,4]. It is unclear whether Mr. Rasouli was misdiagnosed or whether he regained some degree of consciousness over the past year.

Patient's beliefs and values

The legal battle between Dr. Rasouli's physicians and his wife highlights this conflict. The physicians believe that Mr. Rasouli should be transferred to a palliative care program, whereas his wife disagrees. The physicians argue that they have the right to stop medical treatment when futile. However, the family argues that Mr. Rasouli displays signs of consciousness and that hastening death contradicts his religious beliefs [3,4]. This case is currently before the Supreme Court of Canada and judgement is pending.

Summary

This case highlights the uncertainty that is encountered in assessing consciousness and end-of-life decision-making. The evidence highlights the clinicians' limited understanding of these patients, including misdiagnosis and inability to confidently obtain information on QOL. Furthermore, limitations of current studies such as the reliance on functional imaging to obtain insights into MCS awareness undermines our confidence in determining what is best for the patient. However, evidence is clear when it comes to prognosis; these patients are unlikely to recover or gain functional ability. An additional key point to highlight is that Mr. Rasouli's widespread brain damage prevents him from breathing on his own. This state suggests a bleak prognosis for Mr. Rasouli due to more significant brain damage compared to other MCS patients. Despite the prognosis, some families hold to their religious beliefs demanding continuation of treatment. This conflict between patients' wishes, physicians' expertise and evidence highlights the difficulty in implementing EBM in everyday practice.

Resolving the EBM conflict is further complicated when considering resource allocation. In this case, the use of intensive care resources could be viewed as unfair when critical patients are deprived of such access. The use of finite resources, when futile, is difficult to justify especially when death is imminent. This argument is the essence of the legal battle raised by Mr. Rasouli's physicians. The ruling on this issue will have important implications on end-of-life care, especially considering the aging Canadian population as well as the continuous advancement of medical technology.

ARTICLE 2: CLINICAL TRIAL OF MULTIPLE SCLEROSIS LIBERATION THERAPY

Multiple sclerosis (MS) is an inflammatory, demyelinating disease that mainly affects the central nervous system (CNS). In MS, the body's immune system attacks against myelin and oligodendrocytes (cells that make myelin) in the CNS, resulting in a progressive loss of neurons. This neurodegeneration causes irreversible neurological disability including muscle weakness, visual disturbances, coordination issues, and decreased sensation [10]. Additionally, MS can present as acute or chronic attacks of demyelination, the latter being a more progressive development with low underlying levels of inflammation.

The most widely accepted theory suggests that MS is an autoimmune disorder. However, new theories have been proposed leading to the development of new MS therapies. Zamboni and colleagues proposed that MS is caused by abnormality of cerebral venous flow leading to iron deposition in the brain [11], which would elicit an autoimmune response causing demyelination [10]. Zamboni developed a radical approach called "Liberation Therapy", which consists of a balloon angioplasty and insertion of a stent that opens up the veins to improve cerebral venous flow and prevent iron deposits in the brain [11].

Clinical Evidence

Since the implementation of liberation therapy in North America, studies have highlighted several safety concerns including incidents of intracerebral hemorrhage, stent thrombosis, stent migration, and cranial nerve injury. These safety issues have delayed acceptance to conduct liberation therapy trials in Canada [12].

In addition to safety concerns, there is a lack of quality studies that assess the efficacy of liberation therapy. Both of these concerns influence whether clinical trials of MS Liberation Therapy should be conducted at all. In a systematic review, Bhatia et al. failed to observe an association between chronic venous insufficiency and MS [12]. Also, studies conducted by Bagert et al. concluded that methodological problems exist with case reports of liberation therapy in Europe and that more evidence is required before the procedure can be considered safe [13,14]. Therefore, conducting invasive treatment studies of liberation therapy should be approached with caution until the relationship of MS and chronic venous insufficiency is better established.

Patients' beliefs and values

Case reports demonstrate that patients choose to undergo liberation therapy for many reasons; the most common being a lack of available and effective treatments [14]. In recognizing the limited number of treatments available to patients, a survey by a team of researchers in British Colombia followed 80 Canadians who travelled abroad to receive liberation treatment. These patients were not responding to other treatments and opted to undergo liberation therapy. Half of the patients felt improvements after surgery, whereas half noticed no change or worsening of symptoms [15]. One patient reported a stroke and another reported a heart attack post-surgery. Other common complications included bleeding and anaesthetic-related issues [15].

Patient advocacy groups

Many patient advocacy groups exist and are coordinated through the MS Society of Canada [9,16]. Patient-lead advocacy groups have been influential in changing the outlooks of government officials concerning the funding for MS patients to undergo liberation therapy and for conduction of clinical trials. One example is Premier David Alward, who in his political campaign outlined the plan to establish a fund for MS patients in New Brunswick to pursue liberation therapy abroad [17]. More recently, patient advocacy groups have influenced other Canadian provinces including Saskatchewan, Manitoba and Newfoundland to commit to funding studies that investigate the efficacy of liberation therapy.

Summary

The MS case highlights the conflict between medical evidence and patients' demands. The main requirements to conduct large clinical trials are evidence of some benefit and demonstration of no serious safety concerns. Despite failure to meet both of these requirements, advocacy groups have succeeded in gaining funding to conduct clinical trials. The implications of this development are far reaching and dangerous. First, this case demonstrates how political pressure can affect the scientific process, which should instead be objective. Secondly, conducting clinical trials with significant concerns over subjects' safety are unethical because they subject patients to unnecessary risks. Finally, clinical equipoise indicates that there should be genuine uncertainty of the efficacy of treatments. In the case of MS, liberation therapy appears to be inferior compared to other proven therapies, such as interferons [18]. Therefore, it is unethical to assign a subject to the inferior arm (i.e. liberation therapy) as a lack of equipoise exists for such a trial.

The EBM model demonstrates the various forces that influence decision-making. In this case, the evidence suggests that a large clinical trial of liberation therapy for MS is unjustified. Physicians and researchers should use their knowledge to empower policy makers and solidify the scientific process to ensure its objectivity.

CONCLUSION

The cases presented here demonstrate that conflicts arise between evidence, clinician's expertise, and patient's values. How should medical decisions be made when conflicts arise? The best approach is to ensure there is effective communication between patients, their families and the clinician for shared decision-making.

Shared decision-making is a collaborative process where the patient, their family, and the physician work together to arrive at the best medical choices. In order to put shared decision-making into practice, a number of recommendations include: (i) establish a conducive atmosphere, (ii) determine patient's preferences, (iii) identify options, (iv) discuss and understand patient's beliefs and values (v) explain medical information and ensure understanding, (vi) share personal recommendations with the patient, and (vii) make or negotiate a decision in partnership with the patient [19].

One of the strengths of EBM is its usefulness in approaching decisions related to individual and population-level medical care. In Rasouli's case, applying the EBM model helps analyze the components affecting decision-making at the patient level. In the MS case, the EBM model assesses the components influencing the establishment of a large trial.

It is important to emphasize that the EBM model should be used in decision-making related to clinical and research settings; however, that is not necessarily what happens in practice. The MS case demonstrates the danger of not following EBM, such as influencing the objectivity of the scientific process and subjecting patients to unnecessary risks. Therefore, it is crucial to alert stakeholders (i.e., clinicians, patients, policy makers, etc.) of up-to-date information, as well as ensuring accessibility of this evidence. Most importantly, stakeholders will need to understand and evaluate this evidence to make appropriate decisions in clinical practice and research.

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The Faculty of Medicine Student Mentorship Program: A new initiative

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BACKGROUND

The Faculty of Medicine Student Mentorship Program is a novel initiative that was introduced in September 2012 with the vision of creating an open forum to promote self-reflection, student health and well being, as well as personal and professional competencies within the medical student community.

Rationale

As prospective medical professionals, we are challenged each day with the balancing act of juggling personal ambitions, social life, and professional responsibilities. For incoming medical students, the rapid transition into medicine, the need for prioritization and time management, and the capacity to balance personal habits with professional obligations can be quite overwhelming. The Student Mentorship Program was designed to create a safe and open space for medical students to discuss these concerns, learn from one another's experiences, and develop an individualized plan of action. The idea of mentorship was built upon the rationale of empowering students with the ability to:

1. Develop a self-reflective foundation that allows them to recognize and get help early
2. Discuss and develop a healthy and balanced approach to psychosocial and physical health throughout medical school
3. Create a strong social network of interpersonal relationships among colleagues

FORMAT

Mentoring Centre

The Mentoring Centre is one of two initiatives started by the Student Mentorship Program. The centre is located in the Roger Guindon Library, and is open every Monday and Wednesday from 1 pm until 4 pm. Students are able to come by (with or without an appointment) and chat with mentors. Two mentors are always present at the Mentoring Centre, and an effort is made to ensure one bilingual mentor is available on any given day. Mentors typically provide advice on study strategies, time management, exam preparation, stress management, and career preparation. All students are reassured that visits are confidential.

The Mentoring Centre provides one-on-one services to students who have questions regarding both personal and professional development. In the first semester (October-December, 2012), there were 40 total visits to the Mentoring Centre by 25 different students. The data regarding the total number of visits in the current semester (January-May, 2013) is unavailable at the present time, but will be analyzed further in the future.

Tutoring centre

It was identified by the mentors that numerous students came to the Student Mentoring Centre for inquires related to academic concepts covered in the previous weeks. To better address this need, we successfully designed and implemented the Tutoring Centre in January 2013. The Tutoring Centre runs every Monday from 1 pm until 3 pm. During that time, two mentors run a tutorial based upon the academic concepts learned by first year medical students in the previous week. For instance, one tutorial was based upon discussing the basics on how to approach an electrocardiogram (ECG), and its applications to Cardiology. The purpose of the Tutoring Centre is not to undertake didactic teaching, but rather to provide medical students with a space to discuss and learn from one another, as well as understand strategies employed by the mentors in their experiences of the subject matter. Depending on the tutors' preferences, the style of the tutorial often varies from week to week. For example, some tutors will frame the tutorial based on a pre-determined set of objectives, while other tutors prefer to work from a PowerPoint presentation.

TUTORS

To ensure sustainability of the Student Mentorship Program, the key was to create a centre directed by the students and for the students. The idea was to reinforce an environment of reciprocity and sharing of personal experiences among medical students. Consequently, the tutors in 2012 included a group of 8 second year medical students who were selected for the program based on experiences and passion for mentorship, as demonstrated both through their applications and interviews. Moreover, active efforts were made to ensure that a bilingual group of mentors were recruited to both reflect the diversity of the medical student community, as well as the unique approaches to addressing the array of student-specific concerns.

Training

At the start of the term, every mentor participated in a day of mentorship training provided by the Student Academic Success Services at the University of Ottawa. In tandem, all mentors also received four training sessions during the course of the year in topics identified as being especially relevant to medical students including: stress management and healthy behaviours, time management and procrastination, learning styles, and facili-

tation of academic study group sessions discussed below.

Role

The primary role of student mentors is to act as a facilitator, actively listening to student concerns or inquiries, identifying potential problem-solving strategies, and developing a plan of action with the student. Unique to this reciprocal relationship is the sharing of professional experiences and information to allow for students to learn from one another. In parallel, mentors also play a critical role in identifying and disseminating resources beneficial for student specific concerns. For example, a frequent concern that students raise is their personal interest in undertaking medical research, but a lack of knowledge regarding the process. In such a scenario, the mentors can very effectively integrate not only their personal experiences as medical student researchers, but also as mentors who are trained to help students identify research-related resources offered by the Faculty of Medicine. Lastly, an integral part of the job of mentors is to understand the scope of the Mentoring Centre and know when, where, and how to refer students for additional help if needed.

STUDENT COMMENTS

Mentors always hear positive feedback from the students who visit the Student Mentorship Program. The following are quotes from students who have participated in the program, and are testaments to the beneficial impacts this program has on the first year students.

> *"The Mentoring Centre is a wonderful resource to have available, especially in first year where it is difficult enough trying to adjust to a new school, a new program, and a new set of academic and professional obligations. Knowing that I could bring my questions and concerns to upper year students anytime, not only helped me with the stress of adapting to the curriculum, but also provided me with fellow colleagues to talk to about any concerns I had as a medical student. The mentors were consistently willing to go above and beyond to make sure all my questions were answered, and took the time to help me through any difficulties I was having. The support I received from the mentors has been invaluable to me in so many ways, and has been a major contributor to my successful adjustment to the medical program at the University of Ottawa."* – First Year Medical Student

> *"Having support from upper year students through the Student Mentoring Centre is invaluable as they are able to relate to the concerns we have. I've found it particularly useful in helping me determine what study strategies might work best for me, how to manage stress, and learning about what summer opportunities are available for medical students. The mentors are very approachable and are always happy to provide support and advice."* – First Year Medical Student

Members of the Faculty of Medicine administration team have noticed the influence of this new initiative. Dr. Louise Laramée, Assistant Dean Student Affairs, strongly supports the Student Mentorship Program, and encourages students to participate. Other members of the Student Affairs Office have also heard great feedback from students.

> *"The services provided by the mentors have helped students modify and develop new study skills needed to succeed in medical school. We have noticed that several students frequent the Centre on a regular basis, which indicates that they find the services beneficial. Nearly half of first year students have attended either a one-on-one session with a mentor or have attended a study group. At the Student Affairs Office, we often hear the positive impact that the Centre has had on students' lives. Since frequenting the Centre, a student has told me that they were better able to adapt and transition through their first-year in medicine."* – Melissa Barton, Lead Councilor, Student Affairs Office

WHAT ARE OTHER FACULTIES DOING?

The University of Ottawa has a total of 19 Mentoring Centres. Each centre provides their own initiatives which are largely dictated on the nature of studies pursued. For instance, the Faculty of Arts offers workshops on writing style, and tutoring services for a variety of topics such as philosophy, whereas the Faculty of Law delivers exam preparation sessions, and resources for mature students. The Faculty of Science has also developed a Science Buddies program where senior students meet with new students and can answer questions one-on-one. Another unique program, held by the Health Sciences Mentoring Centre, offers support and resources through online discussion forums.

Moving forward, the other initiatives held by different Mentoring Centres could help shape the services offered by the Faculty of Medicine Student Mentorship Program to better meet the needs of the students. However, a more formal evaluation of such needs is required before novel initiatives are implemented, given the success of what is already in place.

CHALLENGES

The Student Mentorship Program faced relatively minor obstacles during its first year of implementation. One of the primary challenges identified was promoting student attendance as the year progressed. The mentors presumed this trend was due to students becoming more comfortable with the curriculum, and the demands of medical school with time, thereby decreasing the need to utilize the services offered by the Student Mentorship Program. Moreover, based on personal communications with a number of first year students who visit the Mentoring Centre, it was identified that many students continue to be unaware of the variety of services offered. For example, when one mentor

posted on the Facebook group that mentors could provide advice on how to secure summer research positions, approximately five students came forward requesting more information on the subject. Evidently, these students were looking for advice regarding career development, but were unaware that mentors could provide tools and resources to support job searching.

In order to increase attendance, one recently implemented strategy that seems to be effective is to have the first year class presidents of both the Anglophone and Francophone streams make announcements as to the services offered. For example, the mentors currently send a weekly announcement to the presidents to advertise the weekly tutorial. To increase awareness of the services offered by the Student Mentorship Program, we plan on developing a hand-out outlining this information which will be distributed to the incoming first year students during their Orientation Week. Furthermore, the mentors plan on preparing brief documents that will be available online through the Faculty of Medicine Mentorship website, addressing common concerns faced by students such as "How to Organize Electives," and "What is a Medical Student Performance Record?"

FUTURE DIRECTIONS

The Student Mentorship Program has been a success thus far because of the support of the Faculty of Medicine, the dedication demonstrated by the student mentors, as well as the interest and gratitude of the participating students. Moving forward, we plan on using feedback forms to further identify student concerns, and services offered by the program that require improvement. In doing so, we can not only better equip the mentors with the necessary training and teaching tools, but we can also develop resources such as brochures, pamphlets, modules, and themed workshops to address common student concerns. Given the passion and interest demonstrated by the medical student body, we intend to further expand the Student Mentorship Program through accruement of funding, as well as increased promotion and accessibility of the services offered.

The goal of the Student Mentorship Program is to foster an environment that enhances the personal and professional well being of the student community. This initiative has been highly successful in its first year of implementation, and we look forward to continuing this program in the years to come.

The unsung value of local peer-reviewed publications

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Students, faculty and staff at the University of Ottawa may be familiar with the locally-produced and independently-run student newspapers The Fulcrum (published in English) and La Rotonde (published in French). These regular publications are free of cost to the University readership, and are widely distributed fixtures on newsstands across campus. The Fulcrum and La Rotonde are not only important outlets for voicing student opinions and publicizing campus events, but are also excellent avenues for showcasing vibrant student culture and creativity through art and poetry. However, the unsung academic value of local student-run publications resides in the undercurrent of work that takes place during the submission, review and editing phases that precede publication and print. In this brief commentary, I focus on the recent revival of the University of Ottawa Journal of Medicine (UOJM) and assert that UOJM offers the students of the Faculty of Medicine an unrivalled opportunity for honing writing and editing skills. Indeed, I believe that this enterprise can help to compensate for the progressively atrophying formal education in writing within post-secondary curricula.

A common weakness of many undergraduate programs in science across Canada is the underrepresentation of scientific writing in the academic curricula. From my personal experiences and through discussions with my peers, it is clear that over the course of a four-year Bachelor of Science program, students produce little more than a handful of written research assignments. Furthermore, students are often graded with minimal feedback on their written work, therefore minimizing the formal development of their writing skills. Arguably, these limitations are due to growing class sizes and the time-consuming logistical nightmare of grading hundreds of multi-page writing assignments. Herein lies an important disconnect between the content of post-secondary education and the 'real-world' requirements of many careers in science. Fortunately, for students of the Faculty of Medicine at the University of Ottawa, the UOJM offers a rich opportunity to fill this void.

The UOJM was originally a quarterly publication founded in the 1960's, and met its demise in the 1970's due to receding interest in the journal [1]. After a 40 year absence, UOJM was resurrected in 2011 and has since produced two high-quality issues containing a wide range of articles uniquely geared toward the readership of the Faculty of Medicine. Unbeknownst to many students and faculty of the University of Ottawa medical campus, the processes leading to the publication of each issue of UOJM offers a highly valuable resource for the development of students' skills in scientific writing and also provides students with a gentle immersion into the peer-review process.

This year, the UOJM editorial team is comprised of over 30 dedicated student editors who are divided into multiple editing groups. Every article submission received at UOJM is rendered anonymous and independently dissected by three to four editors, who each generate a systematic report documenting the strengths and weaknesses of the manuscript. Ultimately, these reports are amalgamated into a single document that is returned to the submitting author. The document received by the author contains detailed discussions regarding the strengths and weaknesses of the manuscript, constructive criticisms, and suggestions for how to improve the manuscript for publication. These comments are wide-ranging and can include suggestions for generating an improved 'flow' and narrative through the reorganization of thoughts, highlights of logical errors, and may even extend into the minutiae of sentence structure, word-selection and verb-tense. From my experience, manuscript reviews from larger international journals, or even feedback on writing assignments in advanced graduate-level courses, will rarely delve into such detail regarding the 'writing' per se. Therefore, individuals who take the initiative to submit a manuscript to UOJM are rewarded with unparalleled feedback on their writing and a unique opportunity to locally hone their writing skills – completely free of charge. The fruits of their labor are further sweetened by the prospect of immortalizing their work in the journal of their future alma mater – something to surely take pride in.

In a manner that complements the development of writing skills of students in the Faculty of Medicine, UOJM also affords students with the unique and highly valuable opportunity to take on editorial responsibilities and participate in the critical review and appraisal of submitted manuscripts. As a new Sectional Editor at UOJM, I have witnessed these positive experiences first-hand. The UOJM editors are guided through a step-wise training process that provides them with the insight to better understand the role of a reviewer in a peer-reviewed publication. The editors are exposed to highly diverse writing styles and gain a deep appreciation for the range of writing skills within their academic community. As such, in addition to promoting the development of the writing skills of their peers (as described above), UOJM editors also personally benefit from the enlightening exercise of compiling detailed and objective reviews of submitted manuscripts. The simple process of critically assessing a manuscript can greatly consolidate an individual's own perspectives on the art of writing, and can therefore serve as an education in writing in itself. Thus, there is considerable educational worth in the 'extracurricular' activities surrounding UOJM that is largely overlooked. I assert that faculty members should encourage students to submit articles to UOJM

or apply to become a member of the UOJM editorial team to take advantage of this beneficial academic support system.

In closing, the UOJM provides a unique resource for students to develop their writing skills and also offers an opportunity to independently participate in the peer-review process at an early stage in their scientific careers. Authors who submit their manuscript to UOJM receive detailed and constructive critical feedback from the UOJM editorial team that is unlikely to be found elsewhere during their post-secondary education. In addition, UOJM editors are exposed to the process of peer-review editing which can indirectly benefit the individual's own development as a writer. Although contributors to UOJM may not receive the same prestige or accolades as publishing in large international journals, I believe that the UOJM enterprise is fertile grounds for the academic development of students at the Faculty of Medicine and for the local promotion of scientific literacy in general. Only time will demonstrate whether this unsung value can acquire broader acclaim, or whether the UOJM will recede into the depths of literary hibernation as it did in the 1970's.

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Mentee vs. mentor: A debate on the use and efficacy of platelet-rich protein injections for the treatment of soft tissue musculoskeletal injuries

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The Altitude Mentoring Program was established to empower undergraduate students from underrepresented populations to pursue careers in healthcare. This is achieved by nurturing high quality relationships with medical student mentors who help these students realize their potential as future healthcare professionals. The mentors work with the first year students to the skills and competencies necessary to excel in a future healthcare career. My mentee –Subhan– and I decided to focus on a project that would equip him with an arsenal of research skills including: literature review, evaluating evidence, scientific writing andusing referencing software. The goal was to set him up with his first publication such that he might be a competitive applicant for summer research opportunities.

After making a shortlist of areas in medicine that interested the undergraduate student, we sought out controversial topics within these disciplines. Eventually, we settled on the use and efficacy of platelet rich protein (PRP) injections for the treatment of soft tissue musculoskeletal injuries.Subhan argued for the use of this therapy and Iargued against.PRP is blood plasma enriched by platelets that contain cytokines and growth factors to stimulate healing of bone and soft tissue. Tiger Woods, Troy Polamalu, Kobe Bryant and Rafael Nadalare just a few examples of professional athletes who have made headlines using this controversial treatment; we are about to examine whether or not it is merited.

FOR PRP INJECTIONS - Subhan Sediqi

SAFETY

Patient safety is a primary concern when determining any choice of therapy. PRP injections are autologous, meaning they are created from the patient's own fractioned blood [1]. Due to their origin, these injections have been consistently shown to be safe and to yield no adverse side effects [2]. Furthermore, in two recent studies PRP injections have trumped the gold standard of corticosteroid injections in terms of reducing pain and increasing articular function in soft-tissue tendon inflammation [3, 4]. Given the risk factors and adverse side effects associated with corticosteroids, PRP injections are becoming an increasingly viable option.

Subhan Sediqi
First year health sciences

EFFICACY

A recent double blind study, in which patients suffering from Osteoarthritis (OA) were injected with either PRP or a saline placebo, determined that the PRP group exhibited a greater amount of symptomatic relief (including a significant reduction in pain) compared to the placebo group [5]. Additionally, recent literature has supported the beneficial effect thatPRP injections can have on decreasing patient-reported symptoms of pain and quality of life in OA [6, 7]. Another alternative, hyaluronic acid

AGAINST PRP INJECTIONS - Nicholas Paterson

SAFETY

PRP injections are being portrayed as a ''wonder drug'' without sufficient evidence supporting their application in the clinical scenarios in which they are being used. PRP injections are administered for a variety of conditions including: lateral epicondylitits, osteoarthritis, knee ligament tears, plantar fasciitis, and rotator cuff injury [1]. From a safety standpoint, the potential adverse effects from the injections themselves are fairly benign (pain, nerve injury, infection), but the long-term repercussions from the therapy are unknown [14]. There has been a significant amount of publicity regarding PRP injections thanks to elite athletes opting for these novel treatments. This begs the question as to whether this therapy is being driven by research or, perhaps more likely, the market.

Nicholas Paterson
First year medicine

EFFICACY

Considering the importance of "evidence-based medicine" in clinical practice, it is surprising how little substantiation there is to support PRP efficacy. The literature almost containsmore reviews than clinical studies. Existing studies consist primarily of anecdotal reports or case studies, and many of the recent publications are either poorly designed, retrospective, have small sample sizes or do not use placebo controls [5]. A few controlled, higher-levelstudies exist, but much of the evidence has

(HA), is a popular viscosupplementused in OA treatment but has been associated with a small, clinically irrelevant benefit and an increased risk of serious adverse events [8]. PRP injections have yielded significantly higher patient satisfaction scores than HA injections for the treatment of OA [9, 10]. PRP injections have also been shown to be effective in soft tissue musculo-skeletal injuries such as epicondylitis, where the PRP group had a greater impact on function and repair after 6weeks when compared with autologous whole blood (control)[11]. Plantar fasciitis is another disabling condition where PRP injections demonstrated superior results over the standard corticosteroid injection[12]. Finally, supraspinatus partial-tear injuries in the rotator cuff that were treated with ultrasound-guided PRP injections were favourable to dry-needling (similar to acupuncture) in both reducing pain and disability[13].

CONCLUSION

In theory, a patient could delay invasive and costly surgeries or experience less pain in the time leading up to a scheduled surgery by undergoing PRP injection therapy. Furthermore, if a patient is inoperable, or has failed after surgery, this therapy could be of great value once appropriate dosage and timing schedules are better developed. There is a large body of evidence in support of the ability for PRP injections to significantly reduce pain, increase function, and improve quality of life. As PRP injection protocols are better refined, I expect these results to continue. These early positive clinical results combined with the feasibility of the therapy, which can be delivered in an out-patient setting, suggest there is great potential for this treatment and I anticipate future research endeavours to continue to demonstrate this.

not supported the use of PRP in varioussoft-tissue conditions. One study demonstrated no clinical or ultrasonic advantage of PRP over placebo in chronic Achilles tendinopathy at 1 year [15]. PRP injections used concurrently with anterior cruciate ligament surgery allografts showed no discernible clinical or biomechanical benefit at 2 years [16]. Furthermore, using PRP in a mesh matrix applied to the site of the tendon-bone interface in rotator cuff surgical repair revealed no effect on biological repair, function or clinical ratings scales - it may have even been deleterious [17]. Finally, treatment of Achilles tendon ruptures using PRP injections had worse clinical scores than the control at 1 year[18].

CONCLUSION

It is important to note that PRP injections are being used for many conditions that have been largely proven to resolve with rest and/or conventional anti-inflammatory or ice therapy [1]. Furthermore, many studies focuse on minimal reduction in healing timesconferred by this therapy, which, while potentially applicable to the elite athlete, may not be as relevant to the weekend warrior given the unknown long-term risks. The additional cost relative to the alternatives and lack of medical coverage further decreases the accessibility of this therapy. For these reasons and the overwhelming lack of evidence for its use, I cannot recommend PRP injections for soft-tissue injuries.

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Warning: Don't let the fast-track slow you down

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Every autumn in Canada, thousands of graduate students in the sciences apply to federally-funded scholarships from the Canadian Institutes of Health Research (CIHR) or the Natural Sciences and Engineering Research Council of Canada (NSERC). These prestigious and highly competitive scholarships are awarded to graduate students who have demonstrated excellent academic achievement in their undergraduate studies and exhibit high research potential through authorships on scientific publications. After the economic downturn of 2008, federal funds have thinned and, as a consequence, the intensity of competition for graduate scholarships has amplified significantly. For example, in the 2008-2009 funding cycle, 373 Canada Graduate Scholarship (CGS) doctoral research awards were granted nationwide by CIHR with a budget of $36,589,584 [1]. By 2011-2012, the budget was nearly halved (to $19,748,751) and only 197 doctoral students were awarded CGS funding across Canada. Beyond this funding drop, student eligibility for federal funding can also be unjustly compromised. In this article, I examine the 'fast-track' program at the Faculty of Medicine, which enables M.Sc. students to transfer directly into the Ph.D. stream, and how the timing of this process can inadvertently truncate student eligibility for CIHR and NSERC funding. Interest in the fast-track program is steadily increasing and presently, fast-track students comprise over 50% of all Ph.D. students at the Faculty of Medicine (Figure 1) [2]. Thus, I recommend that the administrative bodies within the Faculty of Medicine closely examine these details as they carry serious implications for individual students, faculty members and the academic institution alike.

In September 2009, I enrolled at the University of Ottawa in the M.Sc. program in neuroscience. I quickly developed a passion for my work and decided to pursue doctoral studies through the fast-track mechanism. Since my supervisor was a new faculty member at the time, we were both largely oblivious to the details of the fast-track program – we simply agreed that it was a good idea. After earning faculty approval for my transfer and the necessary paperwork and administrative details were complete, I was enrolled in the Ph.D. program in September 2010 – exactly 12 months after starting in the M.Sc. program. It was a streamlined process and I was pleased with my decision.

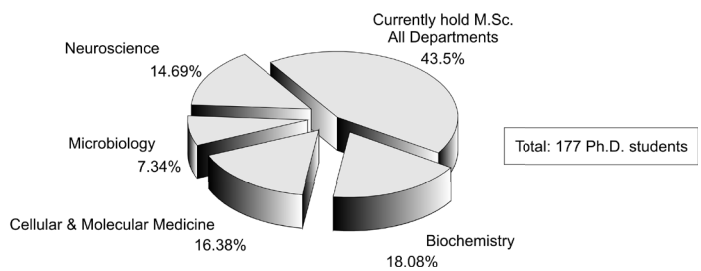

Figure 1: Distribution Ph.D. students at the Faculty of Medicine. Fast-track Ph.D. students (shown by department) comprise 56.5% of all Ph.D. students compared to 43.5% who have previously completed a Master's degree (all departments). Illustration by the Author.

Alongside my fellow peers, I spent a great deal of time crafting and submitting applications to NSERC and CIHR during the subsequent autumn seasons. Persevering through annual rejection letters, I diligently worked on my research project, presented my findings at scientific conferences, and contributed to a modest number of peer-reviewed papers. By autumn of 2012, I was confident that I had achieved sufficient academic and scientific merit to assemble a truly competitive scholarship application. However, it was to my bitter surprise to discover that I was no longer eligible for federal funding due to a perverse technicality directly related to my fast-track transfer.

Both CIHR and NSERC have set scholarship eligibility guidelines based on the duration that a student has spent in the M.Sc. program prior to transferring to the Ph.D. stream. Here, I will illustrate the circumstances that personally I faced in the 2012 application year. CIHR guidelines indicate that if:

> *"The candidate has completed 12 months or more in a Master's degree program prior to transferring to or starting a Ph.D. program...then the maximum amount of time he/she can be registered as a full-time student in a Ph.D. program [to be eligible for funding], as of the application deadline, is 22 months." (Figure 2; Students A & B) [3].*

At the time of application in October 2012, I had just completed 24 months in the Ph.D. program and was therefore ineligible (Figure 2; Student B). Worse yet, if:

> *"The candidate has completed less than 12 months in a Master's degree program prior to transferring to or starting a Ph.D. program...then the maximum amount of time he/she can be registered as a full-time student in a Ph.D. program [to be eligible for funding], as of the application deadline, is 30 months." (Figure 2; Student C) [3].*

In short, these policies indicate that if I had transferred to the Ph.D. stream one semester earlier or one semester later, I would have been fully eligible for submitting a scholarship application in 2012 (Figure 2). A similar rule also negated my eligibility for an NSERC scholarship [4]. In disbelief, I made the necessary telephone calls to plead my case with officials at CIHR and NSERC only to receive apologetic confirmations of my ineligibility. Simi-

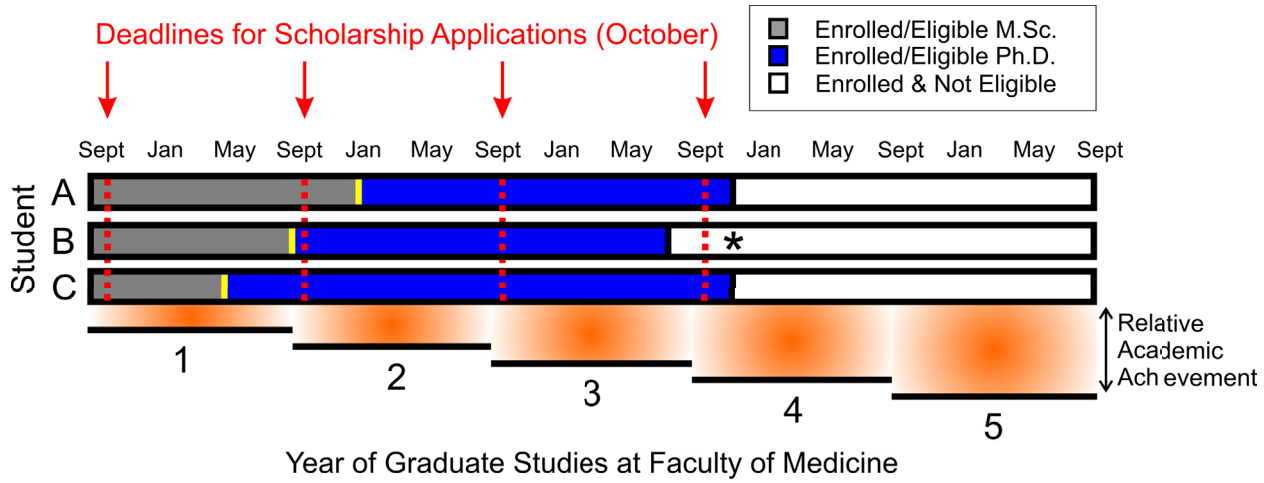

Figure 2. The timing of fast-track transfer to Ph.D. stream can significantly affect student eligibility for CIHR Doctoral Research Scholarships [3]. Five-year study trajectories of three typical fast-track students (A, B, C) are depicted. Each student begins graduate studies at the Faculty of Medicine in September of Year 1 and transfers to the Ph.D. stream at the beginning of different semesters (January, September, May, respectively; yellow bars). Students A & B spend 12 months or more in the M.Sc. program (grey) before transferring to the Ph.D. program; these students are eligible (blue) to apply for federal funding (red arrows and dashed lines) up to 22 months of full-time registration in the Ph.D. program. Student C spends less than 12 months in the M.Sc. program before transferring to the Ph.D. stream and is eligible to apply for federal funding up to 30 months of registered full-time Ph.D. studies. The asterisk (*) highlights the discordance between the number of application opportunities Student B is eligible for compared to Students A & C, despite identical durations spent in a graduate program between all three students. NSERC guidelines subject Student B to a similar disadvantage [4]. Illustration by the Author.

lar appeals were made with administrators at the Faculty of Medicine, but also to no avail. This ultimately rendered my glowing scholarship application, of which I was quite proud, completely and utterly useless. I felt cheated. After all, it was only paperwork hindering my scholarship eligibility.

After speaking to other graduate students about my experience, I was disturbed to discover that this was a recurrent problem. Poor timing of fast-track transfers at the Faculty of Medicine had afflicted several students before me and, with little doubt, others in preceding years. As such, many well-deserving students have been barred from applying to scholarships at the time when their academic dossiers are arguably at their pinnacle. Unfortunately, these students and their laboratories quietly absorbed their frustrations, ultimately leaving successive students susceptible to this technical trap. This was clear evidence outlining the damaged lines of communication between students, faculty members and administration.

Federally-funded graduate scholarships not only bestow prestige upon the awarded student, but they also benefit the laboratories and the academic institutions in which they are held. To illustrate this, consider the benchmark CIHR or NSERC doctoral research scholarship worth $21,000/year for up to 3 years [3, 4]. These awards are sufficient to finance the annual stipend of a doctoral student that would have been otherwise deducted from the operating grants of the host laboratory. If one considers that a typical laboratory often includes multiple graduate students, the sum of multiple student stipends can be a substantial financial burden on the sustainability and productivity of any given laboratory. With the help of externally-funded graduate scholarships, laboratories can direct greater resources toward the materials necessary to execute important research projects. In turn, the academic institution stands to benefit from increased research productivity. These are laudable advantages for all members of the academic institution at large.

Students work extremely hard to compile competitive scholarship applications. To support these efforts, and for the greater benefit of its academic community, the Faculty of Medicine must revise the current execution of fast-track transfers to maximize the duration of scholarship eligibility for its students. It is necessary to emphasize that the specific semester in which a student transfers to the Ph.D. program is unlikely to impact their education or academic achievements (as depicted in Figure 2). One might also appreciate that a first-year graduate student preparing for a transfer will rarely carry the foresight to consider their future funding eligibility. With a simple change of administrative practices, future fast-tracked Ph.D. students – some of the Faculty of Medicine's best and brightest – will never need to experience the deep disappointment of being unjustly excluded from national competitions when at the peak of their competitive edge.

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Ethics and stem cell research: The Knotty Business

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RESEARCH ETHICS: AN INTRODUCTION

Ethics is an important part of biomedical as well as clinical research. Prior to the First World War, there were no Food and Drug Administration (FDA) or Institutional Review Boards (IRBs) and hence, no set rules regarding the use of human subjects in research. The first significant sets of regulations were not put forth until the end of the Second World War. In 1946, a US military tribunal opened proceedings against a handful of German physicians for conducting crimes against humanity during the Holocaust [1]. Two years later, the Nuremberg Code was established, making voluntary consent of human participants mandatory, as well as declaring that the benefits of research must exceed its inherent risks [1]. In 1964, the Declaration of Helsinki followed suit and dictated that, in addition to voluntary consent, laboratory and animal experimentation must always precede research on human subjects. Ever since its conception, the declaration is revised on a regular basis [2].

Another scandalous case of human experimentation occurred in the United States between 1932 and 1972 [3]. The Tuskegee Syphilis Study, quoted as "arguably the most infamous biomedical research study in the history of the United States", was a clinical project conducted on low-income African-American males, of whom most were infected with syphilis [4]. The issue with the trial was that many of the subjects were denied penicillin treatment that had become available in the 1950s. Many participants later succumbed to the disease. To the government's embarrassment, the study was finally terminated in 1973 by the US Department of Health, Education, and Welfare after the story went public [3]. Despite being known for its lack of ethical conduct, this study played an important role in the formulation of a new set of guidelines, outlined in the Belmont report, which govern research on human subjects in the United States. Drafted in 1979, this report includes three main principles—(1) Respect for persons, (2) Beneficence, i.e. maximizing benefits and minimizing risks, and (3) Justice, i.e. equal and fair distribution of benefits and risks of research [5].

With the establishment of FDA, IRBs, and a number of documents that protect and respect the status of human participants in research, it was almost impossible to imagine anything that would penetrate the stout walls of ethical guidelines. In 1998, the very first human embryonic stem cells (hESCs) were derived from an embryo and cultured in a laboratory setting [6]. With the advent of an entirely new field of research, bioethicists around the world had to reconsider the current bioresearch guidelines, not only regarding research involving adult humans, but also in terms of defining the moral status of a human embryo. As a result, the ethics review boards underwent an overhaul to accommodate for rules and regulations regarding experimentation in this novel field of research. Fifteen years later, the use of hESCs in research is still a hot topic debated globally.

The field of stem cell research holds enormous potential for understanding human biology and for developing new treatments for incurable diseases. However, there are a few things to consider from an ethical standpoint. In this article, the ethical issues involved in hESC research are succinctly discussed both from a scientific and a religious/spiritual perspective. A brief discussion of iPSCs as a probable solution and alternatives of hESC research is also included.

A SCIENTIST'S PERSPECTIVE

Almost 15 years have passed since the derivation of the first hESC line. This field of research has made immense strides and is continuing to do so albeit at a slow pace. These stem cells are derived from the inner cell mass (ICM) of the blastocyst, approximately five days post-fertilization. From a scientific research standpoint, hESCs offer the greatest potential in terms of cellular differentiation—the point of origin, so to speak, of all the future cell lineages. This limitless potential is also termed the property of pluripotency. Due to this property, they are one of the primary regenerative tool candidates for the treatment of a variety of degenerative diseases involving diverse organ systems including bone, cartilage, nervous or immune and may even be used to treat diverse diseases such as Type 1 diabetes [7].

The non-scientific community often tends to wrongly associate hESCs with cloning. The mere mention of the word 'cloning' in any social setting is enough to set off a heated debate between the proponents and opponents of stem cell research. In fact, cloning simply describes producing identical copies of a single unit. For example, making identical cells from a single cell, something the human body does on a regular basis. Additionally, people tend to forget that stem cells are being used to treat leukemia patients on a daily basis. This treatment, which uses specific blood-derived hematopoietic stem cells, has been in use for almost half a century [8]. The scientific community believes that the public needs to be better educated about the science of stem cell research and the potential it holds for the treatment of diseases [9]. Realizing the therapeutic potential that stem cells hold requires large investment in research. In the United States, a majority of the funding is obtained through the federal government [9]. The commitment of funds not only helps to further develop the field in a direct way, but also strengthens public confidence and approval. In addition, public funding ensures sound

social policy by encouraging stem cell research topics that reflect social priorities, which might not be considered if the research is funded by the private sector alone [9].

Scientists believe that hESCs are morally equivalent to any other cell type in the body since they are obtained from the embryo, otherwise known as a collection of cells [10]. In Canada and the United States, hESCs used in research are obtained from pre-implantation embryos. These are reproductively unviable by-products of in-vitro fertilization, or so-called "spare embryos", that are used for research once informed consent and approval are received from the donor. This is a far cry from fears of assault on human life. However, for the communities who consider an embryonic stem cell to be a life form, this argument is redundant.

One of the major sources of confusion, which caused the ban of hESC research during the Bush administration, was the difficulty in differentiating between reproductive and therapeutic cloning. The former process, which resulted in Dolly the sheep, is unacceptable in humans. However, in the latter, no in utero implantation is performed, and therefore no 'cloned human being' is expected [11]. As previously mentioned, the biggest advantage of the pluripotent cells obtained from this embryo is their use in research. In 2009, the Obama administration gave a green light to the field of stem cell research by allowing generation of new hESC lines, in addition to the preexisting ones, for the sole purpose of research.

RELIGIOUS/SPIRITUAL PERSPECTIVE

In 2001, the head of the Roman Catholic Church, Pope John Paul II, told the former US President George W. Bush that hESC research is an evil practice akin to infanticide, euthanasia, and abortion [12]. In 2005, James Dobson, former Chairman of American organization called "Focus on the Family", compared scientists undertaking hESC research to Nazis. He mentioned that the discoveries made during human experimentation in the Holocaust might have benefitted mankind, but was undoubtedly not the right approach to do so [13]. Another instance worth quoting comes from an online religious organization called "Ontario Consultants on Religious Tolerance", based in Ontario, Canada. The website states that if a human embryo, two weeks after conception, is considered a person, then hESC research constitutes first-degree murder. However, if it is not a person, it is morally acceptable [14]. This statement and a plethora of statements made by a number of religious and cultural organizations leave a lot of loose ends and even more unanswered questions. The main question is: At what point post-conception is a human embryo really considered a human being?

Many religious communities believe that life begins at conception. They agree that an embryo or a fetus, in itself, is genetically human and possesses the potential to develop into a complete human being [15]. A question that is most concerning is whether it is even morally appropriate to manipulate or destroy a human embryo for the purposes of research and therapy. However, some traditions do believe that, although an embryo represents a human life, sacrificing one life in order to save and preserve other lives is acceptable [16]. Despite the difference in opinions regarding hESC research, the non-scientific community in general believes that adult stem cell research is a potential solution since it does not involve destruction or manipulation of a human embryo and because it makes use of an individual's resident stem cell populations to repair and regenerate damaged tissue.

iPSCS: THE SOLUTION?

Somatic cell nuclear transfer (SCNT) is a therapeutic cloning procedure that involves isolation of nuclear material from a somatic cell and transferring it into an enucleated oocyte, thereby generating a "non-traditional" embryo [17]. While these embryos are strictly prohibited for in utero transfers, the very nature of SCNT research involved is rife with ethical concerns and is enough to set off a debate regarding human cloning. In 2006, however, the regenerative medicine community around the world was left awestruck when Japanese clinician-scientist Dr. Shinya Yamanaka and colleagues successfully reprogrammed mouse skin fibroblasts back to their pluripotent stem cell state (termed induced pluripotent stem cells or iPSCs) using a cocktail of genes [18]. This was subsequently reproduced the following year in adult human skin fibroblasts. These iPSCs were initially thought to be an "ethical dilemma-free replica" of ESCs and it was assumed that iPSCs could replace hESCs. Unfortunately, the substitution of hESCs to iPSCs does not appear to be that straightforward. Although both cell types are pluripotent in nature, they do exhibit differences at the epigenetic level (gene expression changes that do not involve a change in the sequence of DNA). Dr. George O'Daley, a senior clinician-scientist at the Harvard Stem Cell Institute in Boston, believes more research on iPSCs is required in order for these cells to be labeled as a safe replacement for hESCs in research and therapy [19].

Some researchers do, however, believe that iPSCs will replace the need to use hESCs. Yamanaka however, believes that to every pro in research, there exists a con. "Now, we can avoid using human embryos. So that is very good," he mentioned to the Toronto Star in October 2009 [20]. "But, at the same time, we can make germ cells—sperm or egg, from iPSCs. So potentially, we can make new life from skin. That is the biggest ethical issue" [20]. In addition, the low cost of generating iPSCs and the ease of accessibility to somatic cells would propound the need to generate gametes in the future [21].

EXTINGUISHING THE FIRE: THE SEARCH FOR NON-EMBRYONIC ALTERNATIVES

A number of scientists around the world are trying to quench the fiery debate involving hESCs by moving away from methods that involve the destruction of human embryos.

Dr. Mick Bhatia, a scientist at McMaster University's Stem Cell and Cancer Research Institute, published a study in which they bypassed the embryonic stage altogether by reprogramming adult skin cells to progenitor blood cell types. These cells would be used to replenish the blood supply of cancer patients follow-

ing chemotherapy [22]. Another Canadian scientist, Dr. Freda Miller, hopes to find new ways of activating and mobilizing the body's own resident stem cell populations to repair damaged tissue [23]. She proposed using neural stem cells to stimulate growth of neurons in hopes of replacing neurons damaged by stroke and other neurodegenerative diseases [23]. Another source of stem cells being considered for therapeutic use is amniotic fluid or umbilical cord [24, 25]. This field, although in its infancy, is promising mainly because the cells could be harvested at an early developmental stage [24, 25]. However, more research is required in order to confirm the potency of stem cells derived from these sources.

CONCLUSION

A vast majority of Canadians and Americans (approximately 60%) agree that the human embryo deserves moral respect and a special status [8]. However, they also believe that if appropriate measures are in place, the benefits of using hESCs supersede [8].

As it stands, it is safe to assume that the potential of hESCs in treatment of various diseases is unparalleled. Despite the introduction of iPSCs and other non-embryonic sources of stem cells, hESCs are the only pluripotent cell type that have been approved for clinical trials, and therefore remain the 'gold standard' of human stem cell research. If hESC research can be properly regulated, approval of such research by the general public may be increased. Unfortunately, as religion and culture coexist in our society, having a consensus on difficult ethical issues such as the use of hESCs is, as they say, a Herculean task.

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Genetically engineered bacteria as cancer fighting agents

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ABSTRACT

The objectives of this paper are to review recent developments in using bacteria as cancer fighting agents. This new and exciting field of research has shown promising results. The most advanced and well-studied genetically engineered bacteria are discussed here. These bacteria have effectively been used to visualize tumours using bioluminescence or diagnostic imaging technologies, and to treat tumours through direct cell killing, bactofection, and alternative gene therapy. Because of the positive outcomes seen in vitro and in animal models, many of these genetically modified bacteria are currently being taken to clinical trials. Overall, using genetically engineered bacteria to combat cancer is a promising and growing area of research, and will hopefully lead to new and better treatments for cancer patients in the near future.

RÉSUMÉ

Le but du présent article consiste à faire une revue des plus récents progrès dans l'utilisation de bactéries comme agent de lutte contre le cancer. Ce nouveau domaine captivant de recherche a montré des résultats prometteurs. Cet article porte sur les bactéries génétiquement modifiées les plus poussées et les mieux étudiées. Ces bactéries ont été utilisées avec succès pour visualiser des tumeurs grâce à la bioluminescence ou les techniques d'imagerie diagnostique. Elles ont aussi été utilisées pour traiter des tumeurs par l'entremise de la destruction directe de cellules, la bactofection et la thérapie génique. Grâce aux résultats positifs obtenus lors des essais in vitro et avec des modèles animaux, plusieurs de ces bactéries génétiquement modifiées font maintenant l'objet d'essais cliniques. Dans l'ensemble, l'utilisation des bactéries génétiquement modifiées dans la lutte contre le cancer est prometteuse et constitue un volet de recherche en pleine progression. Il est espéré que cette recherche mènera bientôt à de nouveaux et meilleurs traitements pour les patients atteints de cancer.

INTRODUCTION

Cancer is the most prominent cause of death in developed countries, with over 12 million people worldwide being diagnosed each year. Current conventional cancer therapies such as chemotherapy, radiation, and surgery, havemany negative side effects, and patients will oftenrelapse [1, 2].New cancer treatments are being developed in order to more specifically and effectively target cancerous tissue, which would reduce side effects and help to completely eradicate tumours. One such method is the use of live, attenuated, genetically engineered bacterial strains to visualize, selectively target, and act as anticancer agents in vivo. The idea of using bacteria as a cancer therapy startedin 1890, whenAmerican surgeon William Coley treated cancer patients with "Coley's Toxin",comprised of heat-killed Streptococcal organisms and Serratiamarcescens, and observed tumour regression [1, 3, 4]. Since then, scientists have discovered that engineered anaerobic or facultative anaerobic bacteria can selectively target tumours due to thehypoxic and necrotic environments within them, which are necessary for the survival of these bacteria[1-5].Genetically engineered bacterialocalize and grow exclusively in cancerous tissue. This means that they can be used to visualize tumours usingbioluminescence or diagnostic imaging technologies. They can also be used to treat tumours through direct cell killing, alternative gene therapy and a mechanism called bactofection, in which bacteria are used as a vector to deliver genes.

METHODS

A total of sixdatabases:PubMed, Medline/OVID, Biological Abstracts, Scopus, Web of Science, and Google Scholarwere used to search for articles relating to the topic. Articles were selected for if they were written in English and published in January 2010 or later.Reviewing thetitle and abstract of each paper was the preliminary method for consideration, which then led to selected articles being thoroughly analyzed. This resulted in some initial papers beingexcluded if their topic was covered in a more recent with additional information to offer. In a few instances, papers were excluded due to uncertainties found while reading through the methods, results, or discussion.For the purpose of composing this review paper additional background information was derived from some older sources published as early as 1997. Sample search terms include "bacteria AND cancer therapy", "imaging AND bacteria AND cancer". Of the approximately 80 original articles reviewed, 54 were included in this review, and thereforethis paper reflects a qualitative review of the evidence-based literature.

SHORTCOMINGS OF CONVENTIONAL CANCER THERAPY

Two major shortcomings of current conventional cancer therapies are hypoxia-related resistance, and toxicity to healthy tissue. These differences in tumours can cause problems for certain cancer therapies and one example of this is how hypoxia leads to treatment resistance for many anticancer drugs and radiotherapy. Many systemic treatments currently used, such as chemotherapy, immune therapy, viral therapy, and targeted therapy,are toxic to both healthy tissue and cancerous tissue [6]. Often, patients are not able to receive systemic therapy because they are too unwellfor treatment, as classified by the ECOG performance status (see Appendix for explanation of scoring). An ECOG performance score of 0-2 deems the patient well enough toundergo systemic chemotherapy, whereas a score of 3+means systemic therapy is not recommended as there is a high chancethat the treatment will do more harm than good.

IMAGING OF TUMOURS

Various imaging techniques have been used to more effectively visualize cancerous tumors. Currently, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans provide the best contrast and resolution, but are very expensive. The contrast dye is often toxic to the kidneys and makes patients feel unwell. Improvements in imaging would not only make patient more comfortable, but would also help improve contrast, resolution, and potentially decrease the amount of malignancies that areoverlooked. Bone scans areused in cancer patients to determine if the tumour has metastasized to the bone. Because these techniques are expensive, patients are usually screened or observed on a routine basis using ultrasound technology. Ultrasounds, however, are not as useful since they can only observe structures close to the surface of the body. Moreover, the accuracy of the findings depends on the availability ofspecially-trained individuals to adequately and accurately analyze the low resolution images (Figure 1).

SELECTIVE REPLICATION

The exact process of how several bacterial species selectively infiltrate and replicate within tumours is unknown. The vasculature in tumours tends to be leaky, leaving large gaps between the endothelial cells of the vessel walls. These gaps are large enough for bacteria toaccess the tumourboth passively and actively usingchemotaxis. Bacterial infection induces the production of inflammatory cytokines such as tumour-necrosis factor alpha (TNF-α) within the tumour, which increase vascular permeability [5, 7]. The immune-suppressed micro-environment of the tumour provides protection from the host's immune system which,in combination with the anaerobic and nutrient-rich necrotic environment, leads to bacterial colonization of the tumour. However, these genetically engineered bacterial strains tend to only colonize the inner hypoxic and necrotic areaswithin the tumour, as the outer rim receives adequate blood supply [5, 7-10]. Bacteria that are found in other parts of the body tend to be cleared by the immune system. For example, one strain of Salmonella has a replication ratio of 1000:1 - tumour to healthy tissue [1]. Damage to healthy tissue by these bacteria is therefore limited, and if the bacteria colonize undesired areas, antibiotics can be used to successfully clear them from the body.

BACTERIA FOR TUMOUR VISUALIZATION

Many bacterial strains have been tested for their use

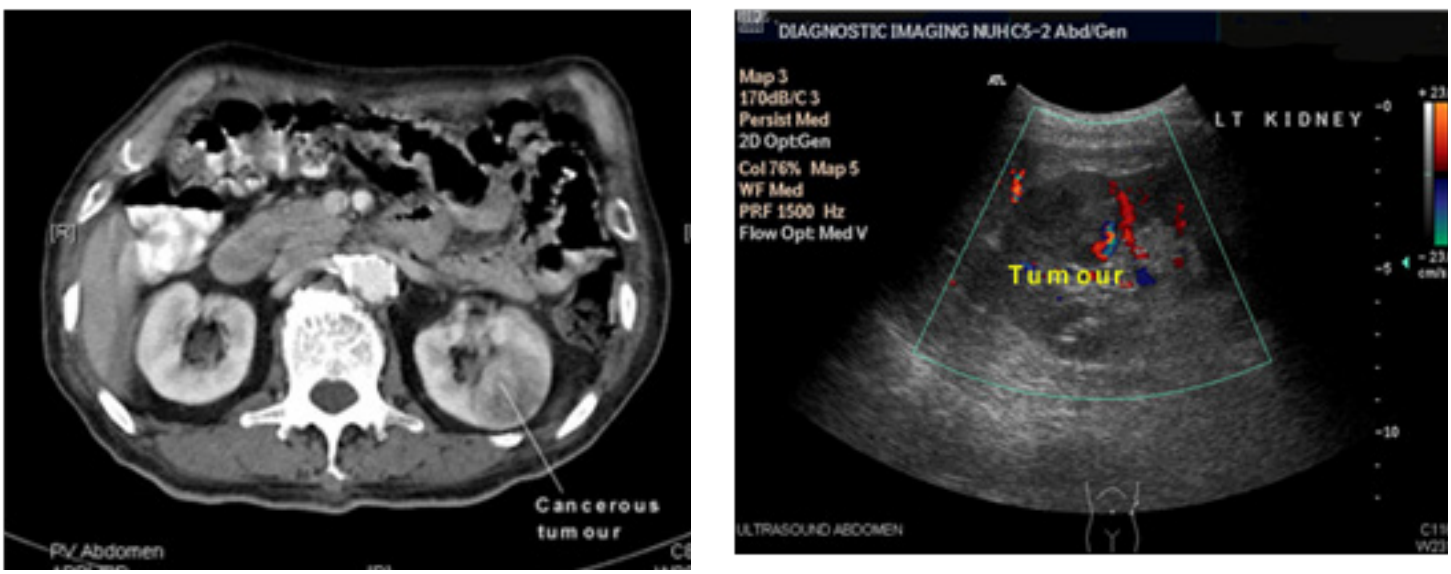

Figure 1: A kidney tumour depicted in both images, on the left is a CT scan and on the right is an ultrasound, adapted from C.C. Min, 2013. It can be observed that the CT scan provides an image with a higher contrast and resolution compared to the ultrasound.

in visualizing tumours through bioluminescence, with green fluorescent protein (GFP) and the bacterial lux system, as well as with magnetic resonance imaging (MRI)using magnetotactic bacteria. Bioluminescent imaging (BLI) is a powerful visualization tool that uses a plasmid to express luminescent genes such as GFP or lux. The LuxCDABE operon produces light at a wavelength of 490nm and does not require the addition of a substrate in order to do so [11]. In earlier studies, pathogenic strains of Salmonella typhimurium containing the lux operon were used, but these bacteria localized in the abdomen and neck in addition to the tumour. It was later found that non-pathogenic strains are less likely to colonize healthy tissue, which may be due to their inability to effectively adhere to or infect host cells[11]. For example, non-pathogenic strains of Escherichia coli K-12, Bifidobacteriumbreve, and S. Typhimurium that were transfected with a plasmid containing the lux operon werefound to only localize within the tumour[12]. Hayashi et al. in 2009 labeled multiple bacterial strains with GFP and observed similar tumour-targeting abilities in vivo[13]. Firefly luciferase is another common BLI gene being studied at this time and this protein catalyzes reduced luciferin to create yellow-green light of wavelength 562nm among other products [11].

The use of Magnetotactic bacteria such as Magnetospirillum magneticum AMB-1 allow for tumour visualization using MRI due to their magnetosome, an organelle that stores iron [14]. The magnetosome significantly affects transverse relaxation of MRI, thus producing a highly contrasted image of the tumour. Studies done in mice show an increased contrast in MRI images using AMB-1 and this is currently being considered as a potential tool for locating and tracking cancer progression [14]. Similarly, overexpression of bacterial ferritin-like storage proteins such as the bfr gene products can elicit the same effect. The bioluminescent and iron-storage genes have inducible promoters that can be induced by exogenous ligands such as L-arabinose, allowing for external control over their expression [11, 15].

Both of these methods are non-invasive, but bioluminescence technology, being more affordable and accessible than MRI, may have more potential as a widespread diagnostic tool in cancer. The quality of BLI images are limited by light scattering and absorption by the tissues as well as being two-dimensional, therefore lacking depth and spatial resolution. The lux system does not have the issues with light scattering and absorption, but is now being combined with CT scanning to obtain a 3D high contrast image [11]. The magnetotactic MRI images have more contrast and spatial resolution compared to normal MRI tumour imaging. Both of these methods to obtain bacterial distribution and cell numbers overcome the ex vivo analytical methods which are both time consuming and expensive.

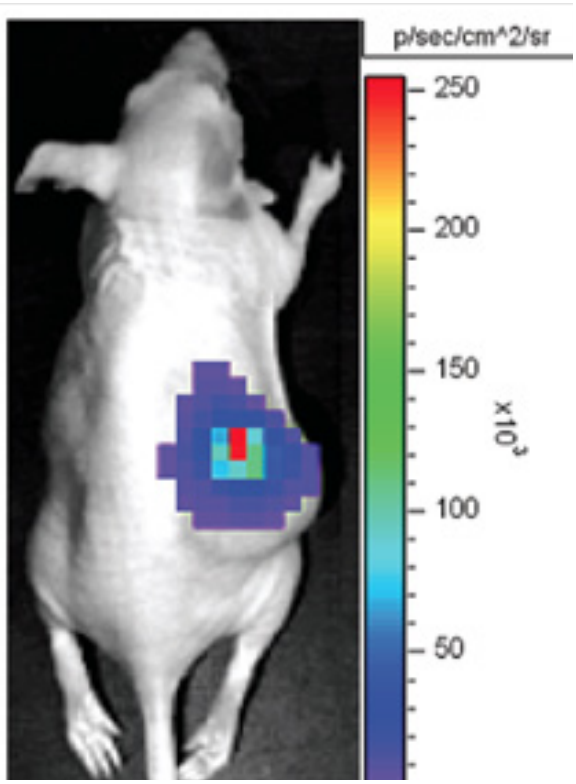

Figure 2. Image of a BLI scan on a rat adopted from Baban et al. 2010. The rat was injected with Bifidobacteriumbreve expressing the luxADCBE system. Thisbacteria is shown to specifically colonize a lung carcinoma that was injected into mice subcutaneously.

TREATMENT: DIRECT CELL KILLING

Direct cell killing involves live replication competent bacteria such as Clostridium and Salmonella, which mainly rely on their natural oncolytic activity to eliminate tumours [2, 8]. Many of these strains release toxins that either kill cells directly through lysis or protein synthesis inhibition, or interfere with the cell cycle inhibiting its progression. For example, Clostridium perfringens type A strain produces an enterotoxin (CPE), which has been shown to exert a cytotoxic effect on pancreatic tumour cells, leading to necrosis and inhibition of tumour growth [16]. Patyar et al. speculate that plasmids may be introduced into these strains, containing additional genes that encode toxins found in a different species, in order to enhance their lethal effect. Despite their treatment potential these bacteria can also harm normal tissues and thus a more efficacious method being studied is Bactofection.

TREATMENT OF TUMOURS: BACTOFECTION

Bactofection usesnon-invasive bacteria as a vector to deliver therapeutic cytotoxic genes localized on plasmids into cancer cells to induce cell death. This delivery process either requires bacteria to directly enter the cancer cell, or the use of a conjugational apparatus. Ideal therapeutic proteins for conjugation consist of anti-angiogenic molecules,

apoptosis-inducing genes, and toxins [2, 16, 17]. For example, S. choleraseuis transfected with a plasmid containing the endostatin gene, an endogenous angiogenesis inhibitor, inhibited tumour growth by 40-70% by decreasing tumour vasculature and expression of vascular endothelial growth factor (VEGF) [17]. Salmonella strains are the most widely used in bactofection studies, and have been effectively used in experimental models consisting of plasmids carrying cytokine interleukin genes [18]. These genes induce tumour cells to express and release large amounts of cytokines that help stimulate an immune response against them. In another study, non-pathogenic Escherichia coli strain BL21(DE3) expressing the anti-HER2 affibody on its surface allows selective internalization into HER2 positive cancerous cells. This E. coli strainalso contains the phage φX174 lysin gene, which triggers the autolysis system of the tumour cell upon thermal shock, and the eukaryotic GFP to allow for visualization [19].

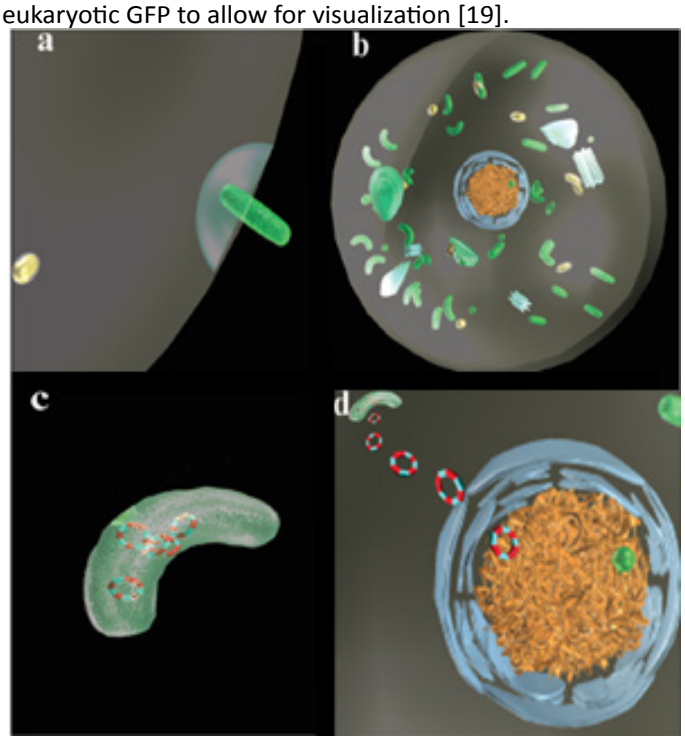

Figure 3. Image depicting bactofection adopted from Baban et al. 2010. a): the bacterium invades the cell. b) Bacterial vectors escape from phagosome and replicate in the bacterial cell. c) Lysis of the bacteria facilitates release of therapeutic DNA into host cell. d) Therapeutic DNA plasmid may be randomly make its way into the nucleus where it can be transcribed.

A similar method of cancer treatment uses viral vectors to transport therapeutic genes directly into the nucleus of tumour cells for integration into the DNA. In bactofection, plasmid trafficking into the nucleus is considered the rate-limiting step. To compensate,some bacteria cantranscribe the therapeutic genes intomRNA containing eukaryotic transgenes, and release it into the host cell's cytoplasm for translation [2, 16]. Viral vectors can insert 8-10kB, whereas plasmids can contain

Table 1: Comparison of viral and bacterial vectors in cancer therapy. Adapted from Palffy et al. 2006 [20].

	Viral Vectors	Bacterial Vectors
Safety	+	+
Efficiency	+++	+
Inexpensive	+	+++
Ease of production	+	+++
Ease of delivery	++	+++

up to 15kB. Bacterial artificial chromosomes (BAC) can contain up to 150kB inserts and may be used in the futureto allow the expression of more therapeutic genes [20]. However, the amount of DNA that can currently be recombined into a plasmid is a limitation of both viral and bacterial vectors. Furthermore in direct contrast to viral vectors, bacteria can readily be terminated from the human body by antibiotics making them a safer treatment option for cancer patients.

TREATMENT: ALTERNATIVE GENE THERAPY

Alternative gene therapy (AGT) uses genetically engineered bacteria that are transfected with plasmids containing genes encoding desirable therapeutic proteins, cytotoxic peptides, anticancer agents, and pro-drug converting enzymes [1, 2, 16, 17]. Unlike bactofection, AGT uses bacteria that produce the therapeutic polypeptide in situ stimulated by low molecular weight inductors, and thus offers more control over the treatment [20]. A number of anticancer genes have been successfully cloned into Bifidobacteriumand Salmonella plasmids. One of the most influential genes being an apoptosis-inducer called tumour-necrosis factor-related apoptosis-inducing ligand (TRAIL) [1, 2]. The results of one study using a plasmid containing the gene for TRAIL transfected into Bifidobacterium

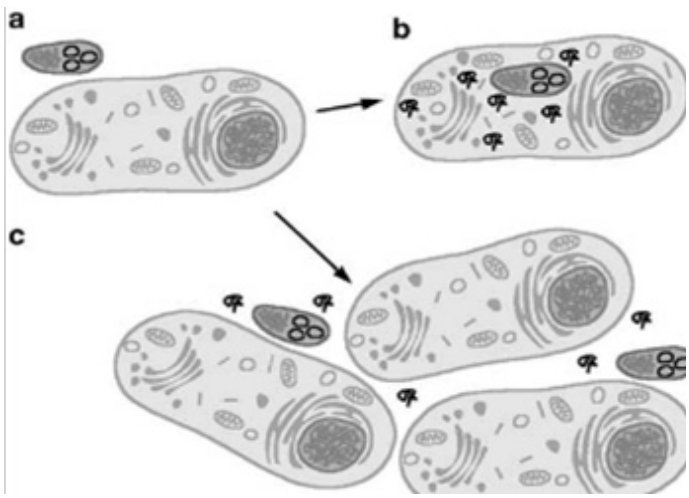

Figure 4. The figure above, adopted from Palffy et al. 2006 [20], shows how alternative gene therapy works. a) The bacteria istransformed with plasmids containing the therapeutic transgene. b)Transgene expression occurs within the bacterium once it penetrates the cancer cell. c) Transgene expression occurs in the bacterium and is exocytosed into the interstitial space.

resulted intumour volume reduction by 82.6% [21]. Many other therapeutic proteins used in AGT tend to target apoptosis, angiogenesis, cytokines, and pathways inhibiting the cell cycle. The prodrug therapy strategy uses plasmids expressing an enzyme that can convert a non-toxic prodrug into a toxic cancer-killing drug. Since tumour-targeting bacterial strains are only found within the tumour itself, the prodrug can only be activated within the tumour and thus, beneficially, eliminates toxic effects to healthy tissues normally seen with a systemically administered drug [2, 17]. Another promising example of AGT is described in Minton's review article using clostridium transformed with the cytidine deaminase (CD) gene, which converts 5-fluorocytosine (5FC) to 5-fluorouracil (5FU) [22, 23].

The use of bacteriain AGT requires its persistence in the target tissue to elicit anticancer effects. A major issue associated with this is the toxicity of the required dose for effective therapeutic results. A key aspect of AGTis the ability to control expression of the therapeutic proteins through inducible promoters. This ensures the bacteria do not act in any other tissues within the first few hours when the bacteria are not yet localized to the target tumour. Despite the ability to control trans gene expression, Stritzker et al. found that bactofection proved to be more efficient than AGT when using Listeria monocytogenes[24]. This may be due to the fact that bactofection uses more virulent strains to allow for better bacterial invasion, which results in a superior long-term effect unlike AGT, where bacteria must persist in the tumour throughout therapy to be effective.

CLINICAL STUDIES

Many bacteria in each of these therapeutic approaches have been taken to clinical trials (Table 2, 3) and some of the significant clinical trials are described below.

Table 2: Genera of bacteria well studied in each therapeutic approach, adapted from Palffy et al. 2006. [20]

Therapeutic Approach	Suitable Species	References
Direct Cell Killing	Clostridium, Salmonella	[25-28]
Bactofection	Salmonella, Listeria,	[29-31]
	E. coli, Clostridium	[32-33]
Alternative Gene Therapy	Bifidobacterium	[18, 34, 35]

The live attenuated S. typhimurium strain VNP 200009 has completed Phase I clinical trials. It uses direct cell killing to elicit tumoricidal effects and has been successful in treating advanced or metastatic solid tumours [36]. Other live attenuated bacteria like Clostridia and Bifidobacterium will likely undergo human clinical trials soon. New strains starting preclinical research as tumoricidal direct cell killing agents are Salmonella choleraesuis, Vibrio cholerae, and Listeria monocytogenes [23].

The Clostridium Novyi-NT strain is currently in Phase I clinical trials for treatment of chondromas. It is incapable of producing its exotoxin, which protects the patient, and has been shown to destroy hypoxic tumours and force certain types of cancer, namely chondromas, into complete remission. It was shown in preclinical trial phase that 30% of mice were completely cured, and all had a significant response to the bacteria [37]. The bacterial infection is contained to the site of the tumor and the inflammatory response contributes to the destruction of tumour cells via the production of reactive oxygen species, proteases, and other degradative enzymes [38].

Bactofection has been used successfully in studies with mice to treat melanoma, colon carcinoma, and lung carcinoma. One example is the strain Salmonella choleraesuis used to target melanoma by targeted gene delivery using thrombospondin-1. This approach significantly reduced tumour growth in the melanoma model [39, 40]. S.typhimurium producing CD is currently in phase II clinical trials and significantly improved colorectal cancer patients and induced remission [41, 42].

Salmonella strains combined with either nitroreductase (NR) or CD are undergoing phase I clinical trials in cancer patients with success observed in vivo. TAPET (Tumour Amplified Protein Expression Therapy) uses VNP20009, discussed above, in addition to expressing an E. coli CD, which preferentially delivers CD and other anticancer drugs to tumours (43). VNP20009, which selectively colonizes colon tumours, can express the prodrug-converting enzyme HSV-thymidine kinase (TK). Also, expression of HSV-TK enhances antitumor activity when its corresponding prodrug, ganciclovir, is also introduced [44,45].

Bacterial proteins and toxins are now being experimented with to interfere with cancer cell growth. One such protein called ATP-01 has shown to induce tumour regression in breast cancer patients and has been proven to have anti-HIV characteristics. Another protein, azurin p28 is in phase I clinical trials and has shown significant benefits with little toxicity to the patient. In many instances, p28 has been shown to cause partial or complete regression of metastatic solid tumours in stage IV cancer patients who have tried other therapies without any success [46].

Protein toxins such as diphtheria and Pseudomonas exotoxin are potent cell killing agents and so they must be targeted for use in cancer therapy to avoid harm of healthy cells. So far, they have been conjugated to cell-binding proteins such as growth factors and monoclonal antibodies, thus binding and killing cancerous cells while sparing healthy, normal cells [47]. A phase I clinical trial for treatment of malignant astrocytoma using a recombinant interleukin-4-Pseudomonas exotoxin (IL4-PE) is underway, after significant results

Table 3: Relevant clinical trials, the phase and status listed below with the various cancers being treated. Adapted from Patyar et al. 2010 [23].

Therapeutic Strain	Clinical Trial Phase	Status	Disease Conditions
VNP20009- S. typhimurium	Phase I	Completed	Advanced or metastatic solid tumours [36]
Clostridium Novyi-NT	Phase I	Ongoing	Chondroma [37]
TAPET – CD: VNP200009 expressing E. coli CD	Phase I	Completed	Head, neck, and esophagus cancer [36]
Tf-CRM 107: transferrin-diptheria toxin conjugate	Phase I	Ongoing	Brainentral nervous system tumours [47]
IL4-PE: interleukin-4-Pseudomonas exotoxin	Phase I	Ongoing	Brain entral nervous system tumours [48]
IL 12-PE: Interleukin-13-Pseudomonas exotoxin	Phase I	Ongoing	Malignant glioma, glioblastomamultiforme, anaplastic astrocytoma, anaplastic oligoden droglioma, mixed oligoastrocytoma [49]

were found in mice with glioblastoma[48]. Some other important PE conjugates currently in clinical trials include IL-13 and a monoclonal antibody that recognizes a carbohydrate antigen on metastatic adenocarcinoma cells [49].Lastly, two diphtheria toxin conjugates are also of significance and in clinical trial stage I for treatment of brain tumours and metastatic carcinomas [50].

FUTURE DIRECTION OF BACTERIAL USE IN CANCER THERAPY

Tumour-targeting bacteria are being developed to overcome the limitations of conventional cancer therapy. The necessary and specific advancements of cancer therapy include improving gene delivery through novel vectors, improving specificity in the targeting of tumours, and reducing treatment toxicity to the patient to thus improve the therapeutic index of these novel treatments. Bacterial cancer therapies are not intended to replace conventional therapy but to create new treatment strategies incorporating their use [51]. Increasing the number and variety of available treatment options fordifferent cancers may facilitate more patient-focused therapy, allowing for improved remission and survival rates. These novel therapies can also provide an alternative when current methods fail to provide an adequate anti-cancer effect in the patient. Techniques involving bacteria are also more economical than viral vectors, and are a low-cost alternative to many therapies currently employed for use in cancer treatment.

Tumour imaging is moving towards combined modality use to increase the amount of detail obtained. As current technology improves, becomes more available and cost effective, it is being complemented by new imaging techniques such as BLI and the use of magnetotactic bacteria in MRI. Since no current diagnostic imaging such as CT, MRI, or PET give a comprehensive picture of a tumour, BLI and magnetotactic bacteria can be used to help gain additional vital information. BLI alone has its limitations, which include two-dimensional imaging lacking depth, poor spatial resolution, light scattering, and absorption by the tissues. However, combining this method with CT scanning helps to obtain a 3D high contrast image, but more research into this technology is warranted in the future [11]. For animal models, combined PET/CT and BLI/CT scans have been observed to obtain more information from a single scan on a single subject, providing a more comprehensive picture, while also being more efficient and cost effective [52].

An important issue to address regarding these new bacterial cancer treatments is the potential for these therapeutic bacterial strains to acquire antibiotic resistance, in which case they may no longer be approved for use as a cancer therapy. Should the patient develop an infection bacterial strains can be easily eradicated with antibiotics,making them safer than other transport vectors like viruses. However, some side effects have been noted due to the interaction between the immune system and the therapeutic bacterial strains;further investigation and testing in this area is required to improve the safety of these noveltherapies. Future studies may focus on understanding the underlying mechanism of the antitumor effects mediated by bacteria involving patient immune responses, in addition to evaluating their effectiveness [6].

Lastly, many of these new bacterial therapies do not completely eradicate tumours. Therefore, the combination of therapy with chemotherapeutic treatments is still necessary at this time. Bacterial therapies can have either adverse or beneficial effects when used in combination with other anti-cancer therapies. For example, some of the bacteria that affect angiogenesis have been shown to reduce the efficacy of other anti-cancer drugs [54]. There has been some proof of the “bystander effect” when using bacterial therapy and certain chemotherapeutic agents which provide an extra anti-cancer effect to the tumour [6]. A last major concern is the potential of the engineered bacteria to acquire DNA mutations in their therapeutic genes. If these mutations create any loss of functionality they may lead to a wide variety of problems such astherapy failure, infection, and other unwanted negative effects [23].

CONCLUSION

In recent years, many advances have been made us-

ing genetically engineered bacteria for cancer therapy. Certain strains can elicit anti-cancer effects through direct cell killing, bactofection, and alternative gene therapy as described in this review article. However, the success in many studies is just beginning to be translated into human clinical trials. Although much of the preclinical researchis promising, further investigation and development of bacterial cancer therapy is necessary to overcome its limitations, improve safety and efficacy, and reach its full potential. In the future, genetically engineered bacteria will likely be used for cancer therapy in combination with current therapies to achieve the desired synergistic anti-cancer effects and thus improve cancer survival and remission rates.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

A major strength of this paper is that it highlights the most relevant and promising research on well-studied bacteria for use in cancer diagnosis and therapy. It explains and summarizes the variousbacterial techniques used to image and treat cancer, and gives suggestions for future research. A limitation of this review is that not all relevant studies and papers were included and no studies that may have negative evidence towards bacteria as cancer-fighting agents were included. The more reliable and relevant studies in medicine are those that have been brought into clinical trials and demonstrate significant effects observed in human cancer patients. Some studies discussed were new and need more work. As this is a rapidly growing area of research, many of the items in this review are being improved upon in ongoing studies. Should this review prompt you to seek more current information, further literary inquiries are recommended.

APPENDIX

ECOG (Eastern Cooperative Oncology Group) Performance Status is used by physicians to measure a cancer patients' well-being and activities of daily living, in order to make decisions about further treatment and palliative care.

Grade	ECOG
0	Fully active, able to carry on all pre-disease per formance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

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Pulmonary Hypertension: Difficult diagnosis, challenging prognosis, poor outcome

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ABSTRACT

"We all let her die" is the title of a Toronto Star news article published in April 2006. This news article described the story of Brooke Di Bernardo, a 14-year-old that passed away from advanced stage pulmonary hypertension after being misdiagnosed for four years. In light of this story, the following manuscript will discuss pulmonary hypertension in terms of its symptoms, diagnosis, causes, incidence, classification, pathology, as well as current and future treatments.

RÉSUMÉ

« We all let her die » (Nous l'avons tous laissé mourir) est le titre d'un article paru dans le Toronto Star en avril 2006. Cet article de presse décrivait l'histoire de Brooke Di Bernando, une jeune femme de 14 ans décédée des suites d'une hypertension pulmonaire à un stade avancé après avoir fait l'objet d'un diagnostic erroné pendant quatre ans. À la lumière de cet article, le présent manuscrit discutera de l'hypertension artérielle pulmonaire en fonction des symptômes, du diagnostic, des causes, de l'incidence, de la classification, de la pathologie et des traitements actuels et futurs.

"WE ALL LET HER DIE!"

A competitive swimmer and a horse enthusiast, Brooke was an excellent athlete [1]. However, at the age of 10, Brooke started to experience shortness of breath and fatigue after only a short ride. After being admitted to the hospital, the doctors were able to rule out a few of the common possibilities for her symptoms, including asthma, allergies and hormonal imbalance, but failed to give a definitive diagnosis. Unfortunately, Brooke's symptoms continued to worsen and she started experiencing episodes of flushing from doing simple chores, followed by turning pale, and eventually fainting. Several more trips to the hospital resulted in yet more negative tests, including an echocardiogram (ECHO) that revealed no cardiac abnormalities. At this point, Brooke was referred to a psychiatrist for evaluation, and they suggested that her symptoms were merely a plea for attention. Brooke continued to suffer through two more years of shortness of breath and exhaustion until, after one of her worst episodes, she was transferred to Sick Kids hospital in Toronto. An X-ray and ECHO analysis were conducted and revealed that her right ventricle was enlarged and her left was failing. The doctors were able to diagnose Brooke with a very rare disease: advanced stage pulmonary hypertension (PH). At this point, the physicians considered a lung transplant for Brooke. Unfortunately, she passed away from heart failure within 24 hours of her diagnosis [1].

WHAT IS PULMONARY HYPERTENSION?

Although technology-enhanced simulation has been used in mCompared to the systemic circulation, the pulmonary circulation has low resistance but can accommodate a high flow [2, 3]. Moreover, the smaller arterioles have a very delicate structure, composed only of a thin single layer of endothelial cells (ECs) [3]. These unique properties allow for gas exchange and reoxygenation of blood in the lungs [3]. Consequently, disruption of this delicate balance can lead to several possible disease states, PH included. PH is a syndrome that results from restricted flow through the pulmonary circulation, thus leading to increased pulmonary vascular resistance [4]. PH is characterized by degradation of the smaller pulmonary vessels, remodelling and occlusion of the larger pulmonary vasculature, endothelial cell dysfunction and vasoconstriction [2, 5]. In response to the increased afterload, the right ventricle (from which originates the pulmonary circulation) undergoes compensatory changes such as hypertrophy and remodelling [5]. Eventually, the right ventricle enlarges to the point where the hypertrophy is maladaptive, leading to decompensation and failure.

PH: SYMPTOMS AND DIAGNOSIS

The non-specific and general nature of symptoms presented plays a large role in misdiagnosing the earlier stages of PH. At these early stages, patients merely experience unexplained dyspnea and decreased exercise tolerance [3] . Therefore, the low incidence rate and absence of significant cardiac abnormalities at the earlier stages explain why PH is more likely to be missed. As the disease progresses, patients can suffer from syncope and peripheral edema, making it more likely for PH to be diagnosed successfully, however it becomes more challenging to treat [3, 6]. To confirm a PH diagnosis, the pulmonary artery pressure (PAP) is directly measured by right heart catheterization (RHC), in which a balloon-tipped catheter is advanced through the jugular vein and into the pulmonary artery [3]. PH is defined the following measurements: a mean PAP ≥ 25mmHg at rest, reduced cardiac output and pulmonary vascular resistance greater

than 3 Wood Units combined with pulmonary capillary wedge pressure ≥15mmHg [4, 7]. A RHC is required to confirm the diagnosis, classification and assessment of severity of PH [7]. Other methods of PH assessment include ECHO and chest radiography. However, unless it is in the later stages, it is very difficult to detect PH using these methods. Thus RHC remains the gold standard for PH diagnosis [3, 7].

PH: CAUSES, CLASSIFICATION, INCIDENCE AND PREVALENCE

Since its discovery nearly a century ago, significant progress has been made in terms of classifying PH. According to the most recent and updated classification of the World Health Organization, PH is divided into several categories based on the pathologic and genetic origins of the disease, as well as the type of the associated disease (Table 1) [8]. The first PH group describes Pulmonary Arterial Hypertension (PAH), which is associated with structural abnormalities to the pre-capillary pulmonary arteriolar microvessels [3, 8]. The prevalence of PAH is about 6.6-15 cases per million adults while its incidence rate is 1.1-2.4 cases per million per year according to the most recent epidemiology studies in Europe [9, 10]. PAH can be further sub-classified into idiopathic PAH (IPAH), when the cause of the disease is unknown and the hypertension occurs as a primary disease process [8]. IPAH accounts for almost 46% of PAH cases in the United States according to the REVEAL registry, the largest PAH registry to date [11]. IPAH is most likely the type of disease Brooke Di Bernardo was exhibiting since it usually occurs in younger individuals without showing any pattern of inheritance or family history. On the other hand, PAH can be hereditary and has been reported to have an autosomal dominant pattern of inheritance, mainly linked to mutations in the Bone Morphogenetic Receptor Type II (BMPR2) gene [8]. PAH is classified under the third subtype when it is drug or toxin induced [4, 8]. Examples of such drugs include anorexigens, which are appetite suppressant drugs that contributed to a PAH epidemic in Europe in the 1960s [4]. PAH can also occur in association with other diseases, such as HIV infection or congenital heart disease, and has a higher prevalence in patients with connective tissue diseases [8, 11]. When PAH occurs as a secondary disease process, it is classified as associated PAH [8]. PH can appear in association with left heart disease, in which case it would be classified under the second group [8]. In the third group, PH appears as a result of lung disease such as chronic obstructive pulmonary disease (COPD), emphysema or chronic exposure to high altitude [8]. PH can also occur after a pulmonary embolism, in which case it is classified under the fourth group, chronic thromboembolic pulmonary hypertension (CTPH) [8]. The fifth and last group of PH consists of several forms of PH where the etiology is unclear or multifactorial [8]. A summary of PH classification, including incidence and prevalence of each major group, is included in Table 1.

PH: PATHOLOGY

Our knowledge and understanding about PH pathology has evolved over the last one hundred years since its research began. Some of the histological features associated with PH include arterial remodelling causing increased thickness of the arterial vessel layers (intima, media and adventitia) and leading to pulmonary arteriolar narrowing and even occlusion [5, 12]. These abnormalities are combined with a broad imbalance in the vasodilative/ vasoconstrictive mediators within the pulmonary vasculature [4]. This imbalance presents itself as a decrease in vasodilators (e.g. Nitric Oxide (NO) and prostacyclins) and an increase in vasoconstrictors (e.g. endothelin- 1 and thromboxane A2) resulting in an overall vasoconstrictive pulmonary environment [4]. Complex plexiform lesions can also appear in the later stages of the disease. These lesions are often referred to as the hallmark of human PH and are composed of dysregulated, hyper-proliferative and apoptosis-resistant vascular cells [5, 12, 13]. More recently, inflammation and metabolic imbalance are becoming increasingly recognized as key modulators of PH as inflammatory cells are strongly associated with pathological lesions from PH patients [13, 14]. Also, a shift from normal metabolic pathways

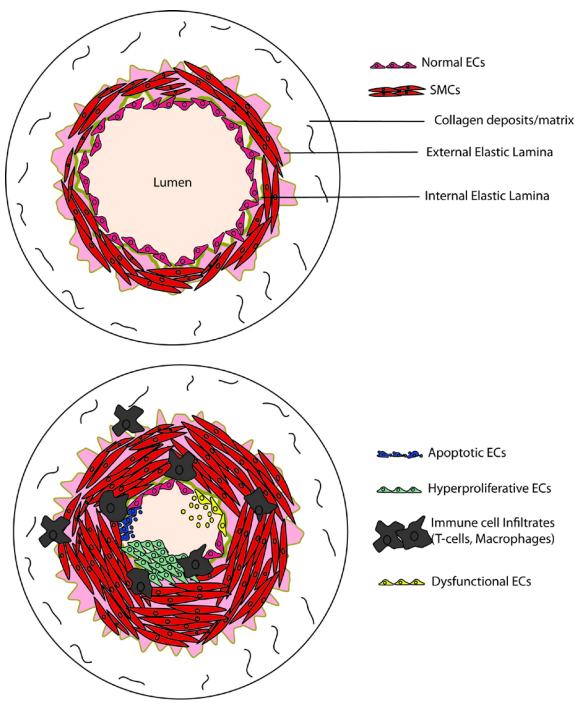

Figure 1: Summary of the pathological events observed in PH. A normal pulmonary arteriole (top) is composed of the following three layers: the internal layer (intima) composed of endothelial cells (ECs), the middle layer (media) composed of smooth muscle cells (SMCs) and the outermost layer (adventitia), composed of connective tissue. The internal and external elastic laminas separate these three layers. In PH, there is evidence for an increase in SMC proliferation which, combined with inflammatory cells infiltrates, lead to thickening of the media. This is also accompanied by endothelial cell apoptosis and selection of apoptosis resistant hyper-proliferative ECs that obstruct the lumen of the blood vessel. Dysregulation of ECs is also observed with increased production of vasoconstrictor factors and decreased production of vasodilators.

has been noted in the vascular cells in PH patients and animal models, and has been proposed to contribute to the hyper-proliferative phenotype observed [14]. A summary of some of these pathological pathways is included in Figure 1.

In some cases, as in the case of PH owing to left heart disease, the cause of PH is known, however, the precise mechanisms of cause of some of the other groups of PH are largely unknown. For example, there are several hypotheses that attempt to explain the mechanism of group 1, PAH, development. Currently, several lines of evidence are pointing to endothelial cell (EC) injury as part of the initiating mechanism leading to PAH [5]. Apoptosis in ECs may lead to degeneration of the fragile lung microvessels and induce a reactive process. This process in turn causes subsequent inflammation, as well as EC and smooth muscle cell proliferation, ultimately resulting in the PAH phenotype [5]. Still, EC apoptosis alone does not seem sufficient to explain all of the changes that occur in the pulmonary vasculature in PAH patients. Thus, more research is necessary to address alternative pathways that might be involved.

PH: TREATMENT

In most forms of PH, the increased vascular resistance is coupled with a broad imbalance in vasodilative/ vasoconstrictive mediators [4]. Thus, current PH treatments attempt to restore this balance in the pulmonary vasculature (vasodilator therapies – table 1) [4]. Current PH therapies include endothelin-1 receptor antagonists (e.g. bosentan), prostacyclin derivatives (eg. treprostenil) as well as phosphodiesterase type 5 (PDE5) inhibitors (e.g. sildenafil) which potentiate the nitric oxide-dependent vasodilatory pathways [4]. While these drugs succeed in reducing the vascular resistance and pulmonary artery pressure, as well as delay the progression of the disease in some patients, they still lack the ability to reverse remodeling within the lungs and thus fail to cure the disease [4]. Data from six different registries indicate a PAH mortality rate of 44% (total of 4,525 patients) within the first five years of enrolment, regardless of treatment options [6]. Since a lung transplant is the only current treatment option for PAH that is possibly curative, it is clear that new therapeutic options are necessary to improve prognosis.

PH: THE HORIZON

Several alternative therapies are currently being explored. Imatinib is a tyrosine kinase inhibitor that is currently being considered as a therapeutic option for PH [15]. Imatinib functions to inhibit signalling through the platelet-derived growth factor (PDGF) receptor which, in PH, leads to smooth muscle cell proliferation [15]. A randomized double-blind placebo-controlled phase-II clinical trial demonstrated a promising decrease in pulmonary vascular resistance and an increase in cardiac output in PAH patients treated with Imatinib. Further investigations in a phase III clinical trial are being conducted in order to determine if Imatinib can be used for treating PH [15]. Another interesting therapeutic option for patients with PH is targeting metabolic dysregulation using Dichloroacetate (DCA) [16]. A human clinical trial is currently testing the ability of DCA to reverse the hyper-proliferative phenotype observed in vascular cells in PAH (NCT01083524 – Phase I).

Still another potential field of PH therapeutics is exploring the use of cell therapy or combined gene and cell therapy, where a stem or progenitor cell's therapeutic potential is enhanced by transfection with a target gene [5]. Results from the first clinical trials using endothelial progenitor cells (stem cell precursors of endothelial cells) in PAH patients showed improvement in pulmonary capacity and absence of adverse effects [17]. Another human clinical trial being conducted is the Pulmonary Hypertension: Assessment of Cell Therapy (NCT00469027 – Phase I) or PHACeT clinical trial, which is using EPCs transfected with eNOS to enhance their therapeutic potential. The results from these clinical trials will pave the road for establishing new innovative therapies for PH.

CONCLUSION

Pulmonary hypertension is a devastating pulmonary cardiovascular disease that is challenging to both diagnose and treat. It is a rare disease and usually presents with non-specific symptoms in the patients. The story of Brooke Di Bernardo illustrates how PH can be misdiagnosed as a more common disease. In cases of successful PH diagnosis, current treatments can only slow its progression, with no success in reversal of the vascular remodeling. Thus, effective novel therapies are urgently needed.

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Table 1: Classification of Pulmonary Hypertension according to the Dana point WHO classification [8] as well as incidence, prevalence and treatment options.

Sub-group	Treatment Options	Incidence	Prevalence
Group I - Pulmonary Arterial Hypertension (PAH)			
- Idiopathic PAH - Heritable PAH - Induced by drugs and toxins - Associated PAH - Persistent pulmonary hypertension of the newborn - PAH secondary to veno-occlusive disease and/or pulmonary capillary hemangiomatosis	Vasodilator therapy: Sub-group/ Case specific [4]	1.1-2.4 cpm/yr [9, 10]	6.6-15 cpm [9, 10]
Group II - PH owing to Left Heart Disease (LHD)			
- Systolic dysfunction - Diastolic dysfunction - Valvular disease	Surgical [18]	--	8.6 - 83% (of patients with LHD) [18]
Group III - PH owing to lung disease and/or hypoxia			
- Chronic obstructive pulmonary disease - Interstitial lung disease - Other pulmonary diseases with mixed restrictive and obstructive pattern - Sleep-disordered breathing - Alveolar hypoventilation disorders - Chronic exposure to high altitude - Developmental abnormalities	Vasodilator therapy: Sub-group/ Case specific [19]	12.9-23.9% (of patients with lung disease) [19]	--
Group IV - Chronic thromboembolic PH			
	- Surgical removal of emboli - Vasodilator therapy [20]	0.5-3.8% (after acute PE) 10% (after recurrent PE) [20]	--
Group V - PH with unclear multifactorial mechanisms			
- Hematologic disorders - Systemic disorders - Metabolic disorders - Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis	Sub-group/ Case specific	--	--

Abbreviations: cpm= cases per million adults; PE=Pulmonary Embolism

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Closing the fasciotomy wound following compartment syndrome

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ABSTRACT

Compartment syndrome is a common and severe medical condition that can lead to ischemia and ultimately tissue loss. Fasciotomy is the most effective treatment for patients with compartment syndrome. However, closing the fasciotomy wound often presents a problem because of edema and skin retraction. As a result, numerous techniques have been devised to optimize wound closure. Each technique achieves closure differently and has its own advantages and disadvantages. In this review of the literature from 1990 to 2012, common techniques will be discussed along with their important findings pertaining to wound closure. A decision-making algorithm has been devised to assist in the appropriate selection of technique to optimize fasciotomy wound closure.

RÉSUMÉ

Le syndrome du compartiment est un trouble médical courant, mais grave qui peut entraîner l'ischémie et, ultérieurement, la perte de tissus. La fasciotomie est le traitement le plus efficace pour les patients présentant un syndrome du compartiment. Par contre, la fermeture de la plaie après une telle intervention peut s'avérer difficile à cause de l'œdème et de la rétraction cutanée. En conséquence, de nombreuses techniques ont été conçues pour optimiser la fermeture de la plaie. Chaque technique permet de fermer la plaie de façon différente, et comporte ses avantages et ses désavantages. Cette revue, qui a été publié sur le sujet entre 1990 et 2012, aborde les techniques courantes, de même que les constatations importantes relativement à la fermeture de la plaie. Un algorithme décisionnel a été conçu pour aider à choisir la bonne technique en vue d'optimiser la fermeture de la plaie après une fasciotomie.

INTRODUCTION

During compartment syndrome, there is an increase in the interstitial pressure within closed and unforgiving osteofascial spaces. It is caused by numerous injuries including fractures, crush injuries and burns [1]. The compression of vascular structures within these spaces leads to muscle and nerve ischemia. If ischemia remains for two hours, nerve damage and tissue necrosis occur [2]. In a study of 108 patients admitted to the hospital with leg problems, 14% of patients with leg pain and 9% of patients with leg fractures were diagnosed with compartment syndrome [3]. To date, fasciotomy is the most effective treatment for patients with compartment syndrome. However, the fasciotomy wound often presents a problem for physicians performing primary closure due to the persistent tissue edema and skin contracture [4]. Furthermore, fasciotomy wounds are often aesthetically unappealing and this can be debilitating for the patients. In a study of 60 patients following fasciotomy wound closure, 23% were upset by the appearance of the wound and did not expose it, 28% changed hobbies and 12% changed occupation [5].

Currently, there are numerous techniques in literature that attempt to optimize closure. However, each technique has its own advantages and disadvantages that must be taken into consideration. To aid clinical decision-making, this paper will provide a discussion of pertinent features of each technique. This paper reviews literature from 1990 to 2012 that describes wound closure techniques. Relevant information extracted include:

- Time to wound closure: The time taken from implementation of the technique to the time of wound closure
- Cost: The cost associated with using a particular closing technique
- Advantages/Disadvantages compared to other techniques
- Outcomes: Complications, revisions, loss of sensation, and management requirements
- Total number of patients and fasciotomy wounds for each technique

RESULTS

Split-thickness skin grafting

Split-thickness skin grafting is the most common procedure to close fasciotomy wounds [6]. It uses a skin graft from a donor site to reduce the apposition required for skin closure. As a result, this technique is often tension free. However, this technique requires another operative procedure, results in another wound, complicates wound care, extends hospital stay by roughly 3-5 days, and requires immobilization of the wound. There is also chance that the graft may fail. The final result is a thin, aesthetically unappealing scar without sensation [4, 7, 8] (see Table 1).

Table 1 : A detailed study evaluating the split-thickness skin graft technique for fasciotomy wound closure.

Author	Medina, C. et al.[9]
Year of publication	2007
Number of patients	6
Average closure time	9.2 days
Complications in patients	3 reported scar pain, 5 reported numbness of extremity, 5 unsatisfied with result
Management	Daily dressing changes

Secondary intention

Secondary intention uses only skin contraction to heal the fasciotomy wound. This technique is a simple and practical approach for patients who are able to manage their wounds without direct supervision. It reduces additional scars from skin grafting, reduces hospital stay in comparison to other techniques and the need for a second procedure, which reduces management costs [10] (see Table 2). Dressings are changed 1 to 3 times a day and can be used in conjunction with other closing techniques, if needed. The disadvantage is that complete healing takes an average of 3 to 4 months depending on the size of the wound and normalization of the scar contour takes roughly 4 years [10].

Vacuum-assisted closure (VAC)

VAC uses negative pressure to exploit the elastic properties of the skin. This causes stretching of the skin, reduces edema, promotes blood flow, lowers bacterial counts and increases the tissue granulation rate to ultimately create a wound that is more conducive to closure [11]. However, this technique requires dressing changes roughly every 3 days and is very expensive to use. Furthermore, VAC itself may fail to provide adequate skin edge approximation for final closure and as a result, another closing technique would be required [12] (see Table 3).

Table 2 : A detailed study evaluating fasciotomy wound closure-using healing by secondary intention.

Author	Boxer, L. et al.[10]
Year of publication	2003
Number of patients	2
Average closure time	9.2 days
Complications in patients	3 reported scar pain, 5 reported numbness of extremity, 5 unsatisfied with result
Management	Dressings changed 1-3/day

Dermal apposition

Dermal apposition takes advantage of the elastic properties of the skin. Essentially, a constant load is placed on the wound margin resulting in a gradual increase in skin length and reduction in force required to maintain that length. With cycles of re-loading the wound margin, primary closure is possible [16]. In the literature, there is a plethora of techniques and variations that take advantage of dermal apposition, including the vessel loop shoelace, sub-cuticular suture, Ty-Raps, Sure-Closure, Dynamic Wound Closure, STAR and Silver Bullet Wound Closure Device (SBWCD).

The shoelace technique uses staples and vessel loops to gradually appose the wound margins. This technique can readily

Table 3 : Detailed research studies from 1990 to 2012 evaluating the vacuum-assisted closure technique for fasciotomy wounds. Studies that did not provide the information are listed with a "-".

Author	Yang, C. et al.[13]	Zannis, J. et al.[6]	Saziye, K. et al.[12]	Kakagia, D. et al.[14]
Year of publication	2006	2009	2011	2012
Number of patients	34	370	7	25
Average length of wound	-	-	27 cm x 9.4 cm	-
Number of fasciotomy wounds	68	-	-	42
Average closure time	6.7 days	5.2 days	11 days	-
Complications in patients	None	25 patients required a second procedure	2 required a second procedure to close	5 required a second procedure to close
Limitations noted	-	-	-	Expensive and requires second procedure
Management	Dressings changed every 3 days	Dressings changed every 2-3 days	Dressings changed every 2-4 days	Dressings changed every 3 days
Cost	-	-	-	$176.09/day

Table 4 : Detailed research studies from 1990 to 2012 evaluating various dermal apposition devices for fasciotomy wound closure. Studies that did not provide the information are listed with a "-".

Author	McKenney, M. et al.[4]	Taylor, R. et al.[17]	Zorrila, P. et al.[20]	Medina, C. et al.[9]	Geertruida, A. et al.[16]	Kakagia, D. et al.[14]
Year of publication	1997	2003	2005	2007	2010	2012
Technique	STAR	Skin anchors	Shoelace	SBWCD	Ty-raps	Shoelace
Number of patients	13	5	20	8	13	25
Average dimensions of wound	7.6 cm	28 cm x 8.5 cm	-	-	-	-
Number of fasciotomy wounds	-	6	-	-	23	40
Average closure time	2.9 days	11.5 days (range 6-14 days)	8.8 days	7.4 days	6.3 days	-
Complications in patients	1 with superficial infection	None	1 with scar contracture	2 with scar tenderness, 2 with numbness of extremity, 3 unsatifsfied with results	1 required a second procedure	6 required replacement of device
Limitations reported	-	Excessive skin tension	Tightening was done in the operating room	-	Small wound dehiscence occurred once device removed	-
Management	Daily tightening	Tighten every 1-3 days	Tightening every 48 hours	Daily tightening	Tighten every 24-48 hours	Daily tightening
Cost	-	-	-	$575/device	$23.73 for a 30 cm wound	$18.26/day

be performed with materials found in an operating room. Compared to the VAC technique, the shoelace approach takes less time for closure, is considerably less expensive, and does not require a second procedure for closure [14].

The sub-cuticular suture technique uses sutures to appose the wound edges, taking roughly 7 to 11 days for wound closure [13]. This technique, like the shoelace, uses readily available materials and has a lower cost in comparison to commercial dermal apposition devices. Disadvantages include inflammation around sutures and suture breaking requiring replacement [17,18].

Commercial devices such as Sure-Closure, Dynamic Wound Closure, STAR and the Silver Bullet Wound Closure Device may result in wound closure in only 4 days [13]. However, they are expensive to purchase and they must be made available beforehand. For example, the Sure Closure device costs between $300 and $500 [15].

With all dermal apposition techniques, the biggest disadvantage is that they cannot be applied until the edema settles, which often requires 3 to 5 days postoperatively. They also require the wound to be immobilized during treatment. Once the technique is applied, the constant tension from the devices can cause skin necrosis and recurrence of compartment syndrome. As such, close monitoring of the limb during closure is often required [17].

DISCUSSION

Currently, there are numerous techniques described in the literature pertaining to the optimization of wound closure following fasciotomy. Once the advantages and disadvantages of each technique are understood, a clinician can decide which technique to use to optimize fasciotomy wound closure for a particular patient. A potential algorithm to assist the decision-making process includes taking into consideration the financial investment for a wound closure, the patient's preference and the patient's current medical conditions. The clinician should first consider the financial restraints and whether or not the fasciotomy wound requires a significant financial investment. This is especially important in healthcare settings with limited resources. The next question is which approach is best, given the patient's preference and the patient's current medical conditions. Patients may prefer one technique to another or the state of the patient's health may dictate the use of one technique over another. As described in the Results section, each technique has its own niche and will best fit a particular type of patient.

LIMITATIONS

Articles were searched from 1990 to 2012 and as such, techniques that were made popular and studied prior to 1990 (skin grafting) were not found in this literature search. From the 38 articles identified from the literature search, only 20 were

found to contain pertinent information. Furthermore, not all detailed studies found in the tables included pertinent information, such as the costs, the number of fasciotomy wounds and the fasciotomy wound dimensions. This makes it difficult to accurately compare studies using the same technique.

CONCLUSION

Compartment syndrome is a common and often severe condition that is managed with fasciotomy. There are currently numerous techniques described in the literature to close a fasciotomy wound. It is important to be aware of the numerous techniques and to have an approach to choose one technique over another for a particular patient. When deciding which technique to apply, financial restraints, the patient's preference and the patient's current medical conditions will be important to consider. Having the knowledge and a simple algorithm will help optimize wound closure promptly with as little complications and costs as possible to both parties.

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Associations between neighbourhood walkability, active school transport and physical activity levels in primary and secondary school students: A pilot-study

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ABSTRACT

Objectives: This longitudinal pilot-study examined the associations of neighbourhood walkability with active school transport (AST) and pedometer-determined physical activity (PA) immediately before and after the transition from primary to secondary school.
Methods: Fifty-five grade 6 students were recruited from 4 primary schools in Ottawa in May/June 2012. They were asked to complete a diary indicating their mode of transport to/from school for 1 week and wear a SC-StepMX pedometer for 8 consecutive days. 48 study packages were returned at baseline and 29 at follow-up (September/October 2012). The Walk Score® application was used as a proxy for walkability around the home and around the school. The associations of walkability with AST and average daily step counts at both time points were respectively examined with binary logistic regression and linear regression models adjusted for gender.
Results: At baseline, only walkability around the school was positively associated with AST (OR = 1.04). At follow-up, higher Walk Score ratings around the home and the school were both associated with greater odds of AST (OR = 1.12 and 1.29 respectively). Furthermore, walkability around the home was associated with higher step counts with a large effect size ($\eta 2 = 0.19$).
Conclusions: There was a negative association between having a regular medical doctor and high self-perceived health, modified by age. The findings suggest that individual access to care does not predict health in the same way as physician density.

RÉSUMÉ

Objectifs: Cette étude pilote longitudinale vérifiait l'association entre les quartiers favorables à la marche, le transport actif scolaire (TAS) et le niveau d'activité physique (AP) déterminé à l'aide d'un podomètre, immédiatement avant et après la transition de l'école primaire à l'école secondaire.
Méthodes: En mai et juin 2012, 55 élèves de la sixième année ont été recrutés dans 4 écoles primaires d'Ottawa. On leur a demandé de remplir quotidiennement un journal de bord dans lequel ils devaient indiquer leur mode de transport pour se rendre à l'école et en revenir durant une semaine. Ils devaient également porter un podomètre SC-StepMX durant huit jours consécutifs. À la première étape, 48 trousses d'étude ont été retournées à la première étape et 29 lors du suivi en septembre et octobre 2012. L'application Walk Score® a été utilisée comme témoin pour déterminer si le milieu environnant le domicile et l'école était favorable à la marche. L'association entre les quartiers favorables à la marche, le TAS et le nombre moyen de pas faits dans une journée a été examinée respectivement aux deux étapes de l'étude à l'aide d'une régression logistique binaire et d'un modèle de régression linéaire ajusté selon le sexe.
Résultats: À l'étape initiale, seul un milieu favorable à la marche autour de l'école était associé positivement au TAS (RC = 1,04). Lors du suivi, un indice Walk Score élevé aux alentours de la maison et de l'école était associé à une probabilité supérieure de TAS (RC = 1,12 et 1,29 respectivement). De plus, un quartier favorable à la marche autour du domicile était associé à un nombre plus élevé de pas avec une taille d'effet élevée ($\eta 2 = 0,19$).
Conclusion: Ces observations préliminaires suggèrent qu'il peut s'avérer plus important pour les étudiants de l'école secondaire que leur milieu soit favorable à la marche. Puisqu'aucune autre étude longitudinale n'a été menée pour évaluer si l'association entre les quartiers favorables à la marche, le TAS et le niveau d'AP varie au fil du temps, il serait justifié de procéder à de grandes études prospectives.

INTRODUCTION

Recent survey findings indicate that the majority of children and youth do not meet current physical activity (PA) guidelines, which recommend 60 minutes of moderate-to-vigorous physical activity per day [1,2]. Even in the pediatric population, insufficient PA levels are associated with detrimental health parameters such as cardiovascular disease risk factors [3,4], underscoring the need for interventions that promote PA. Since children and youth must travel to and from school on a regular basis, active school transport (AST; e.g. using non-motorized travel modes such as walking and cycling to travel to/from school) is regarded as a promising strategy to increase PA at the population level [5,6].

During the last two decades, there has been a rapid in

crease in the number of scientific studies assessing the association between characteristics of the built environment (i.e. density, land use mix, street connectivity, availability of sidewalks and cycle paths, etc.) and individuals' active transport and PA levels [7]. Researchers have developed composite measures of neighbourhood characteristics that favour "walkability", which refers to the potential for individuals to walk to local destinations [8,9]. Measures of neighbourhood walkability have consistently been shown to be associated with adults' travel mode and PA [10,11]. However, the evidence regarding the association between characteristics of the built environment and children's AST and PA remains inconsistent [12,13]. In their systematic review of 14 studies that used objective measures of environmental characteristics, Wong et al. found that distance between home and school was the only consistent correlate of AST [13].

Giles-Corti et al. [14] hypothesized that the influence of the built environment on AST and PA may be stronger in adolescents than in children because the former generally have greater independent mobility. This concept refers to the degree of freedom of children and youth to move around in public spaces without adult supervision [15]. To date, most studies that examined the association between the built environment and AST have only considered associations with individual characteristics rather than composite measures of walkability [13]. One US study found that characteristics of the built environment had a stronger association with walking in youth aged 12-15 years old compared to younger participants [16]; however the cross-sectional design is an important limitation of this study.

Therefore, the objective of the present pilot-study was to examine the associations of neighbourhood walkability with AST and PA at the end of primary school (grade 6) and the beginning of secondary school (grade 7) among the same participants. The school transition is a major life event that coincides with a large decrease in PA [17]. It was hypothesized that the associations of neighbourhood walkability with AST and PA would be stronger in secondary school.

METHODS

Participants and setting

Fifty-five grade 6 students were recruited from four primary schools in Ottawa (Canada) in May/June 2012 (33.3% response rate). Of these four schools, two were located in census tracts with high population density (3531-4100 inhabitants/km2), according to the 2006 Canadian census data [18]. The two schools were located in lower density areas (988-2159 inhabitants/km2), thereby providing variability in built environment characteristics. Parents indicated their child's prospective school for grade 7 and either their phone number or e-mail address for follow-up purposes. 48 children (24 girls and 24 boys) returned their study package at baseline and 29 (16 girls and 13 boys) at follow-up (September/October 2012). Ethical approval was obtained from institutional Research Ethics Boards and from the 2 participating school boards.

Measures

At both time points, participants were asked to: 1) complete a travel diary indicating their mode of transport to/from school for each day during 1 week; 2) wear a SC-StepMX pedometer (Stepscount, Deep River, ON) on the right hip for 8 consecutive days; and 3) complete a log recording their daily step counts and the time the pedometer was worn during waking hours. This pedometer has been shown to be valid and reliable [19]. Parents of each participant indicated their postal code, which allowed for the estimation of neighbourhood walkability.

Data treatment

Participants were classified as active travelers if they reported using active travel modes for at least 50% of school trips. This classification method showed very high test-retest reliability over two consecutive weeks of measurement [20]. Pedometry data were screened based on established criteria including: 1) between 1,000 and 30,000 steps/day [21]; 2) ≥ 10 hours of data/day [22] and 3) ≥ 3 days of valid data (e.g. meeting the daily wear threshold values) [23]. Application of these thresholds led to the exclusion of pedometer data from 2 participants at baseline and none at follow-up. The postal codes provided by the parent were used as a proxy for residential address, based on evidence that Canadian postal codes are a suitable proxy in urban areas [24,25]. The Walk Score® application (http://www.walkscore.com/) was used as an estimate of neighbourhood walkability around the participants' residence (using postal codes) and around their school (using the street address) at both time points. The Walk Score is a composite measure of accessibility to a variety of destinations including schools, parks, shops, and public transit by walking. Amenities located within a 1.6 km linear buffer contribute to a location's Walk Score, but amenities within a 400 meters buffer receive higher points than those within 800 meters, 1.2 km and 1.6 km buffers. Walk Score ratings range from 0 to 100 with higher values indicating greater walkability. A validation study has found strong correlations between Walk Score ratings and objective measures of the built environment (i.e. residential density, intersection density, street density, average block length and access to public transit) [26].

Analyses

First, Pearson correlations assessed the association between Walk Score ratings around the home and around the school at both time points. Second, the associations of neighbourhood walkability with AST and average daily step counts at both time points were examined with binary logistic regression and linear regression models respectively, and adjusted for gender. The $\eta 2$ statistic was used as a measure of the independent effect size of neighbourhood walkability within the regression models. Analyses were performed with IBM SPSS 20 and the probability of type I error was set at 5%.

Table 1. Descriptive characteristics of the sample at baseline and follow-up.

Variable	Categories	Healthy	Baseline
Gender (n)	Girls	24	16
	Boys	24	13
Travel mode	Active	27 (14G, 13B)	13 (8G, 5B)
	Inactive	19 (9G, 10B)	15 (7G, 8B)
	Missing	2 (1G, 1B)	1 (1G)
Distance (km)	N/A	2.3 ± 2.4	3.9 ± 3.4
Walk Score† around the home	N/A	62.4 ± 17.8	62.0 ± 19.3
Walk Score around the school	N/A	62.0 ± 20.2	61.5 ± 27.8
Average steps/ day	Overall	16,805 ± 3,744*	14,071 ± 3,680*
	Girls	15,235 ± 2,973	12,728 ± 3,301
	Boys	18,447 ± 3,820	15,415 ± 3,662

Baseline data was collected in May/June 2012 and follow-up data was collected in September/October 2012. G = girls; B = boys. †Walk Score ratings range from 0 to 100 with higher scores indicating greater walkability. Walk Score ratings, distance and steps/day are presented as mean ± SD. * denotes statistically significant differences between boys and girls ($p < 0.05$). Two participants provided insufficient information to allow for the determination of their primary travel mode at baseline and one at follow-up

RESULTS

Descriptive characteristics of the participants at baseline and follow-up are provided in Table 1. Baseline data did not differ between participants who provided follow-up data and those who provided only baseline data with respect to gender, Walk Score, AST and PA (all $p > 0.49$). Walk Score ratings around the home and around the school were significantly correlated at baseline ($r = 0.70$; $p < .001$) and follow-up ($r = 0.53$; $p = .003$); therefore, to avoid multi-collinearity, separate models were done to assess the effect of walkability around the home and around the school.

At baseline, Walk Score ratings around the home did not differ between active and inactive travelers (OR = 0.99; 95% CI = 0.96-1.03; $p = .87$), but children attending schools with higher ratings were more likely to engage in AST (OR = 1.04; 95% CI = 1.01-1.07; $p = .03$) (Table 2). At follow-up, higher Walk Score ratings around the home (OR = 1.12; 95% CI = 1.03-1.21; $p = .01$) and around the school (OR = 1.29; 95% CI = 1.00-1.66; $p = .05$) were both associated with greater odds of AST. Of note, these odds ratios represent the change in the odds of AST associated with each unit increase in Walk Score. For instance, a 10-point increase in Walk Score around the home at follow-up would be associated with a 3-fold increase (OR = 3.02) in the odds of AST.

Table 3 illustrates the association between Walk Score and average daily step counts at both time points. At baseline, Walk Score ratings around the home and around the school were not associated with step counts (all $p > .79$). At follow-up, children living in more walkable areas were significantly more active ($F = 5.21$; $p = .03$) with a large effect size ($\eta 2 = 0.19$), but no association was found for walkability around the school ($F = 1.97$; $p = .17$). In all regression models, boys were more active than girls (all $p \leq .04$); however, there were no gender differences in travel modes at any time point ($p \geq .62$).

DISCUSSION

The present pilot-study assessed the influence of neighbourhood walkability on AST and PA immediately before and after the transition from primary to secondary school, a major life event that has been understudied with respect to AST. At baseline, walkability measures were not associated with PA, and only Walk Score ratings around the school were associated with AST. At follow-up, Walk Score ratings around the home and the school were both strongly associated with AST. Walkability around the home was significantly associated to PA with a large effect size; however, this relationship was not found for walkability around the school. Despite some inconsistencies, these findings provide preliminary evidence supporting Giles-Corti and colleagues' [14] hypothesis that the influence of neighbourhood walkability on AST and PA levels is stronger in secondary school students than in primary school students.

Previous systematic reviews have concluded that the evidence supporting associations between neighbourhood walkability (or different built environment constructs), AST and PA is inconsistent and that most included studies were cross-sectional [12,13]. Inconsistent findings could be due to many factors including methodological differences in the assessment of built environment characteristics [13,27] or PA levels [12] and failure to

Table 2. Associations between neighbourhood walkability and participant's primary travel mode at baseline and follow-up.

Time point	Walk Score	Active Travellers (mean ± SD)	Inactive Travellers (mean ± SD)	OR (95% CI)	p-value
Baseline	Home	61.5 ± 17.4	62.8 ± 18.8	0.99 (0.96-1.03)	.87
	School	68.3 ± 18.1	54.7 ± 19.7	1.04 (1.01-1.07)	.03
Follow-up	Home	76.3 ± 9.7	51.7 ± 17.1	1.12 (1.03-1.21)	.01
	School	79.5 ± 1.5	45.9 ± 31.4	1.29 (1.00-1.66)	.05

Differences in Walk Score ratings between active and inactive travelers were assessed at baseline (May/June 2012) and follow-up (September/October) using binary logistic regression adjusted for gender.

consider potential moderators such as age, gender, ethnicity and socioeconomic status [28,29].

In addition, it has been suggested that the influence of built environment characteristics may be additive [7,30], so studies that examine individual characteristics instead of using a composite measure of walkability may underestimate the strength of observed associations. McDonald [31] reported that the direct influence of population density on AST was weak, but that higher density may lead to shorter distances between home and school, which is in turn strongly associated with AST. Furthermore, there may be complex interactions between barriers and facilitators of AST. For example, high density and street connectivity may be associated with both shorter distance to school and heavier traffic exposure [14].

Another potential reason for the lack of association between Walk Score ratings and PA at baseline is that school journeys may account for a lower proportion of daily PA in children than in adolescents [32,33]. Primary school children may accumulate a greater proportion of their PA through active play than secondary school youth. Therefore, low density neighbourhoods with larger lots and cul-de-sacs may be more conducive to active play than high density neighbourhoods with heavy traffic and associated road safety concerns. In contrast, as children get older, active transport (not only to/from school) may become a more important source of PA; hence, walkable neighbourhoods could become increasingly important for fostering PA.

The school transition might be a good time for interventions that promote AST because travel habits are likely to be modified due to changes in school location. In a Scottish study, travel habits explained a significant proportion of the variance in step counts during the trip to school over and above planned behaviour constructs (e.g. attitudes, subjective norms and perceived behavioural control) [34]. In addition, Panter et al. [29] suggested that parental safety concerns might become less influential in travel mode decisions as children acquire independent mobility.

Table 3. Associations between neighbourhood walkability and step counts at baseline and follow-up.

Time point	Walk Score	Variable	F	*p*	η2
Baseline	Home	Corrected model	4.28	.02	.19
		Walk Score	0.04	.85	<.01
		Gender	8.12	<.01	.18
	School	Corrected model	4.91	.01	.01
		Walk Score	0.71	.79	<.01
		Gender	9.38	<.01	.18
Follow-up	Home	Corrected model	4.88	.02	.30
		Walk Score	5.21	.03	.19
		Gender	6.83	.02	.23
	School	Corrected model	2.99	.07	.21
		Walk Score	1.97	.17	.08
		Gender	5.02	.04	.18

Physical activity was measured with SC-StepMX pedometers at baseline (May/June 2012) and follow-up (September/October); that is immediately before and after the school transition.

The main limitations of this study are the small sample size and the low response rate suggesting that the sample population may not be representative of the general population. As a result, there may have been a selection bias with highly active children being more likely to participate at baseline. Furthermore, the small sample size precludes the adjustment of regression models for a larger range of socio-demographic variables that may influence travel mode choices and PA patterns (i.e. parental education and employment status, car ownership). Children may have increased their level of PA when wearing a pedometer; however, a recent review of pedometer use among children reported conflicting findings regarding the issue of pedometer reactivity [35]. Thus, it remains unclear whether reactivity may have contributed to the observed changes in physical activity. However, the observed changes are consistent with the declines in physical activity commonly seen during this transitional period [17]. Further studies are needed to confirm the present findings. Many studies have shown that children are more active during summer months, thus the observed differences in step counts may be partially explained by seasonal variations [36]. In this study, the follow-up was done as early as possible in the school year to minimize seasonality bias. Interestingly, previous research in Toronto (Canada) has shown no seasonal differences in travel modes among 11-12 years old children [37]. The observed decrease in the proportion of participants engaging in AST may be attributable to a 50% increase in the distance between home and school across the school transition [20]. Although Walk Score ratings have been shown to be correlated with other aspects of the built environment (i.e. density, diversity and design), it may fail to capture characteristics associated with younger children's travel and PA patterns. Finally, postal codes were used as a proxy of residential address as required by Research Ethics Boards. Nevertheless, previous research in Calgary (Canada) has shown that 87.9% of postal code locations were within 200 meters of the true address location [24].

The main strength of the study is the assessment of neighbourhood walkability, AST and PA immediately before and after the school transition, a major life event usually characterized by a large decrease in PA levels. Moreover, walkability was assessed both around the home and around the school. The use of an objective measure of PA, rather than a questionnaire, is another important strength because using a questionnaire can lead to a large overestimation of children's PA level [38]. To our knowledge, only one other study has assessed the influence of the school transition on AST [39], but no associations of built environment characteristics with AST and PA were reported.

CONCLUSION

In this longitudinal pilot-study, the association between neighbourhood walkability (as assessed by the Walk Score application) and measures of AST and PA was stronger in secondary school compared to primary school. This suggests that neighbourhood walkability may be more important for supporting adolescents' AST and PA levels. However, given the small sample size, future prospective studies are needed to confirm these findings. Since the school transition has been shown to coincide with a large decrease in PA [17], there is a need for studies to examine whether walkable environments can attenuate this decline.

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Un aperçu des stratégies utilisées par les pays en voie de développement pour réduire les temps d'attente pour une chirurgie de la cataracte: Y a-t-il quelque chose à apprendre?

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INTRODUCTION

Selon une étude récente, la moyenne globale de jours d'attente pour recevoir une chirurgie de la cataracte en Ontario s'élève à 68,8 jours et l'âge moyen des patients est 72,5 ans [1]. De plus, les experts estiment que le taux de chirurgies de la cataracte est corrélé très faiblement au temps d'attente [1]. Cependant, selon une autre étude, les risques de chutes ou de dépression en attendant plus de six mois avec une cataracte non-traitée sont très élevés [2]. Bien que les raisons qui expliquent la situation actuelle en Ontario soient complexes, ce qui est bien connu, c'est que le facteur de risque principal de la cataracte est l'âge avancé. Ceci devient problématique car l'espérance de vie moyenne au Canada est en augmentation constante (Figure 1).

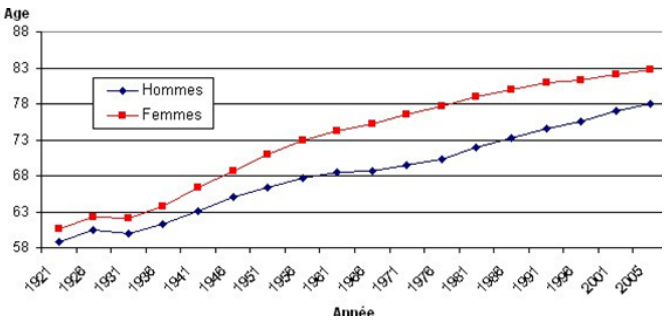

Figure 1. L'espérance de vie au Canada de 1921 jusqu'en 2005.
Sources : 1921 à 1981 : Nagnur D. Longévité et tables de mortalité chronologiques (abrégées), 1921 à 1981, Statistique Canada, Catalogue 89-506, 1986; 1986 : Duchesne, D, Nault, F, Gilmour, H, Wilkins, R. Recueil de statistiques de l'état civil 1996, Statistique Canada, Catalogue 84-214, 1999; 1991 à 2005 : Tableau CANSIM 102-0511, Espérance de vie, table de mortalité abrégée, à la naissance et à 65 ans, selon le sexe, Canada, provinces et territoires, annuel.

D'ailleurs, c'est la cohorte des gens âgés de plus de 65 ans qui occupe 81% des traitements chirurgicaux de la cataracte en Ontario [2-4]. Pour répondre à ce besoin, des avancées techniques significatives ont été développées pour le traitement chirurgical dans les années 1990. Ce qui prenait auparavant de 2 à 3 heures par chirurgie prend maintenant de 20 à 30 minutes. Lors de cette technique, nommée la phacoémulsification, le cristallin de l'oeil se fait désintégrer à l'aide d'une sonde à ultrason sous pression positive. Ceci évite l'effet indésirable de collapsus oculaire. Par la suite, une lentille intraoculaire (LIO) est installée dans la chambre postérieure de l'œil. Cette chirurgie est maintenant considérée comme l'étalon d'or du traitement de cataracte. Cependant, nous avons atteint un plateau en matière d'innovation technologique et le traitement de la cataracte risque de perdre son efficacité à cause de l'augmentation rapide des listes d'attentes. Le but de cet article vise à démontrer comment l'adoption de deux différentes stratégies mises en évidence dans les pays en voie de développement peut améliorer l'efficacité dans les soins ici au Canada. Notamment, selon deux ophtalmologistes africains, le traitement plus « agréable aux patients » est une bonne approche, ou bien selon des études faites en Inde, l'accent doit être mis sur les discussions de résultats positifs du traitement cas par cas pour valoriser le phénomène de « bouche à oreille ».

L'EFFICACITÉ ACTUELLE AU CANADA

Durant mes deux dernières années de médecine, j'ai eu l'occasion de faire plusieurs stages d'observation en ophtalmologie à travers le pays. D'après cette expérience, l'état actuel des soins aux patients diagnostiqués avec une cataracte est très efficace. Selon une étude collaborative d'experts en ophtalmologie faite au Canada en 2009, la cataracte est la cause primaire de perte de vision dans 16% de cas [3]. Le taux de chirurgies de la cataracte est élevé, mais comme ce taux est faiblement corrélé avec le temps d'attente en Ontario, il se peut qu'il y ait un autre phénomène expliquant nos temps d'attente [1, 2, 5]. Le tableau 1 démontre les différences des taux de chirurgies de la cataracte entre l'Ontario et les deux régions ciblées dans ce commentaire: l'Afrique et l'Inde. Avec l'augmentation du besoin de chirurgies de la cataracte et la croissance rapide des listes d'attente, le système canadien doit envisager l'intégration de nouvelles stratégies pour maintenir l'efficacité de ce traitement.

Tableau 1 : Taux de chirurgie de la cataracte en Ontario, en Afrique et en Inde.

Région	Taux de chirurgie de la cataracte par année par 100 000 habitants	Pourcentage per capita	Estimation de la population actuelle
Ontario	540,3	0,54 %	13 505 900[a]
Afrique	<15-150	0,015 – 0,15 %	1,0325 billion[b]
Inde	370	0,37 %	1,2415 billion[c]

Sources des estimations de la population actuelle: a.)http://www.fin.gov.on.ca/en/economy/ecupdates/factsheet.html; b.) http://esa.un.org/wpp/; c.) http://data.worldbank.org/

Tableau 2 : Aperçu non-exhaustif de statistiques sur l'état actuel en Afrique.

Pays	Nombre de personnes aveugles	Causes principales de la cécité	Nombre de personnes atteintes de cataracte en attente	Nombre d'ophtalmologistes	Population
Érythrée[a]	41 700 (50 ans +)	Cataracte (55%), glaucome (15%), DMLA (6%)	22 900 (50 ans +)	8 (4 locaux et 4 expatriés)	5,2 millions
Éthiopie[b]	1,28 millions d'aveugles et 2.96 millions avec une vision basse	Cataracte (50%), trachome (11,5%), cicatrisation de la cornée (8 %), erreurs de la réfraction (8%), glaucome (5%)	638 720	Environ 104 avec un autre 46 chirurgiens de la cataracte	85 millions
Rwanda[c]	30 000	Cataracte (65%)	N/D	11	10,9 millions
Kenya[d]	224 000	Cataracte (43%), trachome et cicatrisation de la cornée (19%), glaucome (9%), cécité chez l'enfant (6%)	107 000 avec une incidence annuelle de 14 500 cas	Environ 85 dont 33 des ophtalmologistes travaillent à Nairobi	41,6 millions
Burundi[e]	87 000	Cataracte (50%), erreurs de la réfraction (10%), cécité chez l'enfant (5%)	48 000 avec une incidence annuelle de 9 600 cas	10 connus (seulement 2 font les chirurgies de la cataracte)	8,6 millions

Sources : a.) Eritrean Rapid Assessment of Avoidable Blindness (RAAB 2008); UNDP Human Development Report 2010; b.) National Five-Year Strategic Plan for Eye Health in Ethiopia 2003-2007 EC (2010/11 – 2014/15), Government of Ethiopia; UNDP Hum Devel Rep 2010; c.) National Prevention of Blindness Plan 2009-2013, Ministry of Health, Rwanda; UNDP Hum Devel Rep 2010 & 2011; UNICEF State of the World's Children Report 2012; d.) Hum Devel Rep 2006, Chief Ophthalmologist of Kenya, Kenyan National Eye Care Plan 2005-2010; UNDP Hum Devel Rep 2010 & 2011; UNICEF State of the World's Children Report 2012; e.) UNDP Hum Devel Report 2010 & 2011; UNICEF State of the World's Children Report 2012.

L'ÉTAT DES LIEUX ACTUEL EN AFRIQUE

Parmi les différents pays du sub-saharien, il existe une grande hétérogénéité dans les taux de chirurgies de la cataracte [6]. Il est important à noter que la cause principale de cécité en Afrique est de loin la cataracte (Tableau 2). Selon une étude en 2001, la cataracte est la cause primaire d'environ 50% des cas de cécité en Afrique. [7]. De plus, les efforts pour trouver des solutions sont en plein essor grâce aux initiatives d'experts internationaux en santé publique qui luttent contre la cécité traitable. Un bon exemple est l'introduction du programme international Vision 2020 « le droit à la vue », qui a comme but principal de sensibiliser les gens au concept de cécité traitable. Ce programme a mis une grande emphase sur la cataracte dans le volet d'Afrique [8, 9]. De plus, Vision 2020 agit comme liaison d'efforts collaboratifs évaluant et comparant les différents programmes de traitement dans plusieurs régions de l'Afrique.

CE QU'ON PEUT APPRENDRE DE L'AFRIQUE

Les efforts pour mieux comprendre et quantifier les besoins pour la cataracte ont été faits en Afrique et les mises à jours de ces travaux sont nombreuses. Nous devons faire de même au Canada. En fait, la première étude de ce genre a été faite en 2009 [3]. En Ontario, il existe un programme gouvernemental provincial de temps d'attente pour chaque hôpital, qui est mis à jour régulièrement. Cependant, une étude des besoins en matière de chirurgies de la cataracte n'a jamais été faite en Ontario. Avec la réduction de 10% du financement des chirurgies de la cataracte par le gouvernement provincial, il existe un risque que plusieurs hôpitaux choisissent de cesser leurs services de cataracte [10]. Je considère l'Afrique comme une région avec beaucoup d'expertise sur l'inaccessibilité des services, car ils étudient ce problème depuis longtemps. Selon un article écrit par deux ophtalmologistes africains et publié en 2001 par l'Organisation mondiale de la santé (OMS), une approche au traitement de la cataracte considérée plus « agréable aux patients » sera nécessaire à l'avenir. En autres mots, dès la première consultation jusqu'au suivi post-opératoire, les soins devraient être pratiques pour les patients et leurs familles [11]. Ceci nécessitera la participation active des communautés dans la planification et le développement des services pour les yeux [11]. Les patients et leur entourage sont directement touchés par la perte de vision due à la cataracte. En Afrique, les gens qui vivent sur les fermes perdent deux ouvriers autrement physiquement habiles chaque fois qu'il y a un patient atteint d'une cataracte – les patients eux-mêmes et les personnes s'occupant des patients [11-13]. Il s'agit donc d'un énorme problème pour ces familles. Pour éviter ce problème au Canada, nous devrions quantifier les besoins de services dans les régions rurales et travailler directement avec ces communautés pour mieux comprendre comment sensibiliser les gens au traitement de la cataracte. La perte de vision due à la cataracte est un problème dévastateur, mais facilement traitable au Canada.

L'ÉTAT DES LIEUX ACTUEL DANS LES RÉGIONS RURALES EN INDE

L'impact social de la perte de vision due à la cataracte doit également être pris en considération. Comme exemple, les résidents dans les zones rurales de l'Inde n'ont pas à s'inquiéter de perdre leur permis de conduire car, en général, ils n'ont pas de voiture [14]. Par conséquent, ces communautés utilisent autres moyens pour guider les personnes âgées atteintes de cécité. Au

sein du village, les enfants guident les membres âgés de la famille par la main et par une attache lors de la marche sur de longu longues distances (figure 2). Au Canada, une technique similaire a été adoptée pour guider les athlètes de haute performance atteints de basse vision [15]. De plus, l'accès aux ressources technologiques en Inde est comparable à celle retrouvée en milieu rural canadien. Les gens sont donc mieux informés des options s'offrant à eux en matière de soins de santé, particulièrement en cas de perte de vision [16-19].

Figure 2: Cet homme a été aveuglé par la cataracte pendant trois ans. Alors que sa famille travaille dans les champs de riz chaque jour, son petit-fils doit s'absenter de l'école pour s'occuper de lui.
Source: http://www.hollows.org.au/news-media/lom-lun

CE QU'ON PEUT APPRENDRE DES RÉGIONS RURALES EN INDE

En Inde, le problème de cataracte non-traitée n'est pas simplement dû au fait que les patients vivent en régions rurales, ou d'un manque de ressources pour accéder à un traitement. Il s'agit davantage d'un manque de communication de la part du patient affecté de cécité avec son entourage par le phénomène de « bouche à oreille » [16]. Ceci est devenu évident après la création de plusieurs camps de dépistage de la cataracte à travers l'Inde dans les années 1980. Selon les critères de l'Aravind Eye Care System, l'accent a été mis sur l'explication des résultats d'acuité visuelle, en s'assurant que la meilleure acuité visuelle soit atteinte de façon chirurgicale ainsi qu'avec des lunettes correctrices appropriées [20]. De cette façon, la satisfaction du patient se fait partager lors de son retour dans sa communauté [16]. Le développement de ce système avait un impact extrêmement positif sur la perception sociale du traitement de la cataracte en Inde. Bien que les coûts des campagnes de dépistage de la cataracte soient élevés au Canada, comme c'est le cas en Inde, les avantages du phénomène de « bouche à oreille » en valent nettement l'investissement.

CONCLUSION ET DIRECTIONS FUTURES

Enfin, les stratégies mises en place par les pays en voie de développement sont des éléments inestimables d'information pouvant être appliqués dans de nombreux domaines des soins de santé au Canada. Afin de comparer efficacement les techniques chirurgicales, nous devons continuer à aider ces pays par l'entremise d'organisations à but non-lucratif, tel que l'ORBIS Flying Eye Hospital [21]. Dans cette organisation, un groupe de spécialistes, en collaboration avec une équipe aérienne mobile, visite différents pays en besoin. Encore plus impressionnant, tous les services de chirurgie oculaire sont installés sur l'avion. Cette innovation comporte plusieurs avantages, notamment l'occasion de traiter les patients dès leur arrivée, utiliser des techniques déjà maîtrisées et fournir une éducation aux médecins locaux. De plus, avec l'approche « ouvert aux patients » (Afrique) et l'emphase sur l'explication de résultats positifs (« le bouche à oreille ») (Inde), il y aura sans doute plus de leçons à retenir des pays en voie de développement.

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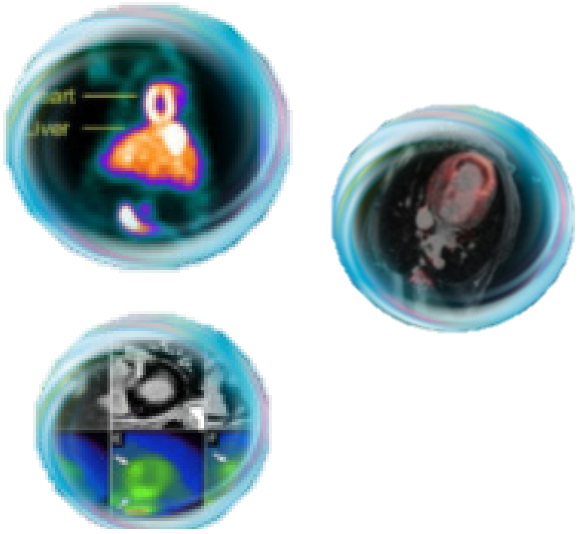

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