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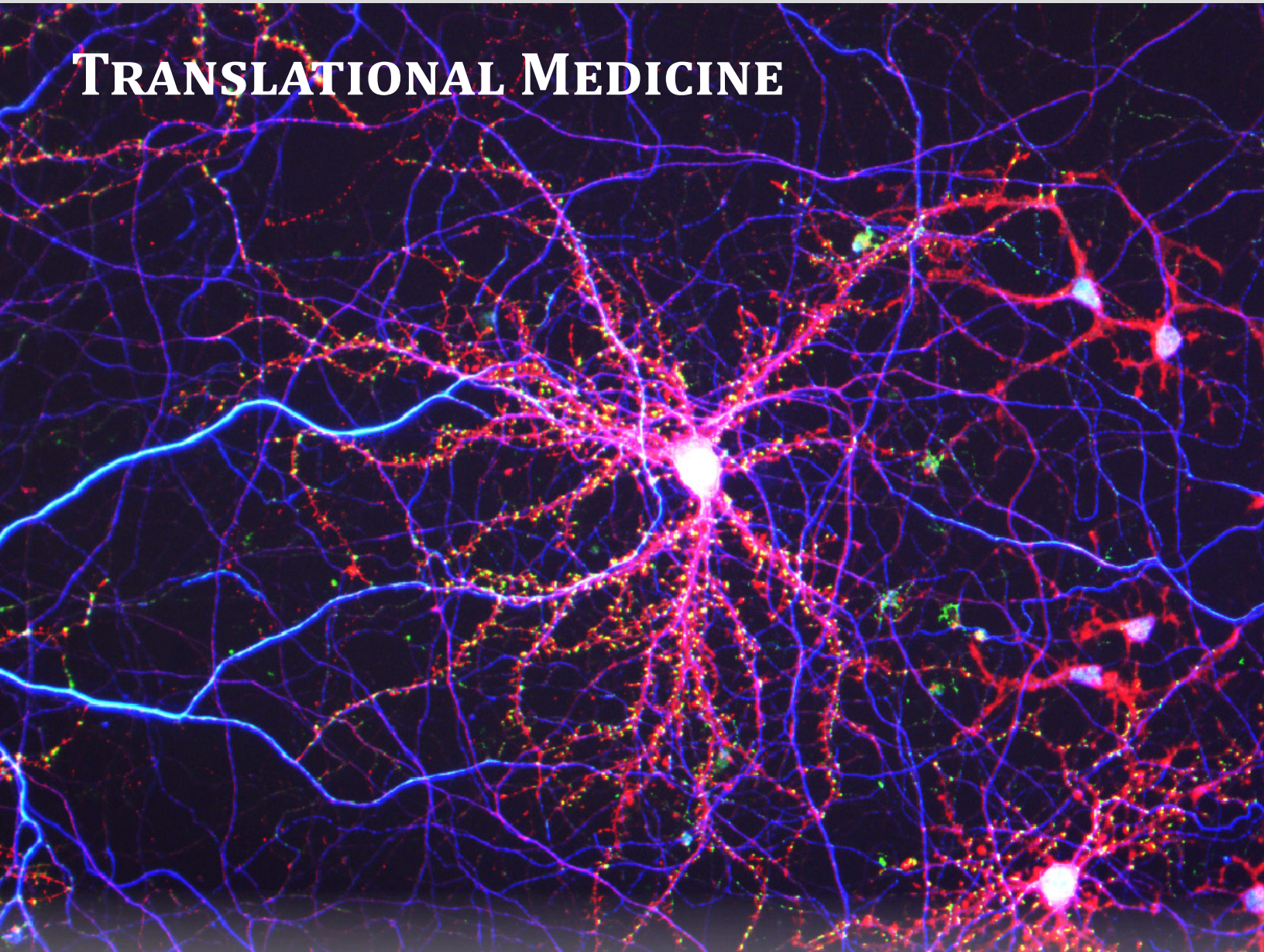
Translational Medicine



FEATURING

Interview with John Bell, Ph.D., Cancer Scientist

University of Ottawa M.D./Ph.D. Program Report

Deep brain stimulation in psychiatry

Stem cells: from basic science to clinical applications

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COVER ART: The cover features an original microscopy image contributed by Wayne Huang, showing a neuron in the centre surrounded by glial cells. The neuron sprouts elaborate dendrites (stained red) which interact with the intertwining network of axons (stained blue), along the junction of which are hundreds of synapses (stained yellow).

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UOJM: Preface

On behalf of the editorial team, we are extremely excited to present you with the second issue of the University of Ottawa Journal of Medicine (UOJM) since its re-launch in 2011. UOJM is a student-run peer-viewed journal that publishes both scientific and non-scientific medical literature, and showcases the scholarly insights, ideas and findings by the Faculty of Medicine students. We accept submissions in both French and English, and represent the only bilingual student medical journal in Canada. We are proud that UOJM is conceptualized, run and published entirely by students. Last year, our goal was to create a medium through which medical students can actively participate in academic writing and peer review. Expanding on that goal this year, we envisioned building a journal that reflects both a quality publication and, equally as importantly, an excellent student experience.

With those goals in mind, we implemented several initiatives to establish a solid framework for the future development of the journal. The first was assembling a board of faculty advisors. We are very fortunate and thankful to have nine distinguished faculty members volunteering their time to mentor the editorial team and to serve as potential reviewers. We are grateful to Dr. Melissa Forgie and Dr. Phil Wells, our sole advisors during our inaugural year who continue to support and guide us. Although students on our editorial team all share a common interest in academic writing, their academic backgrounds and experiences may be very different. To standardize editorial training, we have introduced a journal club within UOJM whereby editors present and discuss articles and participate in editing workshops. Each journal club is mentored by a different faculty advisor and focuses on different types of academic publications.

The review system has been improved with emphasis on better delegation of roles through editing teams, each led by an associate editor and composed of three or four sectional editors. We are especially grateful to our managing editors Tyler Kaster and André Martel for establishing a new Dropbox-based system and for their meticulous effort in managing the flow of documents to ensure the highest efficiency, timeliness and confidentiality. We would like to also express our gratitude to our senior advisors in clerkship – Crystal Cheung, Kyle Fortinsky, Alex Sebaldt, and Laura Shoots – for providing valuable inputs for leadership directions and for serving as promotional liaisons for clerkship students. Last but not least, we like to extend a sincere thank you to our entire peer-review team for their hard work and dedication.

We are pleased to announce that, with kind support from the undergraduate medical education and the graduate departments, UOJM became the first and only student medical journal to our knowledge to actively involve the participation of graduate students at the level of both submissions and peer review. Uniting students in the M.D. stream with those in the M.Sc and Ph.D streams, UOJM is committed to establishing continuous communication and collaboration between future clinicians and scientists. We are grateful to Dr. Ruth Slack, the coordinator of graduate studies, and Dr. Bernard Jasmin, the vice dean of research, for helping us make this vision a reality.

Whereas the inaugural 2011 issue of UOJM was about resurrecting a 40-year old student publication, the story of this issue is about bridging the gaps – the gap between medical and graduate students, the gap between faculty mentors and student editors, and the gaps in the organizational foundation of the journal. Therefore, it was most timely and suitable to have Translational Medicine as the theme of this issue. The goal of translational medical research is to apply findings from basic sciences to produce new drugs, devices and treatment options for patients, thereby bridging "the bench to the bedside". Translational research is the interface between basic science and clinical medicine, and the driving force behind advances in medical treatments and patient care. It is a challenging and costly process that requires collaborative efforts from basic scientists, clinical investigators and epidemiologists.

The impact of translational medicine cannot be better exemplified than two Canadian success stories this past year. In January 2012, NA1, a neuroprotective agent discovered in 2001 [1] by a research team in Toronto, has successfully completed phase 2 clinical trial in stroke patients [2, 3], a tremendous milestone given that over 1000 candidate neuroprotective agents have failed to translate into therapies in humans [4]. A big part of NA1's success can be attributed to the culmination of basic neuroscience findings over the decades that helped further our understanding of the neuronal death mechanism following cerebral ischemia. In the same month that NA1 completed its phase 2 clinical trial, the SAV001 vaccine developed by a research team in London received FDA approval for human clinical trials [5]. SAV001 is the first and only HIV vaccine based on a genetically modified killed whole virus (HIV-1), which, unlike the real HIV virus, is non-pathogenic and can be produced in large quantities. Both NA1 and SAV001 are on the verge of major breakthroughs in clinical therapy.

The two featured articles in this issue both centre on the theme of translational medicine. The first article is an interview with Dr. John Bell, a world leader in oncolytic virus research and a recipient of the OHRI's Career Achievement Award. Dr. Bell shares with us his inspirational career story that spans translational research from *in vitro* studies to clinical trials. In the second article, Dr. Michael Schlossmacher, the director of the M.D./Ph.D program at the University of Ottawa, provides us with a progress report and an overview of the M.D./Ph.D. program since its establishment in 2009.

We are extremely pleased with the selection of articles in this issue as well as the diversity it represents. The issue includes four articles contributed by Francophone medical students, two of which are published in French, and two articles contributed by graduate students. The breadth of the articles range from an original research in clinical epidemiology, to a commentary on an experimental neurosurgery, and to a student's vivid experience volunteering in a maternity hospital in Kenya.

We hope you will enjoy the May 2012 issue as much as we enjoyed putting it together!

Wayne Huang & Yue Jiang
Editors-in-Chief

JMUO: Préface

De la part de l'équipe éditoriale, nous sommes très heureux de vous présenter la deuxième édition du Journal de Médecine de l'Université d'Ottawa (JMUO) depuis son retour en 2011. Le JMUO est un journal évalué par les pairs et mené par les étudiants qui publie de la littérature médicale scientifique et non scientifique, et démontre la perspicacité, les idées et les trouvailles des étudiants de la faculté de médecine. Le JMUO accepte des soumissions en français et en anglais et représente ainsi le seul journal médical étudiant bilingue au Canada. Nous sommes fiers du fait que le journal est conceptualisé, mené, ainsi que publié entièrement par les étudiants. L'année dernière, notre objectif était de créer un moyen permettant aux étudiants en médecine de participer de façon active dans l'élaboration d'œuvres académiques et dans le processus de révision par les pairs. Cette année, nous avons élargi nos objectifs en visionnant un journal qui reflète une publication de qualité ainsi qu'une excellente expérience étudiante.

Avec ces objectifs en tête, nous avons mis en œuvre plusieurs initiatives afin de construire une base solide pour le développement futur du journal. Premièrement, un conseil de membres de la faculté a été assemblé. Nous sommes très reconnaissants d'avoir neuf membres facultaires distingués qui donnent leur temps de façon bénévole afin d'être les mentors du comité éditorial et de potentiellement réviser les publications. Nous apprécions énormément le support de Dre Melissa Forgie et Dr Phil Wells, nos conseillés lors de notre année inaugurale, qui continuent de nous supporter et nous guider. Bien que les étudiants de notre comité éditorial partagent comme intérêt commun l'écriture académique, leurs expériences académiques sont variées. Afin de standardiser la formation du comité éditorial, nous avons introduit un club de lecture pour les membres du JMUO afin de présenter des articles et des ateliers de formation. Chaque club de lecture fut supervisé par différents conseillés facultaires qui se spécialisent dans différents domaines de publications académiques.

Le système de révision fut grandement amélioré en mettant l'emphase sur une meilleure délégation des rôles qui fut accompli par la formation d'équipes éditoriales, chacune menée par un éditeur associé et composée de trois ou quatre éditeurs. Nous sommes particulièrement reconnaissants envers nos gestionnaires éditoriaux Tyler Kaster et André Martel qui ont mis sur pied un nouveau système qui utilise l'application Dropbox, et qui ont consacré de nombreux efforts afin de gérer le flot de documents de façon efficace et confidentielle. Nous aimerions également exprimer notre reconaissance envers nos conseillés seniors qui complètent maintenant leur externat – Crystal Cheung, Kyle Fortinsky, Alex Sebaldt et Laura Shoots – pour leurs recommandations, leur leadership et leur rôle en tant que liaison aux étudiants de l'externat. Finalement, nous aimerions remercier tout notre comité de révision pour leur travail et leur engagement.

Nous sommes aussi heureux d'annoncer qu'avec le support du Bureau de l'éducation médicale de premier cycle et du Département des études graduées, le JMUO est devenu le seul journal médical étudiant à notre connaissance qui encourage une participation active des étudiants gradués au niveau de la soumission et de la révision d'articles. Cette participation permet ainsi l'union des étudiants du programme M.D. aux étudiants complétant des M.Sc. et Ph.D. De par cette nouvelle alliance, le JMUO est engagé envers l'établissement de collaborations et de communications continues entre les futurs cliniciens et chercheurs. Nous aimerions remercier Dr Ruth Slack, la coordonatrice du programme des études graduées, ainsi que Dr Bernard Jasmin, le vice doyen de recherche, pour leur aide avec la transformation de cette vision en réalité.

L'inauguration du JMUO par la publication de l'édition de l'année 2011 symbolisait le retour d'un journal étudiant datant de plus de 40 années. Cette année, le mandat de cette publication est la formation de nouveaux liens – des liens entre les étudiants en médecine et les étudiants gradués, des liens entre les membres de la faculté et les étudiants éditeurs, et des liens permettant l'amélioration du processus de revue et l'organisation du journal. Il était donc approprié et en bon temps d'établir le thème de médecine translationnelle pour cette édition. Le but de la recherche en médecine translationnelle est d'appliquer les trouvailles des sciences de base à la production de nouveaux médicaments, appareils et traitements, formant

ainsi le lien entre les études en laboratoire et la pratique clinique. La recherche translationnelle constitue l'interface entre les sciences de base et la médecine clinique, et est ainsi la force derrière les avancements médicaux et l'amélioration des soins prodigués aux patients. Il s'agit d'un processus très couteux surmonté de défis qui nécessite la collaboration des chercheurs, des cliniciens-chercheurs et des épidémiologistes.

L'impact de la médecine translationnelle ne peut être mieux démontrée que par deux exemples de grands succès canadiens au cours de la dernière année. En janvier 2012, NA1, un agent neuroprotectif découvert en 2001 [1] par une équipe de recherche à Toronto, a complété avec succès un essai clinique de phase 2 chez des patients ayant souffert d'un accident cérébrovasculaire [2, 3], un succès énorme vu les 1000 agents thérapeutiques neuroprotectifs qui n'ont pas pu être évalués chez les humains [4]. Une grande partie du succès de NA1 peut être attribuée à la somme de connaissances en neurosciences de base accumulées au cours de plusieurs décennies, qui ont permis de mieux comprendre les mécanismes de mort neuronale suite à l'ischémie cérébrale. Au cours du mois pendant lequel NA1 complétait ses essais cliniques de phase 2, le vaccin SAV001 développé par une équipe de chercheurs à London a reçu l'approbation de la FDA aux États-Unis pour les essais cliniques chez les humains [5]. SAV001 est le seul et unique vaccin contre le VIH conçu à base de virus entier (VIH-1) mort et modifié de façon génétique, qui constitue ainsi une version non pathogène du virus, et qui peut également être produit en grandes quantités. NA1 et SAV001 sont tous deux sur le point de devenir des grands avancements en thérapie clinique.

Deux articles publiés dans cette édition sont une bonne représentation de la médecine translationnelle. Le premier article fait objet d'une entrevue avec Dr John Bell, un leader mondial dans le domaine de la recherche avec les virus oncolytiques, et le récipiendaire du Career Achievement Award de l'Institut de Recherche de l'Hôpital d'Ottawa. Dr Bell partage avec nous l'histoire inspirante de sa carrière dans le domaine de la médecine translationnelle, racontant le cheminement de ses travaux *in vitro* jusqu'aux essais cliniques. Le deuxième article met en vedette Dr Michael Schlossmacher, le directeur du programme M.D./Ph.D. de l'Université d'Ottawa, qui nous donne un survol du programme et son évolution depuis l'admission des premiers candidats en 2010.

Nous sommes ravis des articles sélectionnés pour paraître dans cette édition et de leur diversité. Cette édition inclut quatre articles rédigés par des étudiants en médecine du volet francophone, dont deux sont publiés en français. Nous y trouvons également deux articles publiés par des étudiants gradués. Les publications sont diverses, s'étalant de la recherche originale en épidémiologie clinique, à un rapport au sujet de la neurochirurgie expérimentale, et à l'expérience d'une étudiante qui a fait du bénévolat dans un hôpital de maternité au Kenya.

Nous espérons que vous appréciez cette édition de mai 2012 autant que nous avons pris plaisir à sa création.

Wayne Huang & Yue Jiang
Rédacteurs en chef

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Medical research beyond the mouse model: An interview with Dr. John C. Bell

Tyler Kaster, BSc[1]

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Dr. John C. Bell

I'm walking down the naturally lit hallway and find myself surrounded by sterile white walls and subdued men and women. I see a middle-aged woman in an oversized chair covering her head with a blue-white bandana. Further down the hall is a young man with a shaved head and prominent scar on his right temple. To my left is a woman running towards the washroom covering her mouth with a hand. I find myself slightly uncomfortable, as if I don't belong in the Ottawa Cancer Centre where all these individuals are battling cancer, the bane of modern medicine.

Cancer is a nasty, devious disease, which has confounded all attempts at a cure. Uncontrolled cellular growth forms malignant tumors which spread to distant parts of the body. Most cancers are treated with one of three approaches: chemotherapy, radiation therapy, or surgery. The goal of each is to selectively target cancer cells, while sparing healthy cells. However, these tools are imperfect and will damage innocent bystander cells, which can lead to many side effects, among them: hair loss, surgical scars, and nausea. Patients often describe the treatment of cancer as worse than the disease itself. However, there is hope for the future of cancer treatment from a radical therapeutic approach being developed by researchers at the University of Ottawa. I am on my way to meet the Canadian, and perhaps international, leader in this exciting field.

I walk up three flights of polished marble stairs to Dr. John Cameron Bell's laboratory, which occupies almost the entire third floor. Dr. Bell was ranked by MacLeans readers in a 2003 online poll as the third most important Canadian. His work has inspired headlines such as "Breakthrough cancer treatment trial" [1] and "Promising new way of fighting cancer" [2]. I am here on behalf of the University of Ottawa Journal of Medicine to find out why Dr. Bell and his work are receiving such acclaim. I call the secretary on the courtesy phone outside a locked door, and she buzzes me into the secure laboratory where I meet the man himself. He's dressed casually wearing an olive-green zip-up sweater and jeans, and has a round, open face, with a genuine smile. We make small talk for a few minutes before moving to a conference room where our real conversation begins.

Dr. Bell's scientific career began at McMaster University where he obtained his PhD in virology in 1983 under Ludvik Prevec, PhD with the thesis: "Studies on NS the phosphoprotein in Vesicular Stomatitis Virus" [3]. After Dr. Bell's PhD he came to the University of Ottawa where he studied molecular signalling in cancer cells as a post-doctoral student under Michael McBurney, PhD in a research group funded by the Terry Fox Foundation. From there he went to the prestigious National Institute for Medical Research (NIMR) in London, England for another post-doctoral research year, this time under the supervision of Gordon Foulkes, PhD, to continue his work on the disrupted molecular pathways in cancer. Both Dr. Bell's initial work with viruses, and his later work with on cancer signalling would play an important role in his future research.

Dr. Bell reflected on the lessons learned from each of these experiences. From his PhD supervisor, "who took me on when I didn't know anything at all…[Dr. Prevec] taught me the scientific principles and how to write scientific papers. He was key to getting me interested in the whole area [science]." While Dr. Bell learned practical scientific skills from his PhD supervisor, his philosophical views on science and collaboration were shaped by his first post-doctoral supervisor. "Mike [McBurney]'s a very open guy, very collaborative and I think all my views about science were in some way moulded by Mike's influence… he thinks anything is possible, and if you think anything is possible then you're not afraid to try things. You're also not afraid to fail and that's key because science is mostly failure." Dr. Bell's time in England at the NIMR was important because of the calibre of scientists who surrounded him. He described it as a "fantastic place to work…the greatest minds in science would come through London…we heard from Nobel Prize speakers all the time".

After his final post-doctorate, Dr. Bell spent several years at McGill before moving in 1989 to his present location at the University of Ottawa and Ottawa Hospital Research Institute. When asked why he chose Ottawa, Dr. Bell attributed his decision to the vision of scientists working at Ottawa. "Mike McBurney was forming this research group, and our vision at the very beginning was to do science that would translate into clinical practice… we started from the very beginning to arrange the clinicians and scientists to work together. This building [Ottawa Cancer Centre] is beautifully setup. Clinics are on the first two floors…we are on the third floor so we actually have an opportunity to interact with some of the clinicians who have offices down the hall from me". This collaboration with physicians is critical to Dr. Bell's work, which was made clear when he said, "You can spend your life curing mice and never get where you need to be. The issues about developing therapeutics for humans are completely different than they are for mice. I have that perspective now because I speak to clinicians… we're honing our therapeutics to deal with the issues that affect cancer patients and not cancer mouse patients."

While the opportunity for collaboration with clinicians was a major reason for Dr. Bell coming to Ottawa, he also values collaboration with other basic and translational researchers. "I love it", says Dr. Bell referring to collaboration, "It's what I think enriches my day…it's really paid off for us…whatever we've given out, we've received back tenfold because we've had great collaboration with people from across Canada". Dr. Bell has worked with researchers from British Columbia, Calgary, Toronto, Hamilton, Montreal, and Halifax. Outside of Canada, he has also collaborated with researchers at the Mayo Clinic and in the United Kingdom.

I had the opportunity to speak with two of Dr. Bell's close collaborators at the University of Ottawa, Dr. David Stojdl (a former graduate student) and Dr. Michael McBurney (a former supervisor), about Dr. Bell, and they both commented on Dr. Bell's ability to function as both team member and team leader. Dr. Stojdl told me, "what separates him most from his peers is his ability to make everyone feel part of a team that is doing something very important…John Bell's humour, focus and natural accord with colleagues and trainees alike, brings these teams together and makes them shine". Dr. McBurney has a similarly favourable view of Dr. Bell, described when he told me, "Dr. Bell suffers from being a very generous guy… He ended up being an important glue that held the research group together. He takes an active interest in everything going on around him and is able to help anybody having technical or intellectual problems".

This team-based approach to tackling complex biological problems has been very successful for Dr. Bell and his collaborators. He has published over 150 research papers (a recent PubMed search yielded 193 results), filed 16 patents and trained more than 40 students. For his pioneering research he received the Researcher of the Year Award in 2000 and the Career Achievement Award in 2010, both from the Ottawa Hospital Research Institute [4]. These awards recognize Dr. Bell for his important contributions to the burgeoning field of oncolytic viruses, a field that he has been instrumental in developing.

Although viruses were known to have cancer-fighting properties as early as 1912 [5], the systematic study of oncolytic viruses is a new field experiencing a surge of interest due to genetic tools which make it possible to engineer viruses that can target tumor cells. In normal cells there are specific enzymes that protect against viruses, which become dysregulated in cancerous cells. This is a weakness that could potentially be exploited to treat cancer. However, first it needed to be shown that organisms without this enzyme were susceptible to viral infection. This led Dr. Bell, with then-graduate student Ninan Abraham (now at University of British Columbia) in 1998 to breed a line of mice which lacked a specific enzyme that protected against viruses and was also dysregulated in cancer [6]. They were able to show that these mice were more susceptible to viral infection than their wild-type counterparts. However, it was not yet clear if this discovery could be exploited and used to destroy cancerous cells.

The big breakthrough came in 1999 over the Christmas holidays. Dr. Bell described this discovery to me, saying it occurred, "when everybody had gone home, and I actually had a chance to work again in the lab…we [himself, David Stojdl, and Brian Lichty] did a few experiments… and recognized very early on that these viruses could kill tumor cells beautifully and did not damage normal cells in the tissue culture plate. Then we started doing mouse experiments and sure enough in mice it was the same." This discovery was the perfect example of scientific discovery that Dr. Bell had described to me. Science requires a combination of hard work (being in the lab at Christmas), collaboration (working with bright people), and luck (science being mostly failure).

The field of oncolytic viruses has advanced tremendously since 1999 from ad hoc experiments performed in an empty lab over Christmas break to the present day where an oncolytic virus startup company was recently acquired for $1 billion [7]. These viruses hold enormous

promise for the treatment of cancer, but in order to benefit the patient, they need to leave the laboratory and move to the patient's bedside. For this reason Dr. Bell, Dr. Harold Atkins (Ottawa Health Research Institute), Dr. David Stojdl (Children's Hospital of Eastern Ontario), and Dr. David Kirn (from San Francisco) formed Jennerex Therapeutics in 2006 to access resources required to bring their novel therapy to market. The results have been very promising so far, with two oncolytic viruses in clinical trials (named JX-594 and JX-929) and another in pre-clinical stages (JX-1395).

In September of 2011, Jennerex published results in the Journal Nature revealing very promising data about the JX-594 virus. Eight patients were given the two highest doses of virus, and the tumors of six of those patients stabilized or decreased in size with minimal flu-like side effects. Dr. Bell described this paper as extremely important for the field of oncolytic viruses because it "showed we could give virus intravenously in a single dose, wait 7 days, and biopsy the patient and find the virus growing in the tumor but not in the normal tissues of that patient". Delivering cancer therapeutics systemically is critical to the treatment of cancer, because as Dr. Bell told me, "the challenge in cancer is not the single tumor that can be removed surgically, it's the metastatic cancer". JX-594 is currently in a Phase 2b multinational trial that will enroll 120 patients with advanced liver cancer who have failed traditional therapies.

There is tremendous potential for using oncolytic viruses as a cancer treatment. Much of this excitement is due to the ground breaking work done by Dr. John Cameron Bell and his collaborators. Despite being a prominent scientist at the forefront of his field, when asked if there was anything else he wanted to mention, rather than focusing on the technical aspects of his work, Dr. Bell stressed how important the public is to scientific research in Canada. "All the science that is done in Canada is supported by Canadians…they pay it through their taxes, they pay it through their donations and everything we do as scientists and clinicians comes from the people of Canada and they should hear about what we do, and they should be thanked for what they do." His message to the people of Canada is that, "Science is really important, and it's important for our economy it's important for our life our health and thank goodness you guys make donations towards it".

The pressure to deliver better health care options and to make them more affordable to governments and individuals is fueled in part by a rapidly expanding pool of knowledge in the fields of clinical medicine, basic sciences and related disciplines. However, there is a growing mismatch between our society's increasingly complex health management needs and the availability of new, validated care options This quote epitomizes Dr. Bell's selfless attitude as described by Dr. McBurney – "John is deserving of success and wears it well. He remains humble". Dr. Bell recognizes the critical role the public plays in determining scientific priorities. Any research endeavour by the scientist is a collaboration between the public, who provides support, and the researcher, who carries out the work. The grand promise of medical research is that one day, the work being funded will improve the lives of its supporters. By acknowledging the key role which others have played in his success, whether they were supervisors, graduate students or the Canadian public, Dr. Bell reinforces my belief that he is a gifted scientist and model Canadian.

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The M.D./Ph.D. program at the University of Ottawa: Overview and first performance report for 2009-2012

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ABSTRACT

In late 2009, the Senate of the University of Ottawa approved a dual degree program that integrated its existing undergraduate medical school curriculum with six established graduate school curricula. The vision behind the newly minted M.D./Ph.D. Program (http://www.med.uottawa.ca/md-phd/eng/index.html) is to attract and train future leaders in health care-related fields, thereby also exemplifying the interdisciplinary efforts in educational and research activities at our bilingual university. During the first three years, the M.D./Ph.D. Program has received 676 applications. As of spring 2012, 40 candidates were interviewed and 11 students were admitted. Our goals for the immediate future include (among others): to promote the pursuit of academic excellence through mentored guidance of all students during their 7 year-long journey; to expose our trainees to the many career opportunities available to physician-scientists; to increase the number of participating graduate programs in the M.D./Ph.D. curriculum; to create a strong foundation for the continued financial support of all M.D./Ph.D. students; and last but not least, to begin tracking the professional paths chosen and contributions made by our trainees. These aims will encompass important outcome measures to ultimately gauge the contributions of the M.D./Ph.D. Program to the success of our university and to Canadian society.

INTRODUCTION

The pressure to deliver better health care options and to make them more affordable to governments and individuals is fueled in part by a rapidly expanding pool of knowledge in the fields of clinical medicine, basic sciences and related disciplines. However, there is a growing mismatch between our society's increasingly complex health management needs and the availability of new, validated care options that can actually be delivered [1]. Because we also witness more and more sub-specialization within health care-related fields, we are facing the increased need for individuals to conceptualize and explore continuously emerging topics that cross conventional boundaries. Accordingly, there is a growing need in Canadian society for well-prepared leaders in the health care profession and in its many allied sectors, who not only have learned the traditional craft of medicine but are also skilled in the pursuit of scientific discovery and knowledge translation. With the creation of its inaugural M.D./Ph.D. Program in Ottawa in late 2009, the university signaled to actively participate in the education of future leaders for Canada's health care services and related biomedical fields.

The M.D./Ph.D. Program at the University of Ottawa seeks to attract and foster the small cadre of individuals that are described by the Canadian author Malcolm Gladwell as "outliers" [2]. Outliers can be found in many incoming medical and graduate school classes around the world. The province of Ontario is home to four M.D./Ph.D. Programs that are located at the: University of Toronto (their dual degree program was founded in 1984) with 4-5 students selected per year [3]; University of Western Ontario (since 1995) with 3-4 new students per year [4]; McMaster University (since 2007) with 3 students selected per year [5]; and University of Ottawa (since 2009) with 3-4 new students chosen per year. Of note, Queens University finalized its planning stage and is scheduled to start its inaugural M.D./Ph.D. Program in the fall of 2012 [6].

Details of the M.D./Ph.D. Program at the University of Ottawa can be found at its website, http://www.med.uottawa.ca/md-phd/eng/index.html. Here, we provide excerpts of the program's structure, a summary of the results available since its inception, and our future goals.

RESULTS

1. General Outline of the Program

A graphic summary of the curriculum is provided in Figure 1. The M.D./Ph.D. Program at the University of Ottawa is offered as a single, integrated curriculum (Figure 1) and combines:

The undergraduate M.D. track: Its curriculum remains essentially unchanged except for an alteration in its timetable: The 4-year medical curriculum is interrupted between the second and third year of medical school to accommodate the student's full-time pursuit of a Ph.D. degree. M.D./Ph.D. students also have to complete graduate course work (1-2 depending on their background) during the first two years of medical school. During summer laboratory rotations, the student registers in the chosen Ph.D. program and develops and initiate his/her research project.

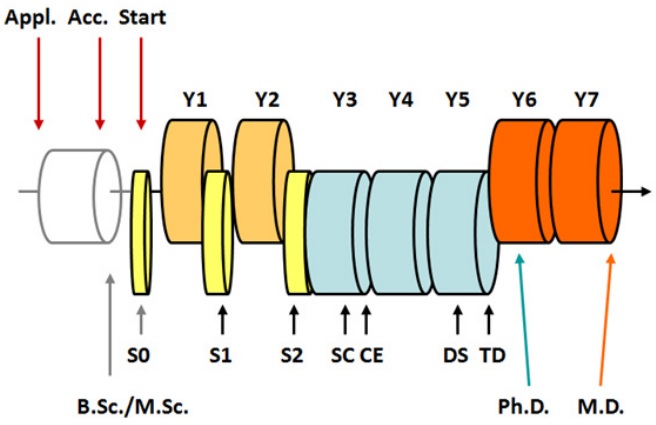

Figure 1. Graphic summary of the M.D./Ph.D. program at University of Ottawa. "Appl. Acc. Start" denote the application to OMSAS in the fall preceding admission, the acceptance, and the start of the seven year program; "Y" denotes year in the program; "S", summer; "SC", seminar course; "CE", comprehensive exam; "DS" department seminar; and "TD", thesis defense. Note, elevated rings (in orange; red) indicate time spent in blocks of the undergraduate medical school curriculum; lowered rings (yellow; blue) indicate time predominantly spent in graduate school-related activities.

The Ph.D. program curriculum: In addition to completing graduate course work during the first year (or first two years) of the undergraduate medical school curriculum, students initiate their research project in their chosen program during the summer months. At the beginning of Year 3 (Figure 1), students formally transfer to the Ph.D. program and complete three years plus one term for a total of 10 sessions of full-time graduate studies. Currently, the M.D./Ph.D. Program has partnered with the following independently approved doctoral programs located at the campuses of the Faculty of Medicine and Faculty of Science to educate our dual degree students: (1) Biochemistry; (2) Biology; (3) Cellular and Molecular Medicine; (4) Human and Molecular Genetics; (5) Microbiology and Immunology; and (6) Neuroscience.

An important feature of the integrated program is its focus on reducing the length of time spent in training. We envision that M.D./Ph.D. graduates will complete the new program in seven (to seven and a half) years rather than the eight to nine years currently required for individuals who complete their degrees sequentially without an integrated structure. The focus on successfully completing a dual degree path within a given time frame represents an essential component of long-standing M.D./Ph.D. Programs; at the University of Ottawa, it will be facilitated by ensuring that trainees will be supervised by faculty members with a proven track record of successfully mentoring Ph.D. students, by the matching of scientific projects of higher probability to move toward completion with the ideal candidate, and through the close mentoring of trainees by dedicated members of the Program committee. Note, that despite the potential benefit of time reduction for these trainees the leadership of our participating graduate programs is committed to holding our students in the combined degree program to the same rigorous academic standard that all Ph.D. students are subjected to during their graduate work.

2. Applicants and Selection

There are three streams from which the university is currently recruiting future M.D./Ph.D. students: (1) Applicants that hold a B.Sc. Honours degree and have a documented record of research conducted during their undergraduate years; (2) Applicants who have already obtained a Masters degree; and (3) Applicants currently enrolled in a Masters program who have not yet completed their thesis. The selection process of students for the M.D./Ph.D. Program is outlined at: http://www.med.uottawa.ca/md-phd/eng/index.html. It entails five steps.

Step 1. Initial Application: Students first apply to the M.D./Ph.D. Program at the University of Ottawa through OMSAS at http://www.ouac.on.ca/omsas/omsas-info/. In addition, they submit a letter of interest and their CV to the M.D./Ph.D. Program committee indicating their graduate program(s) and research topic(s) of interest; they also facilitate the submission of letters of recommendation from previous science teachers or supervisors.

Step 2. Assessment by the M.D. Program: All OMSAS applications submitted to the combined program are initially assessed by the admissions committee of the undergraduate M.D. Program. Applicants will not be admitted to the M.D./Ph.D. Program, if they have not fulfilled all criteria set forth by the M.D. Program.

Step 3. Assessment by graduate programs: Graduate program representatives of the M.D./Ph.D. Program independently review completed applications. A committee formed by directors and administrators of the graduate programs then ranks applicants based on their research experience and scientific potential.

Step 4. Interviews: In the spring preceding admission to medical school, select candidates are interviewed along with other M.D. applicants. A senior member of the M.D./Ph.D. committee participates in all interviews of potential candidates for the combined program.

Step 5. Final admission process: Following the completion of interviews, the M.D./Ph.D. Program committee members submit their final rank list to the Office for the Dean of Admissions. The M.D. Program formally sends an offer letter of admission to each selected candidate including those chosen for the M.D./Ph.D. Program.

Table 1. M.D./Ph.D. Program at the University of Ottawa. Application and admission numbers since approval in late 2009.

	2010	2011	2012
Number of applicants that clicked M.D./Ph.D. Ottawa (via OMSAS) in the fall prior to admission	169	252	255
Number of applicants who passed initial M.D. admissibility criteria for further consideration	49	27	22
Number of applicants invited for interviews after their scientific background evaluation	20	12	8
Number of candidates actually interviewed	16	10	8
Number of candidates ranked following joint interviews	12	7	7
Number of M.D./Ph.D. students admitted as part of the incoming M.D. class	4	3	4
Relative representation of M.D./Ph.D. students per total number of incoming M.D. class	1.83%	1.82%	TBD
Total number of students enrolled in the M.D./Ph.D. Program (as of September)	4	6	10
Total number of M.D./Ph.D. students enrolled in the francophone stream of medical school	1	2	4
Total number of female students in the M.D./Ph.D. Program	0	1	2

3. Recruitment Results (Years 2009 to 2012)

Enrolment numbers since the inception of the program are shown in Table 1. To date, the M.D./Ph.D. Program has received 676 applications (as tracked by OMSAS) over the course of three completed enrollment cycles (mean, 225/year). As of spring 2012, 40 candidates were invited for interviews (~13/yr), 34 applicants proceeded with their interviews (~11/yr), 26 were ranked following their interviews (~9/yr), 16 admission offers were made (~5/yr), and 11 students were admitted. During the early phase of the program, as many as four positions are to be filled annually (see Table 1). In accordance, we calculated an annual acceptance rate of 1.6%. One student who was admitted in 2010 had to withdraw from the combined program citing personal reasons. Among 10 students currently enrolled in the combined program, four pursue their medical studies in the Francophone stream (40%); to date, women are underrepresented (20%). The total group of actively enrolled M.D./Ph.D. students in the Program is expected to reach 28 trainees by 2017.

4. Stipends and Scholarships

In general, M.D./Ph.D. students are subject to the tuition fees for the program in which they are enrolled during any given session of their 7-year study. However, since its inception, endowed scholarships and funding commitments made by the Faculty of Medicine and affiliated institutions have provided financial support for each trainee. All of our first year students received the equivalent of their tuition costs for Year 1 through the "Dean's M.D./Ph.D. Fund". In Year 2, tuition costs for medical school were covered for each M.D./Ph.D. student in the program following applications for support through endowed scholarships that were created in the name of former alumni and through funds provided by the Ottawa Heart Institute. In 2011, each second year student began to apply for external funding from federal and provincial sources in preparation of graduate work beginning in Year 3. During the sessions of full-time graduate studies, the research supervisor provides his/her trainee with a stipend from operating grants. Furthermore, merit-based Graduate Admission Scholarships and Graduate Dean's Scholarships are awarded to M.D./Ph.D. students as per general guidelines (http://www.med.uottawa.ca/md-phd/eng/index.html).

DISCUSSION & FUTURE DIRECTIONS

The driving force behind the newly created M.D./Ph.D. Program at the University of Ottawa was and remains to attract the small number of students with a high potential to grow into future leaders of the health sciences and allied fields. In the past, these trainees' interests to pursue a dual career pathway here in Ottawa could not be accommodated (and as a result, students were lost to other academic centers). However, today M.D./Ph.D. students exemplify the multi-disciplinary nature of the ongoing educational and scientific activities at our bilingual university.

Our shared vision for the immediate and near future of the M.D./Ph.D. Program at the University of Ottawa encompasses 10 specific goals:

1. To promote the pursuit of academic excellence through mentored guidance of all M.D./Ph.D. students in synergy with their supervisors and course directors;
2. To increase the number of women selected for the combined program (from the current low of 20%);
3. To expose our trainees to the spectrum of physician-scientists' activities at regional, national and international levels. Locally, this aim will include coordination with educational activities of the "Clinician-Investigator Program" (C.I.P.) [7];
4. To offer an increasing number of graduate courses during the summer months, which will attract both M.D./Ph.D. trainees and Ph.D. students;
5. To expand the number of participating programs in the M.D./

Ph.D. curriculum, such as through the inclusion of graduate studies in epidemiology after 2013;

6. To create a new forum that fosters the regular exchange between three important constituencies of our student body, i.e., those actively enrolled in the M.D. curriculum with a desire for additional research exposure; students in diverse M.Sc. and Ph.D. graduate programs with a strong interest for exposure to the medical sciences; and M.D./Ph.D. students, who will benefit from a growing cohort of like-minded peers, amid predictable changes in the makeup of their classmates during the >7 year curriculum;
7. To create a well-endowed fund for continuous stipend and scholarship support for all our M.D./Ph.D. students. This aim is of particular relevance in light of the increasing difficulty to secure federal funding support for clinician-scientist trainees in Canada. In the United States, M.D./Ph.D. Programs have grown considerably over the last >30 years in no small part due to the strong support from the National Institutes of Health [8]. We note with great interest that several Ontario-based M.D./Ph.D. Programs have recently announced strong stipend commitments for their enrolled students [3, 6].
8. To provide regular updates on our program's performance and stimulate a provincial and national debate regarding the long term benefits (and costs) of training students in two disciplines. To this end, in 2011 several M.D./Ph.D. students from the University of Ottawa have begun to participate in "CITAC" activities, i.e., the Clinician Investigator Trainee Association of Canada, which holds its annual meeting in the city of Ottawa. Of note, the benefits of C.I.P. and M.D./Ph.D. Programs to knowledge-based industries in Canada have recently been highlighted in a special report delivered to the Council of the Deans of Canada's Medical Faculties [9];
9. To catalogue accomplishments of our current students and future M.D./Ph.D. graduates, and to actively support them in their quest to identify the best career choices for the time after completion of the program;
10. To longitudinally track the career paths chosen and future positions attained by our trainees. This effort will become part of a network comprising all dual degree programs in Canada [9]. Important outcome measures embedded in these ten goals will ultimately help to gauge the contribution of our M.D./Ph.D. Program to the success of the University of Ottawa and to Canadian society.

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Deep brain stimulation for psychiatric conditions: A return to the dark ages or a revolution in treatment?

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The surgical treatment of psychiatric disorders has had a long and controversial past. With the recent rise of interest in the application of Deep Brain Stimulation (DBS) for neuropsychiatric conditions, flashbacks to the dark age of the ice-pick lobotomy may come to mind. The objective of this paper is to briefly outline the history of psychosurgery and DBS (Figure 1), to mention the current indications for DBS in the treatment of neuropsychiatric conditions, and to outline the role of the medical professional in the successful implementation of this technology.

1888	First modern psychosurgery
1935	Moniz performs first leucotomy
1947	Stereotactic apparatus described by Speigel and Wycis
1949	Nobel Prize awarded to Moniz
1952	Delgado describes in detail the implantation of intracranial electrodes
1954	FDA approves first psychotropic drug, chlorpromazine
1955	50,000+ lobotomies done, many by the "ice-pick" method popularized by Freeman and Watts
1969	Introduction of L-dopa
1970	Public backlash against and legislation against psychosurgery
1987	Benabid and Pollack describes DBS for tremor
1993	Benabid and Pollack describes STN DBS for PD
1997	FDA approves STN DBS for advanced PD
2009	FDA grants humanitarian device exemption for DBS and OCD
Present	Intensive basic and clinical research into DBS for many neuropsychiatric disorders

Figure 1. Important Milestones in the History of Psychosurgery and DBS (DBS, Deep Brain Stimulation; STN, Sub-Thalamic Nucleus; PD, Parkinson's Disease; OCD, Obsessive-Compulsive Disorder; FDA, United States Food and Drug Administration).

PSYCHOSURGERY

The idea that surgery may help disorders of the mind has been around for centuries. For example, archaeologists have found evidence that holes were drilled into human skulls for psychological reasons as early as 5000 years ago [1,9]. The first modern psychosurgery was performed by the Swiss psychiatrist Gottlieb Bruckhardt in 1888 [2,9], but the Portuguese neurologist Egas Moniz is often regarded as the founder of this field. With the assistance of neurosurgeon Almeida Lima, he performed the first prefrontal leukotomy in 1935 [2]. According to Moniz, the first 20 operations showed great promise: "35% healed, 35% improved, 30% unchanged, no worsening, no cases of death" [2]. However, many undesirable effects resulting from the surgery were described as temporary, and his inaccurate description of the technical parameters gave rise to skepticism about this initial reporting. This controversy was captured when the German psychiatrist Siegfried Haddenbrock equated leukotomy to the "definitive destruction of the self-confident and free personality of the human being" [2]. Despite this, Moniz was awarded the Nobel Prize in Medicine (1949) for the "discovery of the therapeutic value of prefrontal leukotomy at certain psychoses". A student of Moniz, Walter Freeman, and his colleague James Watts, modified the procedure so that it could be performed in an outpatient setting. This operation, known as the frontal lobotomy, was performed on approximately 50,000 people by 1955 [1,2].

DEEP BRAIN STIMULATION

The idea of influencing the activity of the brain with electrical stimulation to help psychiatric disorders has been around, indirectly, since antiquity. In the text Compositiones Medicamentorum (46 AD), the physician of the Roman emperor Claudius suggested the application of electrical rays on the surface of the head for treatment of headache [3]. Today, the contemporary DBS system consists of an electrode that is implanted in a specific area of the brain and is powered by an implantable pulse generator (Figure 2B). Modern DBS can be traced back to 1947, when Speigel and Wycis described a stereotactic apparatus (Figure 2A) that was used in humans to perform ablative procedures [4]. At this time, intraoperative stimulation was used only to explore brain targets before lesioning. The first applications of this surgery were aimed at avoiding the side effects of the frontal lobotomy [3], but Speigel and Wycis soon turned their attention to the treatment of movement disorders. Importantly, they noticed that stimulation could not only be used diagnostically, but had a therapeutic effect itself [3,4].

In 1952, the Spanish neuroscientist Delgado first described in detail the technique of chronic intracranial electrode

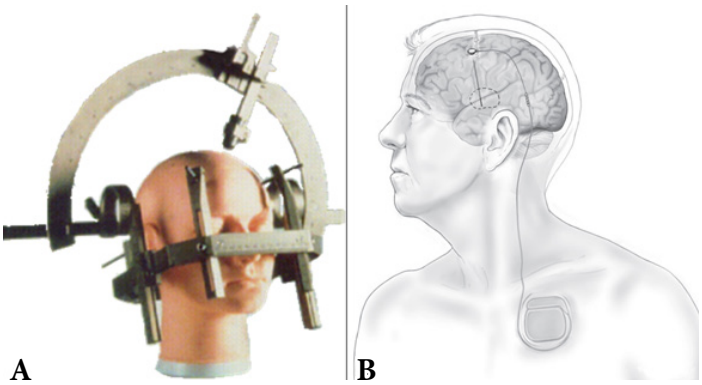

Figure 2. A) Diagram of a typical stereotactic frame. The apparatus is used with a map of brain coordinates to precisely insert electrodes into specific nuclei in the brain. http://www.ariser.info/training/imgproc.php. B) Graphic representation of the modern Deep Brain Stimulation system. An implanted pulse generator and subcutaneous extension wires power implanted electrodes. Image from [29].

implantation in humans, and emphasized its possible role in patients with mental disorders [3,4]. Over the next couple of decades he performed many experiments in animals, of which the most (in)famous was his theatrical demonstration of stopping a charging bull with the press of a button, through remote brain stimulation. He also implanted electrodes in 25 human subjects who suffered from epilepsy or schizophrenia, and in 1969 discussed this research and the ethical implications in his book Physical Control of the Mind: Toward a Psychocivilized Society [3,4].

THE DECLINE OF PSYCHOSURGERY AND FUNCTIONAL NEUROSURGERY

When the United States Food and Drug Administration (FDA) approved the psychotropic drug chlorpromazine in 1954, there was suddenly a chemical treatment for psychiatric disorders. The role of the leukotomy was re-evaluated because it was no longer the only method for treating psychiatric patients. Experts acknowledged that the clinical trials supporting the use of psychosurgery were poorly designed and lacked statistical integrity. As well, the psychological evaluation after the surgery was subjective and lacked scrutiny [1, 9]. It also came to public awareness that the lobotomy was not being used as a last resort (as was its intended use), and there were reported cases in which little investigation was done prior to the procedure [1]. The early experimental phase of DBS has also been deemed "dubious and precarious by yesterday's standards" [4]. Hariz argues in his recent review of this time period that the "errant behavior", "excesses", and "abuses of that early era" were often performed by non-neurosurgeons who worked in isolation [4]. These early abuses, the introduction of psychotropic drugs in the mid 50's, and the approval of L-dopa in the late 60's, led to a sharp decline in psychosurgery and functional neurosurgery. In the 1970's there was great social debate on psychosurgery, and as a result many government bodies enacted legislation aimed at limiting these procedures [5].

MODERN DBS

Psychosurgery and functional neurosurgery continued in a limited fashion until the modern age of DBS (Figure 2B). This era began in 1987 with the publication by Benabid and Pollak on thalamic stimulation contralateral to thalamotomy for patients with bilateral tremor [28]. The fact that DBS is a relatively reversible treatment made it more attractive, and because of its greater safety profile DBS replaced lesioning in the treatment of tremor. In 1993, the same group reported subthalamic nuclei (STN) stimulation for advanced Parkinson's Disease (PD), and documented its safety and efficacy in reducing symptoms such as bradykinesia, tremor, and rigidity [3,4]. In 1995, DBS for tremor was approved in Canada, and gained FDA approval two years later. STN DBS for PD was approved by the FDA in 2002, and one year later the use of DBS for dystonia was granted a Humanitarian Device Exemption. Since then, more than 80,000 patients have undergone DBS for movement disorders, with an impressive safety and efficacy profile when patients are selected appropriately [for example see 6,7,8].

In 2009, the FDA granted a humanitarian device exemption for the treatment of Obsessive Compulsive Disorder (OCD) by DBS. Experimental use of DBS continues in many other neuropsychiatric disorders; the most notable being Treatment-Resistant Depression (TRD) [10, 11, 12, 32]. Fifty percent of functional neurosurgeons are engaged in some form of psychiatric surgery, and most see the use of DBS for the treatment of neuropsychiatric disorders becoming an increasing part of their practice [13]. In fact, there are many emerging uses of DBS (Table 1). Despite this,

Condition	Status (United States)
Parkinson disease	FDA approved
Essential tremor	FDA approved
Dystonia	FDA approved
Cluster headache	Experimental
Trigeminal neuropathy	Experimental
Chronic pain	Experimental
Tourette syndrome	Experimental
Obsessive-compulsive disorder	Humanitarian device exemption
Depression	Experimental
Epilepsy	Experimental
Restless legs syndrome	Experimental
Obesity	Experimental
Addiction	Experimental
Disorders of minimal consciousness	Experimental
Alzheimer disease	Experimental

Table 1. Indications for Deep Brain Stimulation and their current regulatory status. Table modified from [30].

the neural mechanism of action is not completely understood. It is known that there is an immediate, local, inhibitory effect of high-frequency stimulation that simulates a lesion [33, 34]. However, many researchers think that the fundamental mechanism of DBS is through modulation of distributed brain networks by interfering with pathological oscillatory activity [33,34,35]. This is an area of intensive basic research. Given the increased interest in this technology, several ethical considerations must be kept at the forefront of our attention to avoid repeating the injustices of the past.

PATIENT SELECTION

The selection of appropriate patients is an active area of research, and criteria based on recent clinical studies [10, 32] are proposed as follows: (1) Chronic (greater than three years) Major Depressive Disorder (MDD). (2) Failed three medication trials (including different classes and augmentation strategies). (3) Failed at least one course of psychotherapy. (4) Electroconvulsive Therapy (ECT) resistant (greater than five unsuccessful trials). (5) Current Global Assessment of Function (GAF) of less than 50. (6) Current 17-item Hamilton Rating Scale for Depression (HRDS-17) score >20. (7) Mini-Mental Status Exam (MMSE) score >27. (8) No contraindications (Table 2). The criteria will vary for every indication of DBS. The primary caregiver must work with a multidisciplinary team, including the patient's psychiatrist, an independent psychiatrist, a neurologist, and a neurosurgeon, to determine who is a good candidate [21].

Contraindications
Co-morbid psychiatric disorder based on DSM-IV-TR
Alcohol or substance dependence
Current substantial suicide risk
Neurological disorder that impairs motor, sensory or cognitive function
Established cardiovascular disease
Likely to fail to comply with follow-up
Pregnant or plans to become pregnant in next 12 months
Past intracranial neurosurgery
Clinically relevant abnormality on MRI
Unable to give informed consent in accordance with institutional policies

Table 2. Contraindications to Deep Brain Stimulation for Treatment-Resistant Depression. Based on [32].

AUTONOMY & CONSENT

Like any other medical procedure, patients undergoing DBS must give their voluntary and fully informed consent. According to Skuban et al. [17], this requires meeting three basic requests: (1) all medically relevant information about diagnosis and prognosis of a patient's disease, the treatment, its potential risks, and alternative therapies must be disclosed. (2) The patient should have the mental capacity to understand his/her situation and the presented information. (3) The patient must not be coerced or compelled, but autonomously decide on the treatment on the basis of the information disclosed [17]. When communicating with the patient, the medical professional must take into account the unique characteristics of the patient population. These patients have chronic treatment-resistant psychiatric disorders, which may confound their ability to make appropriate decisions. In this regard, it needs to be clearly stated that DBS does not cure any disease, but may provide symptom control. It is the responsibility of the medical team to ensure that all these factors are taken into account before making any decision on treatment.

BENEFICENCE & NON-MALEFICENCE

This may be the most obvious ethical issue: does DBS benefit the patient and do the benefits out-weigh the expected risks? The risks include both the complications of the procedure and the side effects of the electrode stimulation. The complications of the procedure have been well established and include haemorrhage (1.3-4%), seizures (0.4-2.8%), infection (2.8-6.1%), lead migration (5.1%), lead breakage (5.0%), malfunction of the pulse generator (0.4-9.7%), and even death (0.4%) [19]. Side effects from the stimulation can be much more variable as they depend on where the electrodes have been placed and the stimulation parameters. Evidence from STN stimulation for advanced PD suggest that some adverse events include speech disturbances (10.8-33%), memory impairment (1.1-20%), hypomania (4.2-10.2%), depression (1.5-25%), disturbance in patients perception of themselves (66%), and familial problems (50-71%) [19]. However, if these are intolerable, stimulation can be turned off or reduced. For movement disorders such as PD, essential tremor, and dystonia, DBS has been proven effective [6,7,8]. For psychiatric disorders the evidence is promising but much scarcer. A recent paper published by a group led by Andres Lozano at the University of Toronto, showed an average response rate of 64.3% 6 years after DBS electrode placement in patients with TRD [10]. Based on a recent review, an improvement of 35% in a key symptom scale was seen in 50% of treatment resistant patients with OCD [20]. While these response rates might not seem impressive, one needs to remember these patients have severely debilitating disease that had not responded to any type of pharmacological or behavioural therapy. This can be roughly compared to the results of a recent large scale study on the efficacy of pharmacotherapy in MDD. This study showed a response rate of 50% to a single SSRI, and a cumulative response rate of 75% after multiple, sequenced drugs were used [31].

RESOURCE ALLOCATION

Deep brain stimulation is an expensive procedure. A cost-effectiveness analysis should be done to ensure that it is economically viable to perform this procedure on an increasing number of patients [22]. The physician needs to take into account the initial cost of the procedure as well as the ongoing societal

benefit gained from having debilitating symptoms treated. The cost of life-long follow up and potential complications must be weighed against the decreased use of medication and psychiatric hospitalization. Research has shown that DBS for PD is cost-effective [23], but this issue has yet to be addressed with respect to DBS for psychiatric disorders. Bell et al. [23] have suggested that DBS is likely to be cost-effective because the estimated financial burden of psychiatric disease in the United States is $53 billion, and there may be up to two million Americans living with TRD. However, this assertion requires a thorough investigation.

CONCLUSION

The interest in DBS as an option for treatment-resistant psychiatric disorders demands a review of the history of psychiatric surgery and an understanding of how DBS evolved. It is too early to make definitive statements regarding the full potential of DBS in the treatment of psychiatric disease, but there are some clues as to what the future holds. For example, the advent of closed loop DBS (electrodes that can sense and respond to the brain's own electrical activity) will allow more precise modulation of dysfunctional circuits [25, 26]. Despite this, we as medical professionals must keep these advancements in context. We have a responsibility to our patients and society to ensure that we do not return to the dark ages by making the same mistakes as the overzealous generation of past.

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Health equality for all? An overview of the physician's role in ensuring equal health status for Canada's disadvantaged citizens

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Although Canada is a prosperous country that is world-renowned for its public health care system, there exists a clear discrepancy between the health of its poorest citizens and that of the rest of its population. Children with a low socioeconomic status (SES) are more likely to have a lower IQ [1], have a higher lifetime prevalence of schizophrenia [2, 3], major depression [4], anxiety disorders [5], and chronic pain [6]. Adults are at greater risk of severe myocardial infarction, stroke [7], and chronic disease [8, 9]. As a result, wealthy male Canadians live (on average) five years longer than their impoverished counterparts [10]. As health advocates, physicians have the duty to "responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations" [11]. Current and future physicians can help eliminate the gap in health care by focusing on three major strategies. First and foremost, physicians must confront their own preconceptions regarding low SES patients and develop methods for managing each patient in an objective and equal manner. Next, physicians must use innovative strategies to target and communicate directly with these patients and meet their immediate medical needs. Together, the doctor and the patient can then develop novel short and long-term solutions on the personal and societal levels with the goal of eliminating the disparity commonly exhibited in today's system. While this paper will discuss solutions aimed primarily at Ontarians, the general principles are applicable to all Canadians.

According to the Canadian Medical Association's Code of Ethics, physicians have the fundamental responsibility to "treat the patient with dignity and as a person worthy of respect" [12]. Additionally, the Declaration of Geneva (a modern physician's oath adopted on the international level) states that physicians "will not permit considerations of […] social standing or any other factor to intervene between [their] duty and [their] patient" [13]. Nevertheless, physicians are not immune to the disproportionately negative stereotypes about individuals of low SES that have become pervasive among Canadians. Controlled studies have found that physicians report less interest as well as more frustration and anxiety when treating low SES patients [14]. Unfortunately, this phenomenon also affects the up-and-coming generation of physicians. A recent Canadian study showed medical students a video portraying either a patient of an apparently low SES (convenience store worker) or a patient of an apparently high SES (partner at a law firm). The group that saw the low SES patient's interview perceived the patient to be less compliant with his medications, less likely to return to follow-up, and more affected by their illness than those in the high SES group. Ultimately, students who saw the low SES group were significantly less inclined to want that patient in their future practice than the students who saw the high SES patient [15].

Even more worrisome are the studies reporting on physician behavior in response to these stereotypes. Physicians have been found to perceive low SES patients as being more irrational, less intelligent, and less physically active. They viewed these patients as having less self-control and deemed them to be less compliant with physicians' instructions [16]. Gerbert found that physicians who perceive their patient as either unlikeable or incompetent are less likely to offer augmented medication or encourage their patient to telephone and return frequently for follow-up [17]. Despite the strong positive correlations between patient/caregiver education and successful patient outcomes [18, 19], low SES patients receive less education on their condition and prognosis [17, 20]. Additionally, as doctors are more likely to perceive their low SES patients as exhibiting drug-seeking behavior, they are less likely to prescribe narcotics to these patients, regardless of their actual intent. Many of these patients choose to find another doctor, a repetitive cycle that greatly reduces their continuity of care, a factor strongly associated with improved patient outcomes and satisfaction [21]. While a certain amount of clinical judgment is required when prescribing controlled substances, physicians must ensure that they are making the best possible decision based on the facts, without prejudice. Current as well as future physicians need to sensitize themselves to these issues, as well as confront their own judgments and predispositions to disadvantaged patients, so as to provide the most equal and quality care to those most in need.

In order to successfully target the proper population, it must first be understood who is at risk of a low SES in Canada. The National Institute for Health Information (NIHI) cites single parents, recent immigrants, off-reserve aboriginals and people with a long-term disability as being among the most at-risk groups [22]. Additionally, low SES patients may perform less well academically and complete fewer years of school than their middle or upper class counterparts [23]. Accordingly, physicians need to develop specific styles and strategies for communicating with low SES patients. As always, physicians must develop a strong rapport with the patient that is founded on honesty, trust, and cooperation. This will ensure the patient feels safe to discuss any sensitive issues that may be troubling them such as unemployment, substance abuse, and past or current physical/

psychological abuse. Doctors must also take the time to perform a detailed social history on each patient and use this information to develop personalized management plans that conform to their patients' unique religious, financial, and cognitive limitations. For patients without drug benefit plans, physicians must always consider the cost of medications and prescribe low-cost generics when possible. They should assist eligible patients in applying for subsidized benefit programs such as Trillium or the Ontario Drug Benefit (ODB), and spend additional time educating low SES patients on the benefits of treatment and the importance of compliance. Physicians may also use novel resources such as blister packs and easy-to-understand pamphlets to improve the compliance of patients with cognitive deficits and mental disease. Finally, the physician must also be aware of specific community resources that will assist these patients in fulfilling their basic medical and physiological needs. These resources must be non-judgmental, free or low-cost, and accessible by foot or public transit. Specific resources include food banks, shelters, addiction support groups, and residential detoxification programs. Additionally, allied health providers such social workers, foot care specialists, and mental health counselors are valuable resources for these patients. It is vital to remember that health care incorporating community resources and multiple health partners can better address the needs of the patient than one physician working alone.

Once their immediate physiological needs have been met, physicians must take the time to help their patients develop strategies that will allow them to reach their full potential. According to Maslow's hierarchy of needs [24], the next step is ensuring safety and security including stable housing and employment. This is supported by current literature that reports that access to stable housing is associated with fewer emergency room visits and hospitalizations [25], lower rates of hepatitis-C infection [26], less substance abuse, and a higher overall quality of life [27]. While there are publicly funded social housing initiatives across the country, the wait times for these properties are often unacceptable. For example, the current waiting list in Ottawa exceeds 9,500 households and the wait time can be in excess of five years. [28]. To help improve this situation physicians need to lobby the government at all three levels to increase funding allocated towards such social programs. In the short term, patients can be referred to services such as Housing Help or Action-Logement that specialize in finding low-cost housing on the private market. Physicians should subsequently collaborate with patients to develop strategies to secure steady employment, a factor correlated with lower rates of anxiety [29], depression [30], suicide [31], and all-cause mortality [32]. Physicians can refer patients to community resources such as Ottawa's Somerset West Community Health Centre where they can receive training on basic life, employment and technical skills, as well as interview techniques. Patients may also qualify for the Second Career Ontario program, a government initiative that pays up to $28,000 per year to retrain unemployed Ontarians. Aimed at Ontarians who have been recently laid-off, this program was developed to help pay for tuition, books, living expenses, child care, and other costs associated with going back to school. In addition to funding, Second Career Ontario also offers support and career guidance for individuals who qualify for the program [33].

Physicians must also use their influence to make changes on the societal level. At the municipal level, physicians can develop and participate in local initiatives targeted at lower SES populations. One such program in Montreal focused on promoting smoking cessation by teaching motivational, coping and weight control techniques to disadvantaged women. After one month, 31% of participants claimed to have completely quit smoking, while 73% of non-quitters had reduced their consumption [34]. At a higher level, the need for organized, effective lobbying is becoming increasingly important as both provincial and federal governments continue to cut social programming in an attempt to balance the budget. The Government of Canada recently announced a plan to make significant cuts to social programs including the elimination of Service Canada student summer job centres, and has raised the possibility of increasing the qualifying age for Old Age Security and the Guaranteed Income Supplement from 65 to 67 [35]. One day prior to the federal announcement, the Government of Ontario revealed its plans to scale back child benefits and freeze social assistance spending [36]. Physicians must encourage these governments to increase funding for important programs such as subsidized housing, training, and employment programs. Extra funding should be sought for innovative, targeted initiatives like the Newfoundland Mother Baby Nutrition Supplement (a program that was shown to reduce low-birth weight and other birth complications in low SES mothers) [37].

The health disparity between Canada's richest and poorest citizens is unacceptable in a country that prides itself on its policies on diversity and equality. Physicians must work diligently to narrow this gap by confronting and eliminating their own prejudices, by making changes to their own practice and by lobbying for innovative and constructive policy changes at the municipal, provincial, and federal levels. It has taken years to establish this inequality, and there exists no quick and easy solution. However, by partnering with members of public health, non-profit agencies and members of the general public, physicians have the potential to make important changes in the health of Canada's most disadvantaged citizens.

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Stem cells: The future of regenerative medicine?

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INTRODUCTION

The human body is made up of different cell types that make up tissues, organs, and organ systems. These cells originate from a group of cells found in the inner cell mass during initial stages of the developing embryo called the embryonic stem cells (ESCs) [1]. Human ESCs (hESCs) were first isolated in 1998 and the field has grown immensely ever since [1]. Pluripotent hESCs undergo differentiation to produce all the lineages of the body. Each lineage has its own resident stem cell population (commonly known as adult stem cells). Due to their limited potential for differentiation, they are called multipotent stem/progenitor cells. These cells further specialize and terminally differentiate into different cell types of the body. Although much is known about the mechanisms stem cells undertake to self-renew and differentiate, many questions still remain unanswered. Are they effective in cell replacement therapies? Are stem cells the future of medicine?

The field of regenerative medicine encompasses two broad areas—tissue engineering and cell therapy. The former employs the approach of engineering artificial tissues and organs in the hope to replace the damaged ones, whereas the latter includes both embryonic and adult stem cells and the way they can be harnessed to regenerate damaged tissue. The focus of this article is stem cells and their applications in clinic, as discussed below in the heart and the central nervous system (CNS).

HEART

Cardiovascular disease is the leading cause of death in the modern world [2]. The figures for waiting time for a heart transplant following myocardial infarction are staggering—ranging from six months to five years. Therefore, the use of stem cell replacement therapy to replenish the damaged cardiomyocytes is considered to be the holy grail of regenerative cardiology. Although in its infancy, a few randomized clinical trials have been undertaken to test the potential of stem cells in heart disease. The sources of this autologous cell therapy were multipotent cells—bone marrow stem cells (BMSCs) and skeletal muscle progenitors/myoblasts (SMBs). Nine randomized clinical trials (2004-2009) performed on patients with cardiovascular disease (n=50-200) revealed a modest effect of BMSCs in SMBs in heart regeneration based on changes in left ventricular ejection fraction, left ventricle end systolic volume, and left ventricle end diastolic volume [3-11].

The regenerative capacity of the heart was first documented in zebrafish [12] and was further demonstrated to occur in mammals in two recent publications [13,14]. One of the major challenges of cell replacement therapy is the sheer number of cells needed to achieve any significant amount of regeneration in the tissue. In a typical myocardial infarct, close to a thousand billion cardiomyocytes are lost [15]. In order to recover heart function, a large number of transplantable cells are therefore required. Considering the increasing number of cardiovascular disease patients, there is a considerable challenge regarding the scalability of stem cell therapeutics in heart. Hence, a robust therapeutic paradigm needs to be developed in order for therapy to be efficacious in the clinic.

A new concept arising in regenerative cardiology is the activation and proliferation of endogenous cardiac progenitor cells. It has been proposed that the resident cardiac stem cell populations are activated by cues that eventually would result in heart regeneration. In a study by Smart et al [16], it was shown that post-myocardial infarction injury caused an upregulation of the epicardial gene Wt1 in the resident cardiac stem/progenitor cells. These activated Wt1+ progenitor cells contribute terminally differentiated cardiomyocytes post-infarction. This response was primarily mediated by Thymosin β4 (Tβ4), a pro-angiogenic and pro-survival factor that has been previously shown to enhance myocyte survival post-ischemia [16]. Although the endogenous activation of stem cells by Tβ4 is a rather inefficient process given the low yield of cardiomyocytes from the stem cell pool, it is certainly a step towards resident stem cell-based therapy for myocardial infarction in patients. More basic science research are needed to elucidate how endogenous populations of cells in the heart contribute to heart regeneration.

BRAIN & SPINAL CORD

In contrast to the recent finding about resident cardiac stem cell populations, the first publication to document the presence of resident stem populations in the brain was derived from a study in mice in 1989 [17]. These cells were called neural stem cells (NSCs), a multipotent group of cells present in the subventricular zone (SVZ) of the brain. However, NSCs have also recently been shown exist in the subgranular zone (SGZ) of the hippocampus [18].

Adult neurogenesis is controlled by various factors that regulate neural stem/progenitor cell proliferation, migration, and differentiation in the brain [19]. These include growth factors, cytokines, chemokines, neurotransmitters, and hormones. Epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) are two well-studied growth factors known to play a role in the maintenance of NSCs in the SVZ of the adult brain [19]. Sonic hedgehog (Shh) [20] and brain-derived neurotrophic factor (BDNF) [21] are also known to be positive regulators of adult neurogenesis. Although numerous other factors have been implicated in adult NSC regulation, due to the heterogeneity in

in vitro cultures of NSCs and the lack of definitive markers that differentiate NSCs from other stem/progenitor cell types in vivo, the specific role of these factors in NSCs is largely unclear [19]. Therefore, understanding the mechanisms by which growth factors and other extrinsic stimuli specifically target and alter NSC behaviour *in vivo* would be essential in developing therapeutics targeted at patients with neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. In mice models, it has been shown previously by various groups around the world that NSCs mobilize to the site of injury in the brain and replace degenerated neurons [22,23]. However, the mechanisms by which they respond to chronic and acute neurodegenerative changes in humans remains an area of ongoing research.

The spinal cord, on the other hand, does not harbour any resident multipotent stem cells. Due to this reason and the high prevalence of spinal cord injury, there has been a focus on developing therapeutics for spinal cord injury. In addition to BMSCs and mesenchymal stem cells (MSCs), neural progenitor/stem cells are the most promising candidates for treating spinal cord injury [24]. Two recently initiated clinical trials employ the use of oligodendrocyte progenitors and neural stem cells as cellular therapies for spinal cord injury and ischemic stroke, respectively [25,26]. Unfortunately, the clinical trial involving treatment of patients with spinal cord injury using neural stem cells (derived from hESCs) was recently discontinued due to non-medical reasons. However, the study reported no detrimental effects on the patients [27].

INDUCED PLURIPOTENT STEM CELLS – FROM MODELING DISEASE ON A DISH TO THE CLINIC

A multitude of communities and religious groups believe hESCs are obtained from destroying human embryos. This misleading thought consequentially led to ban on generation of any new hESC lines in the United States under the Bush administration, essentially hindering the progress of stem cell research. Although the ban was later lifted by the Obama administration, the global controversy regarding hESCs had motivated scientists all around the world to look for alternatives. In 2006, a Japanese research group led by Dr. Shinya Yamanka developed a technique which enabled them to alter cell fate. Specifically, they were able to reprogram skin fibroblasts to induce pluripotent stem cells (iPSCs) using four factors – Oct4, Sox2, c-Myc, and Klf4, commonly known as "the Yamanaka cocktail" [28]. These cells exhibit properties similar to those of ESCs and have the capability of differentiating into all cell types of the body [28]. Although this is a relatively new finding it soon became a mainstream technique in stem cell research primarily because of the ethical dilemma it bypasses. Skin samples from patients are obtained upon consent. The skin fibroblasts are then reprogrammed into iPSCs. These patient specific-iPSC lines are then differentiated into the defective lineage based on which the disease mechanism is investigated at the molecular level. A number of diseases, thus far, have been modeled on the dish: amyotropic lateral sclerosis, spinal muscular atrophy, Parkinson's disease, sickle cell anemia, and type I diabetes mellitus among others [29].

Some of the diseases for which patient-iPSCs have been generated are genetic in origin. Therefore, scientists are aiming to use gene-targeting to repair the disease-causing mutations in iPSCs, differentiate these cells *in vitro*, and transplant these "healthy" cells back into the patient. An alternative strategy undertaken by researchers is the *in vitro* screening of drug agents that can prevent patient-specific iPSCs from differentiating into the pathological cell types. Therefore, iPSCs are excellent resources for disease modeling and drug testing at pre-clinical level [30]. Although iPSCs are excellent resources for *in vitro* drug testing and disease modeling, ESCs and few other multipotent stem cell populations are currently still our best candidates in translational medicine.

LIGHT AT THE END OF THE TUNNEL

On January 24, 2012, Advanced Cell Technology Inc. published a preliminary report in the journal Lancet on two hESC trials on patients with dry age-related macular degeneration and Stargardt's disease, which are the major causes of blindness in the modern world [31]. In these Phase I clinical trials, the patients were subretinally transplanted with retinal pigment epithelial (RPE) cells derived from hESCs. As opposed to what is usually seen with stem cell transplantations, there was no observed tumorigenicity or hyperproliferation of RPEs. Also, immune rejection was negative after four months of subretinal transplantations. Assessment of visual acuity and function revealed an improvement in the eye that received RPE transplant as compared to the control eye [31]. The results, albeit preliminary, have generated excitement in the field.

CONCLUDING REMARKS

Although stem cell therapies are in their preliminary stages, they are being used to treat patients with cardiovascular disease, spinal cord injury, vision abnormalities, in addition to a host of other diseases. Ever since the first bone marrow transplantation in the 1950s [32], the fields of stem cell research and regenerative medicine have progressed at an astonishing pace especially in the past two decades, holding great potential in the future of medicine.

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What patients don't *see* about the dangers of smoking

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ABSTRACT

While medical professionals are often very well aware of the associations between smoking and cardiovascular health, few are aware of smoking's often detrimental effects on one of the most important senses: vision. Many articles have focused on the associations between smoking, cardiovascular disease, and various cancers; however, few articles have detailed the effects of smoking on eye health. Since approximately twenty percent of Canadians currently smoke, it is essential for future physicians, especially primary caregivers, to be well informed about common eye diseases related to smoking. In this paper we will review the evidence that links smoking to such serious eye diseases as: age-related macular degeneration, cataract, dry eye syndrome, non-arteritic anterior ischemic optic neuropathy, tobacco-alcohol amblyopia, and thyroid eye disease. Awareness of the link between smoking and ocular pathologies can potentially lead to the early detection of other smoking-related impairments that can be addressed before the development of serious, life-altering complications such as cardiovascular disease. Ultimately, this may allow future physicians to have the ability to better encourage patients to modify these risk factors in the maintenance of good health.

INTRODUCTION

Given that smoking continues to be associated with serious health problems, medical students, residents, and physicians in all field of medicine will encounter patients who smoke. Statistics Canada reports that more than one in five Canadians over the age of 12 continue to smoke. Every year in Canada, approximately 47 000 people die as a direct result of smoking [1]. As outlined by the World Health Organization (WHO), smoking is responsible for more than five million deaths worldwide [2]. A recent article by Fortinsky et al. discussed a novel approach to smoking cessation [3]. The authors describe the importance of healthcare professionals providing patients with evidence-based information regarding smoking cessation. Recognizing this evidence based approach, a literature review was conducted with respect to smoking and ocular disease.

Visual impairment is a serious health issue that has been found to affect approximately 1% of the population in Canada [4]. Based on the WHO criteria, the prevalence of low vision and blindness in the Canadian population is 35.6 and 3.8 per 100 000, respectively [4]. Amongst patients with some vision loss, cataracts and visual pathway disease are the most frequent causes while age-related macular degeneration and other retinal diseases are slightly less common.

Vision has been shown to be valued more than any other sense. A recent survey by the KRC research group and the Ocular Nutrition Society showed that 78% of baby boomers rank vision as the most important of the five senses [5]. At the same time 55% of these elderly patients worried about vision loss almost as much as heart disease and cancer [5] and only half of these respondents reported having an eye exam yearly.

Our ultimate goal is to create a succinct and comprehensive summary of the effects of smoking on one of life's most precious senses. The relationships between smoking, coronary heart disease, stroke and COPD have been well-established and discussed in the media. In contrast, there has been much less focus on smoking and eye health.

Research shows that "Cigarette smoking is a substantial source of intake of heavy metals and toxic mineral elements which may have many adverse effects in different organs, including the eye" [6]. Other reports have demonstrated that "cigarette smoking is the leading preventable cause of visual disorders and blindness in the United States" [7]. Along these lines, randomized trials have shown that continuing education programs that teach physicians on how to counsel patients to quit smoking showed a significant effect on helping smokers quit and achieve long-term abstinence [8]. This demonstrates the importance of educating physicians about all evidence-based risks associated with smoking. These can then be integrated into counseling efforts so physicians can effectively offer their patients the most current and best advice in helping them quit smoking.

In the following sections, we will highlight the most prevalent and serious diseases of the eye and their links to smoking.

AGE-RELATED MACULAR DEGENERATION (AMD)

Macular degeneration is the most common cause of permanent blindness in adults over 65 and the most common cause of visual disability in most developed countries [9]. AMD is a complex multifactorial progressive disease with many environmental and genetic influences. It consists of degeneration of the retinal pigment epithelium that is linked to oxidative

stress. AMD can be classified as early or late, with late AMD being further classified as either dry or wet. Dry AMD consists of geographic atrophy of the retinal pigment epithelium and photoreceptor cells which allows visualization of the underlying choroidal vessels. Unlike Dry AMD, Wet AMD is often treatable, and it involves the development of a choroidal neovascularization or detachment of the retinal pigment epithelium [10]. Smoking is widely accepted as the single most important modifiable risk factor for the development and progression of age related macular degeneration [11,12]. Data from well designed prospective, cross-sectional, and retrospective studies have shown associations between smoking and AMD. Smoking has been known to potentially increase ischemia and oxidative stress throughout the body [13].

Women who are current smokers appear to have about a 2.5 fold increase in risk (95% confidence interval (CI), 1.01-6.20 relative risk (RR)) of developing wet macular degeneration. Men who currently smoke appear to have around a 3.3 fold increased risk of developing wet AMD (95% CI, 1.03-10.50 RR)[9,14]. A dose dependent relationship has been found in multiple studies [11,15,16] . That is to say, those with less than a 10 pack year history had a 2.6 times increased risk (95% CI, 0.8-8.2 RR) of developing wet AMD, while those with at least a 20 pack year history had a 9.9 times increased risk (95% CI, 3.5-32.6) [16]. Furthermore, upon quitting smoking, the risk of developing AMD may fall to that of a lifetime non-smoker after 20 years [11], highlighting the importance of educating patients on the importance of early cessation of smoking to prevent worsened eye disease later in life. Figure 1 below illustrates the central scotoma of advanced macular degeneration.

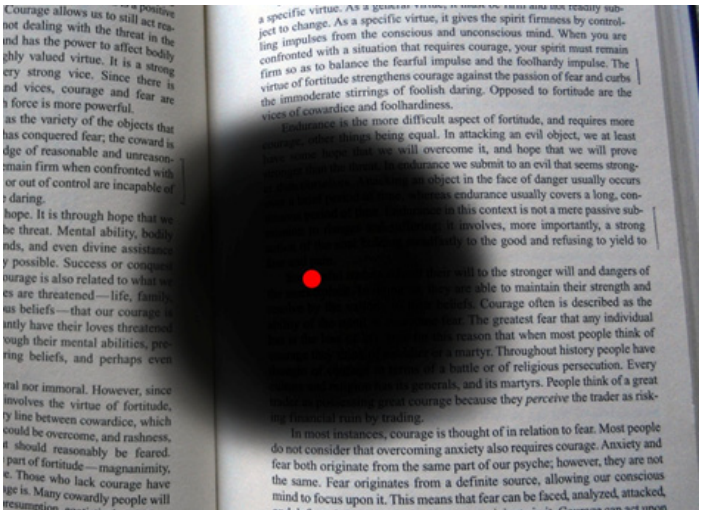

Figure 1. Fixate on the red dot at the center of the image; note how difficult it is to read the text without your macula. This illustrates the debilitating impairment caused by macular degeneration. The authors encourage readers to disseminate this figure to others in order to help illustrate this debilitating disease process.

CATARACTS

Cataract is the leading cause of blindness worldwide with approximately 30 million people affected with serious visual impairment [17]. It is estimated that 20% of the cataracts in the United States may be directly attributable to smoking [18]. Left untreated, cataracts can become troublesome potentially causing angle closure glaucoma and severe lens opacity which may result in blindness unless surgically corrected. The effect of a cataract on vision is illustrated in Figure 2.

It is predicted that smoking depletes anti-oxidant reserves within the lenticular tissue increasing oxidative stress leading to cataract formation. This is because the lens does not have a direct blood supply. Its nutrients are supplied through the fluid that surrounds it (aqueous humor). Therefore, the lens has poor access to anti-oxidants and is susceptible to oxidative stress [10]. Some authors believe that cigarettes cause direct toxicity to the lens through the deposition of heavy metals such as cadmium, which is found in relatively high concentrations in cigarette smoke [17].

Smokers of 20 or more cigarettes per day are potentially twice as likely to develop nuclear sclerotic (the most common type of senile cataract) cataracts compared to non-smokers. They are also three times as likely to develop a particular type of cataract called a posterior subcapsular cataract [9,19]. This finding was significant even after controlling for diabetic patients and those on corticosteroids.

Cataract formation due to smoking appears to be dose dependent. Light smokers (<15 cigarettes/day), moderate smokers (15-24 cigarettes/ day), and heavy smokers (>25 cigarettes/ day) are 2.5, 2.7, and 3 times more likely to develop cataracts than non smokers, respectively [19].

Quitting smoking may confer a significant reduction in cataract formation risk. Research has shown that 10 years after

Figure 2. A landscape scene without cataract (top), the same landscape with a rendition of the way a patient might perceive with cataracts (bottom). Notice the decrease in visual acuity and changes in hue discriminations and colour contrast with cataract formation.

quitting smoking, a smoker's risk of developing cataracts will return to that of a non-smoker [19]. Reducing the incidence of cataract formation through smoking cessation could represent significant cost savings to the health care system by reducing the number of surgical corrections required for cataracts.

DRY EYE SYNDROME

With only the tear film for protection, the eye's surface is the most exposed mucosal surface in the body [6]. The normal tear film of the eye lubricates the eye, provides protection against the environment, smoothes the surface of the cornea, and protects against microbial attacks. It is comprised of three layers. An amphiphilic mucinous layer adjacent to the corneal epithelium, a middle hydrophillic aqueous layer containing lyzozyme and lactoferin to ward off bacteria, and finally a amphiphilic lipid layer which resists evaporation allowing the other layers to function appropriately [20]. Evidence has emerged that smoking causes lipid peroxidation and destabilization of the lipid layer of the tear film [6]. Without the lipid layer, tears evaporate very quickly creating ocular irritation and exacerbating or directly causing dry eye syndrome.

One prospective cohort study imaged the tear film layer in smokers and non-smokers. In the smoking group, they found areas of the cornea where lipids did not spread smoothly over the corneal surface. These patients tended to suffer from dry eye clinical signs like scratchiness, foreign-body sensation, burning, and grittiness compared with nonsmokers [6]. In larger observational studies, the Beaver Dam and Blue Mountain Eye Studies, dry eye symptoms were reported by approximately 15% of smokers [6,21].

In individuals suffering from dry eye syndrome as a result of diabetes, contact lens use, or anticholinergic medications, the avoidance of tobacco smoke is especially important. The tear film in these patients is already unstable and may decompensate under the stress of smoke. Dry eye syndrome can lead to corneal exposure and the breakdown of innate defense mechanisms leading to microbial keratits, a potentially life-threatening eye infection.

NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

NAION is characterized by a unilateral abrupt onset of painless vision loss. Visual recovery is typically very poor with many patients never recovering functional vision in the affected eye. The blood supply to the optic nerve head is provided through the ophthalmic artery via the posterior ciliary arteries. Anterior ischemic optic neuropathies occur when the blood supply to the optic nerve head is compromised. In the case of NAION, a thrombotic mechanism is thought to threaten this blood supply. Chronic smoking is known to promote thrombosis through upregulation of pro-inflammatory cytokines, leukocytosis, increased platelet aggregation, and endothelial cell dysfunction [13].

Current smokers are 16 times more likely to develop NAION compared with non-smokers. On average, smokers develop NAION 13 years earlier than non-smokers [9,22]. Interestingly, the risk of NAION returns to baseline population risk shortly after quitting smoking [13] demonstrating the potential for reversibility of smoking associated damage through early cessation efforts.

TOBACCO-ALCOHOL AMBLYOPIA

Tobacco-Alcohol Amblyopia, also known as nutritional amblyopia, usually occurs in individuals with heavy alcohol consumption and poor dietary habits with smoking being associated [10]. It is a toxic optic neuropathy characterized by a slowly progressing central scotoma involving both fixation and blind spots, demonstrated in Figure 3, resulting in a bilateral reduction in visual acuity less than 20/200. The pathogenesis of this disease is multifactorial and largely unknown. Much consideration has been given to other toxic causes including cyanide from tobacco producing low vitamin stores and low levels of sulfur containing amino acids [10]. Nutritional deficiencies, in particular B-group vitamins such as B1, B6, and B12, along with associated factors such as folate, cysteine, lycopene (anti-oxidant) and protein deficiencies may result in a susceptibility to optic neuropathies [23]. The direct toxic effect of cigarette smoking to the retina in combination with the diminished ability for repair leads to the development of Tobacco-Alcohol Amblyopia.

Smoking cessation and B-vitamin supplementation are the most important steps in the management of this disease. While a prescription of B-vitamin therapy can modestly improve visual function in patients that continue to smoke, their vision will ultimately worsen over time [7,23]. For those patients who are able to quit or significantly decrease their smoking, and increase their vitamin intake, the recovery is generally excellent, and often the scotoma will resolve [7]. This illustrates the importance of early smoking cessation to benefit reversible causes of vision loss.

Figure 3. This illustrates the impairment caused by Tobacco-Alcohol Amblyopia. Fixate on the red dot at the center of the image; note the central scotoma and loss of peripheral visual field. One can only imagine the detrimental impact this would have on a patient's daily functioning and quality of living.

THYROID EYE DISEASE

Thyroid Eye Disease (TED) occurs in the context of a thyroid hormone abnormality, most commonly Graves' disease. Once a patient has Graves' disease, smoking is the most significant risk factor leading to the development of TED [24]. Graves' patients who are current smokers have an 8 fold increased risk of developing TED as compared with non-smoking Graves' patients [9]. In TED orbital fibroblasts are stimulated to deposit glycosaminoglycans. This results in hypertrophy and fibrosis of the extra-ocular muscles as well as expansion of surrounding adipose tissue. The increased volume of the orbital contents leads to symptoms including diplopia (double vision), extra-ocular muscle restriction reducing gaze, exposure keratitis secondary to proptosis, excessive tearing, ocular discomfort, orbital pain, and possibly vision loss due to stretching of the optic nerve.

Studies have shown that cigarette smoke extract stimulates interleukin 1 (IL-1), a pro-inflammatory cytokine in the inflammatory cascade, production in vitro by a tobacco glycoprotein. This suggests that smoking is pro-inflammatory via an increase in IL-1 [25]. Further studies have shown that cigarette smoke extract and IL-1 both cause adipogenesis in a dose dependent fashion [26].

Smoking also causes a more severe clinical course of Graves' disease [9]. This increased severity is dose dependent [26]. One of the standard treatments available to Graves' disease patients is radioiodine therapy. It is unfortunate that current smoking increases the risk for progression of TED even after radioiodine therapy is completed [24].

Evidence exists that quitting smoking can positively impact the clinical course of this disease. Patients who quit smoking experience similar rates of proptosis, diplopia, and total thyroid eye disease as lifetime non-smokers approximately five years after quitting [27].

UVEITIS

The uvea is composed of the iris, ciliary body, and choroid. Uveitis is inflammation of any or all of these structures and can have an inflammatory or infectious etiology. As previously suggested, smoking may be associated with increased inflammation through activation of inflammatory markers such as IL-1. Smokers have twice the risk of having ocular inflammation as non-smokers [28]. More specifically, compared to both non-smokers and past smokers, current smokers are 1.7 times more likely to develop anterior uveitis, 2.7 times more likely to develop intermediate uveitis, 3.2 times likelier to develop posterior uveitis, and 3.9 times as likely to develop panuveitis [28]. This highlights the importance of how reducing a modifiable risk factor such as smoking can significantly decrease the likelihood of developing uveal inflammation.

Although uveitis can lead to many vision threatening complications, concurrent smoking significantly increases the likelihood of developing cystoids macular edema (CME) in the context of uveitis. Cystoid macular edema results from fluid collections within the retina at the macula. Multiple cystic spaces form distorting the normal architecture of the retina and can significantly impair a patient's central vision as seen in Figure 4. Smokers who develop intermediate or panuveitis are eight times more likely to develop CME [28].

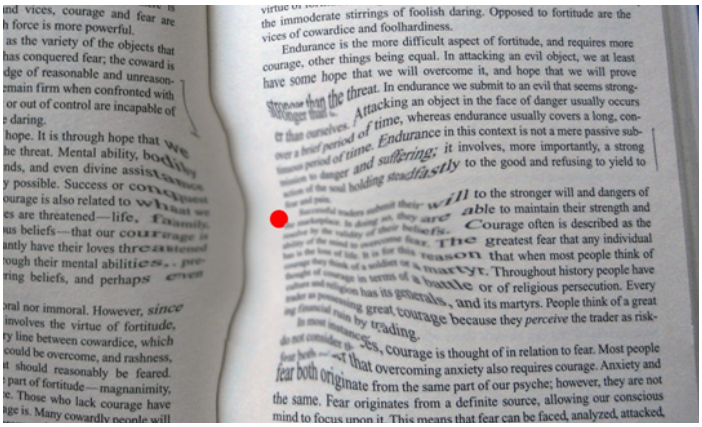

Figure 4. Fixate on the central red dot; this is a depiction of what a patient with cystoids macular edema (CME) might experience. Notice how warped and displaced the text is contributing to serious difficulty interpreting letters and carrying out basic activities of living such as reading.

Smoking associated uveitis is dose dependent. After adjusting for any confounding factors, one study showed that there was a 4% increased risk of CME at presentation for each cigarette smoked per day [29]. Smokers are more likely to develop an infectious uveitis (odds ratio (OR) 4.5) than non-infectious uveitis (OR 2.1) [28].

CONCLUSION

The sense of vision is paramount to a patient's quality of life, yet the deterioration of vision is often overlooked as a common and serious consequence of smoking. Most of the eye diseases mentioned in this paper have multi-factorial causes. The common link is smoking, which is known to be a modifiable risk factor in the context of any illness or impairment. While ophthalmologists are often consulted to manage these eye conditions, as medical students, residents, and primary care physicians, it is imperative that we warn patients of these debilitating diseases.

Counseling smoking cessation before long-term vision consequences unfold can not only preserve quality of life, but may minimize more serious smoking related diseases like stroke and heart disease. Maintaining optimal vision may also reduce the risk of accidents and injuries associated with old age such as falls and hip fractures, which are often linked to high mortality rates.

Research shows that effective strategies in smoking cessation in primary care practice involve intensive interventions in counseling and education for patients on multiple occasions [30]. Through increasing the knowledge of unrecognized health risks of smoking, this study works towards pro-

Table 1. Summary of the key facts to discuss when counseling patients about smoking-related eye diseases.

Eye Disease	Smoking's Influence
Age Related Macular Degeneration (AMD)	• The single most modifiable risk factor for progression of AMD • Dose-dependent relationship (10 pack year history confers 2.5x increased risk, while 20 pack year history confers 10x increased risk) • 20 years after quitting, risk returns to baseline population risk
Cataract	• More than doubles the risk of cataracts • An estimated 20% of cataracts are directly attributable to smoking • 10 years after quitting, risk returns to baseline population risk
Dry Eye Syndrome	• Smoking increases the risk of suffering from dry eye syndrome • Shown to cause lipid peroxidation and destabilization of lipid layer of tear film • Reported in 15% of all smokers
Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)	• Promotes thrombosis formation and increases the risk of irreversible blindness • Sixteen times increased risk compared to non-smokers • Risk returns to baseline population risk after quitting
Tobacco-Alcohol Amblyopia	• Causes nutritional deficiencies most importantly B-vitamins • Direct toxic effect on retina with diminished ability for repair • Reversible with vitamin supplementation and quitting
Thyroid Eye Disease (TED)	• Most significant risk factor in Graves' patients leading to TED (8x risk) • Causes more severe clinical course of TED resistant to radioiodine therapy • 5 years after quitting, risk returns to baseline population risk
Uveitis	• Twice the risk of overall ocular inflammation as non-smokers • Smokers more likely to develop anterior, intermediate, posterior and panuveitis • Smokers are 8x more likely to develop Cystoid Macular Edema (CME) • Evidence of a dose-dependent association

viding information for primary care physicians when faced with potential challenges of multiple interventions and options in smoking cessation efforts. This study also hopes to initiate and spark an interest in research aimed at looking into the impact of counseling that involves education about the evidence-based risks of smoking. Furthermore, we hope this article suggests the importance of regular eye exams in current smokers to help identify and prevent the often detrimental, yet potentially reversible effects of smoking on vision.

As our population continues to age, our healthcare system must continue to move towards more primary and secondary prevention initiatives in order to be financially sustainable. After all, it is far less expensive to counsel our patients about quitting smoking than to bombard our medical system with preventable diseases, often requiring costly medical and surgical interventions. Ultimately, we hope this review can put smoking and eye health into the spotlight and provide a simple framework that may help patients see how quitting smoking can help minimize devastating and preventable ophthalmological consequences.

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Activité physique et santé mentale: *Une revue de la littérature*

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RÉSUMÉ

Les problèmes de santé mentale présentent un obstacle social très important puisqu'ils sont associés à une augmentation du risque de développer d'autres maladies. Depuis longtemps, la pratique régulière d'activité physique est reconnue comme ayant le potentiel de prévenir et de traiter les problèmes de santé mentale. Le but de cette revue est d'analyser l'ensemble des ouvrages abordant la relation entre l'activité physique et la santé mentale. Plusieurs auteurs proposent des mécanismes différents pour expliquer la relation entre l'activité physique et la santé mentale mais la physiologie précise demeure inconnue. Malgré le consensus des effets positifs découlant de la pratique d'activité physique, la littérature scientifique fait état de résultats contradictoires sur les bénéfices psychologiques. Par contre, cette contradiction dans les résultats pourrait être attribuée à des problèmes méthodologiques. Il serait intéressant d'étudier davantage la relation entre l'activité physique et la santé mentale afin de quantifier les paramètres de bienfaits et de dévoiler le mécanisme spécifique. Il serait aussi intéressant d'étudier cette relation chez des populations avec des caractéristiques particulières puisque la majorité des études faites à date a été effectuée avec des groupes hétérogènes. La compréhension approfondie de cette relation serait particulièrement utile lors de la prescription d'activité physique.

Plusieurs chercheurs avancent que certains facteurs psychosociaux défavorables sont associés avec une augmentation de risque de problèmes de santé. À titre d'exemple, Norberg et coll. [1] ont démontré que l'augmentation du risque du diabète de type 2 serait, en partie, attribuable au niveau de stress psychosocial chez la femme. Selon Ferraro et Nuriddin [2], les femmes avec un haut niveau de stress seraient plus vulnérables à la mortalité par le cancer. Étant donné l'impact du profil psychologique sur la santé, il s'avère important de développer des méthodes d'intervention pour assurer le bien-être psychologique chez les personnes et ainsi diminuer les risques de problèmes de santé. D'ailleurs, une étude de Paluska et Schwenk [3], a démontré que la santé mentale était, en soi, un problème social de plus en plus important qui nécessite une plus grande attention de la part des professionnels de la santé. L'objectif de cette revue est de faire un survol de la littérature scientifique abordant la relation entre l'activité physique et la santé mentale afin de mieux comprendre le lien et identifier des aspects qui exigent plus de recherche. Les articles ont été trouvés en utilisant les bases de données Scopus et Pubmed.

Depuis le temps d'Hippocrate, la pratique régulière d'activité physique est reconnue comme ayant le potentiel de prévenir et de traiter les problèmes de santé mentale tels que la dépression et la mélancolie [4]. La pratique d'activité physique est donc souvent suggérée pour améliorer la santé psychologique [5]. Selon Paluska et Schwenk [3], on devrait considérer davantage le potentiel thérapeutique de la pratique d'activité physique pour améliorer la santé mentale. Même s'il y a consensus scientifique sur les effets bénéfiques physiques de l'activité physique, la littérature fait état de résultats contradictoires en ce qui concerne ses bénéfices sur la santé mentale. Les conclusions des recherches tendent cependant à démontrer qu'il y a une relation positive entre le bien-être psychologique et la pratique régulière d'activité physique [6]. Ces évidences ne cessent de s'accumuler au fur et à mesure que les études sont mieux contrôlées [7].

On peut probablement attribuer la majorité des résultats d'études contradictoires à des problèmes méthodologiques liés aux protocoles expérimentaux influençant ainsi la validité des résultats. Par exemple, dans une étude de cohorte examinant la relation entre la pratique d'activité physique, la dépression et la détresse psychologique chez 1190 anciens étudiants de médecine [8], les chercheurs n'ont pas tenu compte de toutes les variables influençant la santé mentale. Certains participants étaient, par exemple, sous traitement pharmaceutique ou professionnel, ce qui a pu avoir un impact sur la relation entre la pratique d'activité physique et la santé mentale. De plus, la variable indépendante, soit la pratique d'activité physique, n'était pas mesurée de façon adéquate. On considérait l'activité physique seulement lorsque celle-ci entraînait de la sudation alors qu'il est généralement reconnu que les bénéfices associés à la pratique d'activité physique peuvent être obtenus bien avant que l'intensité de l'exercice entraîne de la transpiration. L'étude randomisée et contrôlée de De Geus et coll. [9] a aussi été incapable de démontrer la relation entre la pratique d'activité physique et la santé mentale. Dans ce cas, ceci aurait pu être attribué au faible nombre de participants. En effet, ces derniers ont fait appel à un groupe restreint de 19 participants pour chacune des 4 interventions. De plus, les résultats de cette étude ne

peuvent pas être généralisés à l'ensemble de la population puisque les participants étaient des hommes allemands âgés de 25 à 40 ans. Cependant, treize années plus tard, dans une étude de cohorte de 19 288 hommes et femmes allemands, ces mêmes auteurs ont réussi à démontrer que la pratique d'activité physique entraînait une diminution de l'anxiété et de la dépression [10].

La relation entre la pratique d'activité physique et la santé mentale est aussi corroborée par la méta-analyse réalisée par Stathopoulou [7]. Cette dernière comprend 11 études sélectionnées selon des critères stricts pour assurer la validité des résultats. Sous différents paramètres d'activité physique, la méta-analyse démontre un avantage important pour les groupes expérimentaux comparativement aux groupes contrôles. Les principales conclusions de l'ensemble de ces études concernant la relation entre la pratique d'activité physique et la santé mentale font état d'une diminution des symptômes de l'anxiété [3,11-14], d'une diminution du stress [15], d'une diminution des symptômes de la dépression [3,13] et d'une augmentation du bien-être psychologique [11,13,15].

Plusieurs mécanismes ont été proposés pour expliquer les bénéfices de la pratique d'activité physique sur la santé mentale. Cependant, aucun mécanisme précis n'a encore été établi puisque peu de recherches existent à ce sujet. De plus, la majorité des hypothèses proposées n'ont pas été validées dans le cadre d'études randomisées et contrôlées. Les mécanismes proposés se classent dans deux catégories principales, soient les mécanismes psychologiques et les mécanismes physiologiques (Tableau 1) [7].

Tableau 1. Mécanismes proposés pour expliquer les bénéfices de la pratique d'activité physique sur la santé mentale.

Mécanismes psychologiques	Mécanismes physiologiques
Hypothèse de la distraction	Hypothèse des monoamines
Hypothèse d'efficacité personnelle	Hypothèse des endorphines
Hypothèse d'interaction sociale	Modèle thermogénique

Parmi les mécanismes psychologiques, on retrouve l'hypothèse de la distraction qui fait valoir que l'amélioration de la santé mentale serait due à l'oubli temporaire du stimulus déplaisant. Ceci a été démontré par Bahrke et Morgan [12] lors d'une étude dans laquelle l'anxiété des participants a été réduite suite à leur participation à une activité distrayante telle que l'activité physique, la méditation ou une séance de repos. Une deuxième hypothèse suggère que le fait de relever un défi, tel que la pratique régulière d'activité physique, donne à l'individu un sentiment d'indépendance et de succès. L'individu réussit ensuite à transposer cette sensation de contrôle et de succès dans sa vie de tous les jours [3,16]. La troisième hypothèse propose que les bénéfices psychologiques proviennent des interactions sociales associées avec la pratique d'activité physique [16].

Parmi les mécanismes physiologiques proposés, on retrouve l'hypothèse des monoamines. Celle-ci postule que la pratique d'activité physique augmenterait l'activité des synapses aminergiques de la même manière que les antidépresseurs, c'est à dire soit en augmentant la libération des monoamines ou en augmentant la sensibilité des récepteurs aminergiques, le mécanisme précis demeurant encore inconnu [4]. L'hypothèse des endorphines propose plutôt que, lors de la pratique d'activité physique de longue durée, des endorphines seraient libérées. Plus spécifiquement, la β-endorphine serait responsable d'une diminution de la douleur et pourrait créer un état d'euphorie [17]. Un troisième mécanisme physiologique qui mérite d'être mentionné est celui du modèle thermogénique. Ce dernier explique que l'augmentation de la température corporelle serait responsable de l'amélioration de l'humeur après la pratique d'activité physique. Plusieurs chercheurs font valoir qu'un modèle incluant l'ensemble de ces systèmes serait probablement le plus plausible. L'étude de chacun de ces mécanismes ainsi que de leur interaction nécessite plus de recherche [3].

Dans le but de vérifier le lien entre la pratique d'activité physique et l'amélioration de la santé mentale, certaines études se sont penchées sur deux facteurs importants: la nature et l'intensité de l'activité physique. L'étude longitudinale de Galper et coll. [13] comprenant 5451 hommes et 1277 femmes entre 20 et 88 ans dévoila que de compléter 18 à 30 km de marche par semaine serait idéal pour assurer une bonne santé psychologique et qu'à l'opposé, un volume supérieur à cela aurait un impact négatif sur la santé mentale. Certains chercheurs, tels que Bahrke et Morgan [12], croient cependant que les effets bénéfiques de la pratique d'activité physique seraient semblables à ceux des activités de relaxation telles que la méditation. Les résultats de leur étude randomisée et contrôlée pourraient par contre être contestés compte tenu que l'activité du groupe expérimental, c'est-à-dire une marche de 20 minutes sur tapis roulant à 70% de la fréquence cardiaque maximale, n'est possiblement pas assez longue et/ou intense pour obtenir les bénéfices de la pratique d'activité physique sur la santé mentale. De plus, les effets à long terme n'ont pas été mesurés dans cette étude, les participants étant évalués seulement immédiatement avant et après l'intervention. Par ailleurs, d'autres études, telles que celle de Dunn et coll. [18] concernant l'activité physique aérobie et celle de Atlantis et coll. [19] pour l'entraînement en résistance, ont démontré que la pratique d'activité de haute intensité est plus bénéfique pour la santé mentale que celle d'activité physique de basse intensité.

La majorité des études réalisées sur la relation entre la pratique d'activité physique et la santé mentale a été faite sur des populations hétérogènes. Il y a tout de même quelques exceptions dont l'étude de Karelis et coll. [20] qui a étudié les femmes post ménopausées en surpoids et obèses. Il y aurait donc lieu d'étudier davantage des populations avec des caractéristiques particulières pour déterminer s'il existe toujours

une relation entre la pratique d'activité physique et la santé mentale. Il faudrait particulièrement prioriser les études chez la femme puisque la détresse psychologique est plus prévalente chez cette population [21]. Aussi, d'après le sondage de Campbell sur le bien-être des canadiens et canadiennes, la perception que la pratique d'activité physique contribue au sentiment de bien-être mental serait encore plus accentuée chez les femmes [22].

En conclusion, plusieurs études ont réussi à démontrer une relation significative entre l'activité physique et la santé mentale malgré la présence de résultats contradictoires dans la littérature. Différents mécanismes ont été proposés pour expliquer cette relation mais la physiologie précise demeure inconnue. Une augmentation du bénéfice pour la santé mentale pourrait être atteinte en pratiquant des activités physiques de plus longue durée [13], d'intensité élevée [18-19] ou relaxantes [12]. Cependant, des études additionnelles devraient être effectuées pour quantifier davantage la relation entre les paramètres de la pratique d'activité physique et les bénéfices sur la santé mentale. La connaissance de ces paramètres pourrait être utile pour la promotion et la prescription d'activité physique.

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A review of technology-enhanced medical simulation

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ABSTRACT

Over the past fifteen years, technology-enhanced simulation has seen increasing application in healthcare for the purpose of training healthcare professionals. Furthermore, it is projected to play critical roles in standardized assessment of clinical competencies and as clinical research tools. With limited exposure to medical simulation outside of standardized patients, medical students are often unaware of the extent to which simulation is being integrated into their future education and practice. To address this knowledge gap, this article reviews the developmental history of medical simulation and the rationales for its expansion. The various simulation models and their roles within and outside of medical education are discussed, along with evidence of their efficacy and impact on healthcare. Current drawbacks of simulation are outlined, including: high capital cost associated with building and maintaining a simulation center, limited fidelity of simulators, and lack of insights into how to best incorporate simulation into different stages of medical education. Lastly, the article profiles the University of Ottawa Skills and Simulation Centre (uOSSC), and proposes a solution to better incorporate simulation into the undergraduate medical curriculum at Ottawa.

INTRODUCTION

Technology-enhanced medical simulation is defined as using materials and devices adapted to mimic real-life situations for the purpose of medical education [1]. Simulation ranges from inert animal parts to computer-based virtual reality simulators and high-fidelity mannequins. Simulation programs have diversified to train not only physicians but also allied health professionals, and their scope has expanded across both technical as well as non-technical skills, including decision making, teamwork and communication. The primary goal of simulation is to enhance both the quality of healthcare education and patient safety, by allowing medical trainees to develop hands-on skills in a patient-safe environment. The purpose of this article is to help medical students understand the increasing role of simulation in the evolving landscape of healthcare training and practice. The article briefly outlines rationales for simulation, the types of simulators, the advantages and limitations of simulation, and its current utilizations and future directions.

RATIONALES FOR SIMULATION IN MEDICINE

Although technology-enhanced simulation has been used in medical training for the last least forty years, it is only in the last fifteen years that it has achieved widespread application [2]. Multiple factors have contributed to this trend.

Advancement of health care has resulted in shorter hospital stays and clinical visits, but a greater number of inpatients with more severe illnesses. In teaching hospitals, this translated to reduced patient availability for learning and decreased faculty time for teaching [3]. In the meantime, simulators became increasingly available and able to produce a wide variety of medical conditions on demand. Unlike real patients, simulators do not become embarrassed, tired or behave unpredictably, enabling them to reliably provide uniform learning experience for all trainees [4]. In addition, technological advances have led to new imaging modalities and minimally invasive procedures such as laparoscopy, which require development of more complex diagnostic and psychomotor skills and new methods for teaching. Concurrent advances in simulation technology provided a means to teach these advanced skills.

To Err is Human brought to the public attention the unacceptably high prevalence of preventable medical errors leading to death and other adverse outcomes [5]. The report issued in November 1999 by U.S. Institute of Medicine concluded that between 44,000 and 98,000 patients die each year as a result of preventable medical errors, an unacceptably high figure that called for comprehensive effort by healthcare providers and government to prioritize patient safety. Other fields with high-risk performance environments have long and successfully incorporated simulation technology into their training and assessment programs – for example, flight simulators for pilots and astronauts, war games and training exercises for military personnel and management games for business executives [3]. In a simulated environment, medical trainees are able to make mistakes, recognize and correct them without risk of harm to real patients. Related to patient safety issues are the ethical question: is it appropriate to use real patients as highest fidelity resources for teaching invasive procedures to under-prepared and under-supervised healthcare trainees? Simulation offers a means to circumvent such dilemma.

Altogether, the growing application of simulation in medicine can be thought of as a response to the public's demand for assurance that doctors are competent and patients' safety is put first.

TYPES OF TECHNOLOGY-ENHANCED SIMULATORS

Numerous types of technology-enhanced simulators are commercially available today, but most can be broadly grouped into three categories: part-task trainers, computer-enhanced mannequins (CEM), and virtual reality (VR) simulators.

Part-task trainers consist of representations of body parts/regions with functional anatomy for teaching and evaluating particular skills. The interface between the user and the simulator is usually passive, or low fidelity – the user performs some procedure with no response from the simulator. Part-task simulators are now available for at least twenty different medical procedures, including: endoscopy, colonoscopy, laparoscopy, hysteroscopy, hollow organ closure, hip replacement, ophthalmic surgeries, intravenous (IV) insertion, abdominal aortic aneurysm repair, shoulder arthroscopy, breast biopsy, transurethral prostatic resection, interventional cardiology and bronchoscopy [6]. For emergency medicine, Resusci Anne is one of the earliest mannequin simulators created to teach critical life-saving techniques [7]. Although it mimics a full-size adult, it is essentially a part-task trainer with functional anatomy enabling only ventilation and chest compression. Harvey (Figure 1) is the best known and the first modern part-task medical simulator. A full sized mannequin that simulates 27 cardiac conditions, it was developed in 1968 by Dr. Michael Gordon of the University of Miami medical School to teach skills in cardiac diagnosis [6]. Harvey not only demonstrates various physiological parameters but is capable of simulating a spectrum of cardiac diseases by altering these parameters.

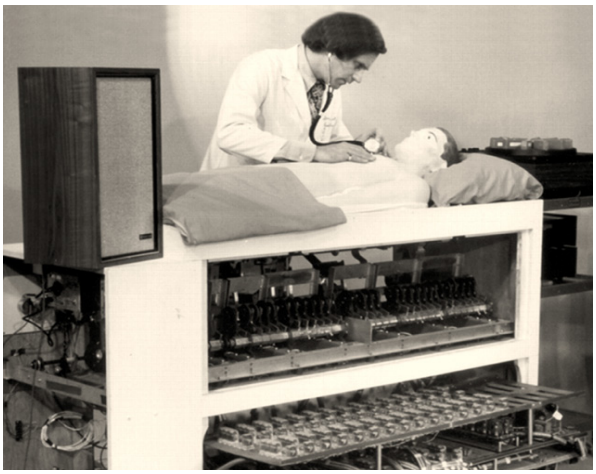

Figure 1. Dr. Gordon and Harvey. Picture adapted from [6].

CEMs are full-body mannequins connected to computers that reproduce not only the functional anatomy but also physiological functions. They are high fidelity, meaning that the interface with user is either active (i.e. responds in a pre-programmed manner) or interactive (i.e. responses varies depending on user action). Training with CEM can focus on either individual skills or teamwork skills, such as those required in an emergency resuscitation scenario. Medical specialties with high risk cases have led the expansion in the use of CEMs. For instance, Sim One, the earliest CEM introduced in 1967, was designed to simulate hemodynamic, cardiac and airway problems and built attached to an anesthesia machine [8]. Although this prototype is no longer in use, its template has been adapted for most current human patient simulators (HPS), the present-day high-fidelity anesthesia simulators [6]. HPS reproduces a variety of physiological functions, including: blood pressures, heart and breath sounds, muscle twitches from nerve stimulation, papillary reflexes, salivation, lacrimation, bleeding and verbal responses. In the operating theatre, it is connected to monitoring systems that display vital signs, electrocardiogram, oxygen saturation and other parameters in real time. The HPS contains multiple preprogrammed patient profiles and can simulate numerous scenarios involving these patients. Furthermore, educators can design customized programs for particular clinical scenarios.

VR simulators simulate the physical world with high fidelity on computer displays, rather than mannequins [9]. In addition to sound and visual feedbacks, recent technological advancement has enabled haptic feedback based on location and depth of touch. The complexity of VR systems ranges from simple techniques such as intravenous cannulation to complex surgical and percutaneous procedures such as laparoscopic cholecystectomy [10] and carotid artery stenting [11]. Beyond its application in procedural training, VR can be applied to facilitate learning in healthcare resource management, decision-making and communication in individual as well as team settings [3].

SIMULATION IMPROVES BOTH MEDICAL TRAINING AND PATIENT SAFETY

As a training tool, simulation serves to bridge didactic teaching and real clinical scenarios, by facilitating transfer of knowledge to clinical skills through repetitive sustained practice. A model for the roles of simulation in every stage of medical training is outlined in Figure 2. A study in 1987 using Harvey showed that senior medical students (n=208) who trained with Harvey during their cardiology elective performed significantly better than their peers who interacted only with patients [12]. The performance was assessed using the simulator as well as patients – students who were better able to interpret findings on Harvey showed enhanced confidence and ability to interpret those same findings on patients at the bedside. Wayne *et al.* reported that simulation-trained internal medicine residents responded as teams to real hospital "codes" (cardiac arrest events) with much greater compliance to established treatment protocols than more senior residents who were not simulator-trained [13]. In surgery, Seymour *et al.* reviewed convincing evidence that skills acquired on VR simulators was transferrable to patient care, helping to improve surgeons' operating room performance [14]. A recent meta-analysis of 609 studies conducted by a group from the University of Ottawa concluded that the use of simulation in medical training has consistently been associated with positive effects on knowledge and procedural skills [1]. In addition to enhanced performance, studies have further demonstrated improved patient safety associated with simulation-based train-

ing. For instance, in obstetrics, Draycott *et al.* have published extensive research demonstrating improved neonatal outcomes of births complicated by shoulder dystocia after implementation of simulation-based training [15]. A list of current simulations projects aimed to improve patient safety can be found at *Improving Patient Safety through Simulation Research website (http://www.ahrq.gov/qual/simulproj.htm).*

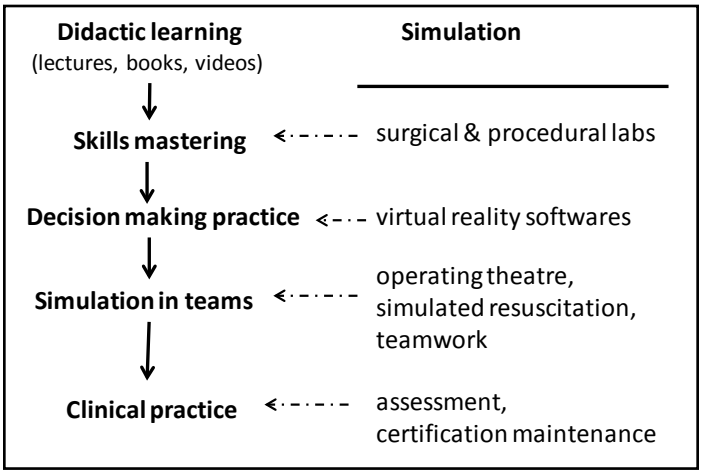

Figure 2. A model for the potential roles of simulation in surgical training.

SIMULATION AS A PERFORMANCE ASSESSMENT TOOL

Recorded performance history on simulators may serve as an objective measure to assess the progress of training and a means for immediate structured feedback [16]. The need for standardized assessment may be especially relevant to surgical training, where it may be challenging to objectively assess procedural skills in the operating room. The standardization, fidelity and reproducibility of medical simulation make the technology well suited to evaluations of clinical competency. For the same reasons, simulation may further be used to certify medical competencies. For many healthcare providers, professional development does not stop after licensing. With ever-evolving practice standards, staff surgeons may wish to learn new operative procedures or practice infrequently used skills. In support of this notion, the United States Food and Drug Administration (FDA) recently decided to implement mandatory simulator training for cardiologists prior to using a new carotid stenting device on real patients [17]. Also, the American Board of Surgery (ABS) now requires that surgery residents complete a course in the fundamentals of laparoscopic surgery to apply for the board's certification examination [18]. In addition to validating acquisition of skills, simulation is also projected to play a role in the maintenance of competency and in helping to define "fitness to practice". For example, the American Board of Anesthesiology (ABA) has mandated participation in a simulation-based course as part of its maintenance of certification (MOC) program for anesthesiologists licensed since 2000 [18].

RESEARCH INVOLVING HEALTHCARE SIMULATION

The last role of medical simulation to be discussed in this article pertains to its research and its use for research. There are two arms of simulation in clinical research [20], as described below:

The first type focuses on determining the clinical impact of simulation as an educational tool. In the past decade, studies comparing the efficacy of simulated training have consistently demonstrated its superiority. However, why simulation works and how better simulation programs can be designed is yet to be fully understood [1] and will be a major research focus. McGaphie *et al.* conducted a thorough qualitative review of simulation-based medical education (SBME) research studies from 1969 to 2009, and presented 12 features and best practice guidelines for how to design simulation programs to maximize educational benefits [19]. Some of the features and their relevant research questions are summarized in Table 1.

The second type employs simulation as a tool to explore performance, behavior and errors in healthcare. If high fidelity simulations are sufficiently representative of the clinical setting in terms of behavior and errors, then analysis of human or device performance on simulated systems should help us to understand and improve clinical performance and outcomes. Simulation has been used to explore the performance of both devices and humans [20]. Devices tested on simulators are often designed for rare but high-consequence events. An example is the assessment of an intraosseous infusion device to treat chemical warfare casualties [21]. In a chemical warfare mass casualty scenario, the protective gear worn by medical personnel, the time constraints, and the casualties' medical condition impose limitations on the establishment of IV access during early treatment of the victims. A spring-driven, trigger-operated intraosseous infusion delivery system was demonstrated on sophisticated simulators to provide an effective solution. Audiovisual recordings of simulated training can be used to study clinical behaviours and the evolution of medical errors [7]. Siassakos *et al.* used obstetric emergency simulation to identify specific aspects of teamwork associated with greater efficiency. The relationship between teamwork behaviors and time to administration of magnesium sulfate, a validated measure of clinical efficiency, was measured. The simulation helped to demonstrate that team behaviors such as early recognition of emergency and effective task delegation and handover were associated with great clinical efficiency [22].

LIMITATIONS OF SIMULATION

Perhaps the biggest hurdle to implementing a high-fidelity simulation centre is its capital cost [2]. In the operating theatre alone, an advanced human patient simulator costs $200,000 and set-ups cost an additional $200,000. Altogether, nearly 10 million dollars went into the construction of the simulation centre at the University of Ottawa [23]. Furthermore, specialized training is required for the staffs who run the centre. Like other aspects of healthcare, the sustainability and growth of simulation training is

Table 1. Critical features of medical simulation and relevant research questions. Adapted from review by McGraphie *et al.* [19].

Simulation Features	Research Questions
A. Outcome measurement & Feedback	Optimal model (faculty vs. device vs. audiovisual) and dose? How to assess quality of feedback? Factors that contribute to skill decay
B. Deliberate practice & Skill acquisition/maintenance	Distributed practice vs. mass practice?
C. Curriculum integration	How and when to best integrate with other learning modalities?
D. Simulation fidelity	Designing multi-modal simulators (e.g. task trainers incorporated into standardized patients) Matching target outcome, simulation duration and resources to real scenarios.
E. Transfer to practice	How skills acquired in simulation labs can be transferred to patient care?
F. Team training	Team size, composition, and roles in simulation programs Are team members interchangeable?
G. High-stake testing	Are simulations reliable and effective assessment and certification tools?

ultimately dictated by returns on investment [24]. Cost benefits are however indirect, intangible and long term [25]. Thus far, it has yet to be established.

Simulation training is not without its shortcomings. A major intrinsic limitation of simulation is its fidelity, which will always be less than real. Certain physiological functions, such as reflexes and changes in skin colour, and the emotional effect of illness cannot be simulated using a equipment [26, 27]. In addition to the equipment fidelity, another limitation is the psychological and environmental fidelity, the degree to which the trainee perceives the simulation to be a believable representation of reality [28]. Because simulators do not portray emotional stress and are not really sick, simulation training does not address the psychosocial aspects of patient care.

Moreover, the current role of simulation is largely restricted to medical training, whereas its roles in performance assessment and research on healthcare behavior and error have yet to be established [2]. As a training tool, access to the simulator is limited and is dependent on the availability of specially trained instructors and operators, and the number of simulators available. Currently, its use in medical education pertains mostly to post-graduate medical trainees. In comparison, the participation of medical students is very limited, due to a combination of 1) insufficient resources to accommodate large numbers of students, and 2) a lack of consensus on how to best integrate simulation into undergraduate medical curricula.

THE UNIVERSITY OF OTTAWA SKILLS AND SIMULATION CENTRE

The first simulation centre in Ottawa was established at the Heart Institute in 1998, at which time it was one of only four in Canada. Today, there are at least eighty medical simulation programs in Canada. With the recent construction of the University of Ottawa Skills and Simulation Centre (uOSSC), Ottawa has the potential to become a national and international leader in medical simulation training and research. The Centre became operational in October 2011, and represents a partnership between The Ottawa Hospital and the Academy of Innovation in Medical Education (AIME) of the University of Ottawa. The uOSSC houses fully functional operating theatres, surgical laboratories, simulated emergency room resuscitation areas and intensive care units [23]. The surgical theatres faithfully mimic the layout of operating rooms at the Ottawa Hospital, with two additional features to facilitate teaching (Figure 3). First, in the place of a human patient is a human patient simulator (HPS), a high fidelity computer-controlled mannequin. Second, all interactions within the operating theatres can be monitored, enabling documentation of performance and live feedback. In the surgical laboratory, trainees can hone their skills in a variety of procedures, from the basic (e.g. suturing, IV insertion, and intubation) to the specialty-specific (e.g. colonoscopy, laparoscopy and knee surgery). Other features include two conference rooms with teleconference capability for debriefing, and six clinical examination rooms.

To address the deficiency of simulation in the undergraduate medical curriculum, one suggestion is to create a procedural simulation course for medical students. Physician Skill Development (PSD), a core part of the University of Ottawa's undergraduate medical curriculum, provides medical students with many opportunities to simulate history taking and physical examination. However, for those interested in pursuing more intervention-based specialties such as emergency medicine and surgery, no procedural counterpart of PSD exists. Currently, Canadian Surgical Technologies and Advanced Robotics (CSTAR) offers a four-day course in the summer where first and second year medical students may obtain hands-on operating experience with the use of simulation. Being the only program of its kind in Ontario, the event is held only at London and charges a fee of $600. In Ottawa, we have the resources and the dedicated

Figure 3. Operating theatre at University of Ottawa Skills and Simulation Centre (uOSSC) as seen from the monitoring room.

teaching faculty to develop a similar program free and accessible to medical students. It can be integrated into the medical curriculum either as a supplemental resource for clerkship students, or, given that hands-on opportunities are extremely limited for first and second year medical students, as a preclerkship elective.

CONCLUSION

In summary, the past decade has witnessed tremendous growth and widespread acceptance of technology-enhanced simulation in medical training, owing to rapid advancements in technology and an increasing emphasis on patient safety. Although ample evidence exists for the effectiveness of simulation in training healthcare providers and enhancing patient safety, the underlying mechanism and understanding how to develop better programs requires further exploration. Furthermore, the emerging roles of simulation in performance assessment, certification, and research on healthcare performance, behavior and errors appear promising, but more evidence is needed to demonstrate efficacy. Lastly, we hope to see a greater distribution and integration of simulation resources into the undergraduate medical curriculum at the University of Ottawa.

DISCLOSURE OF CONFLICT OF INTEREST

The primary author of this article was invited by AIME to write an article on uOSSC and medical simulation as a part of the agreement for sponsorship.

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Individual-level access to a regular medical doctor is not associated with higher self-reported health in Canada

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ABSTRACT

Objectives: The aim of the current study was to examine the relationship between self-reported measures of having a regular medical doctor and self-perceived health in Canada.

Methods: Data from the 2007 to 2008 version of the Canadian Community Health Survey (CCHS), a cross-sectional national survey, were analysed. 119,452 respondents aged 18 years or older were included in this study. Univariate and multivariate Poisson regression analyses were conducted to assess the relationship between having a regular medical doctor and perceived health status. Sampling weights and the average design effect were taken into consideration.

Results: 84.4% of Canadians reported having a regular medical doctor, and among those, 87.3% reported high self-perceived health. However, among Canadians reporting not having a regular medical doctor, 92.1% reported high self-perceived health. Using a stratified multivariate Poisson regression, the adjusted prevalence ratio for the association between having a regular medical doctor and high self-perceived health was 0.99 (95% CI: 0.98, 0.99) for those 18 to 39 years of age, 0.95 (95% CI: 0.93, 0.97) for those 40 to 69 years of age, 0.91 (95%CI: 0.88, 0.93) for those 60 to 79 years of age, and 0.93 (95%CI: 0.84, 1.04) 80 years of age or older.

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.

INTRODUCTION

There is significant evidence that primary care, including the supply of primary care physicians is associated with improved overall health and reduced differences in health across population subgroups [1]. According to the College of Family Physicians of Canada (CFPC), an estimated 15% or five million Canadians do not have a family physician [2]. Despite universal health care in Canada, health service use, including access to primary care, varies by socioeconomic status (SES) [3]. Other countries have found similar trends, for example in Belgium access to general practitioners has been shown to vary by SES [4]. Race has been shown to be associated with overall health and access to a primary care physician for a number of reasons [5]. There is also evidence of a gender-related difference in access to family physicians [6]. Tudiver and Talbot [7] concluded there is a need for examining whether a regular source of primary care would have a positive impact on men's health. As well, physician density is an acknowledged proxy for access to primary care. Sarma & Peddigrew [8] and Macinko *et al.* [9] found that an additional family physician per 10,000 people was associated with a statistically significant increase in self-reported health and other health outcomes in the Canadian and American populations. The aim of the current study was to examine whether self-reported individual-level access to a primary care physician was similarly associated with an increase in perceived health in the Canadian population using data from the Canadian Community Health Survey (CCHS). This question is of particular importance given the CFPC's position statement on the need to-increase-the-number-of-Canadians-with-access-to-a-regular physician [2] as well as evidence of discrepancies in primary health care access associated with sex, age, race, and SES [1, 3-10]. We hypothesized that having a regular medical doctor would be positively associated with high self-perceived health since overall access to care has been found to be associated with increased health [8-9].

MATERIAL & METHODS

The current study consisted of analyses using the Cycle 4, 2007-2008 version of the CCHS, which is a cross-sectional survey on health status, healthcare utilization, and health determinants of the Canadian population. The target population was the Canadian population and the sampling design involved selection from approximately 98% of the target population. The approximately 2% of Canadians who were not eligible to be selected were individuals on Indian Reserves and on Crown Lands, institutional residents, full-time members of the Canadian Forces, and residents of certain remote regions.

A multiple stage stratified cluster sampling design was used, with dwelling as the final sampling unit. The sampling strategy gave relatively equal importance to each province and territory. The provinces and territories were divided into health regions (HRs) and the sample for each province or territory was allocated to the HRs proportionally to their estimated populations. Households were selected in each HR and one member of each household was selected for the 40 to 45 minute interview

composed of the common content, the optional content, and the rapid response content. The total sample size was 132,080 with a total of 131,959 valid interviews conducted. The overall household-level and individual-level response rates were 84.6% and 91.7%, respectively, while the overall national-level response rate was 78%.

The current study population included 119,452 of the CCHS respondents, who were aged 18 years or older, and had responded to the self-perceived health and regular medical doctor questions. We excluded any participants who did not respond to the questions used as covariates in the statistical models with the exception of education and income since they had a large number of non-responses. The main outcome of interest was self-perceived health, originally rated on a five category scale of poor, fair, good, very good, or excellent. In this analysis respondents answering either poor or fair were categorized in the "low" self-perceived health group and those who responded either "good", "very good", or "excellent" health were categorized in the "high" group. The main exposure of interest was having a regular medical doctor, which was a dichotomous variable of the response "yes" or "no" to the question "Do you have a regular medical doctor?"

The proportions of participants who reported high self-perceived health in those with and without a regular medical doctor were calculated. The other covariates considered in the analysis were selected based on evidence in the literature and included age, sex, marital status, total household income from all source, highest level of education completed, type of smoker, and cultural or racial origin. The reference groups were selected as the highest risk group for poor health for each covariate based on the literature, in order to model predictors associated with high self-perceived health. The final analyses conducted were: a log binomial model to test for biological interaction, and unadjusted and adjusted stratified multivariate Poisson regressions. The Poisson regressions were used to calculate prevalence ratios (PR) and 95% confidence intervals (CI) for the association between having a medical doctor and high self-perceived health, after taking potential confounding or effect modifying covariates into consideration. All point estimates were weighted to the Canadian population, and the average design effect was taken into consideration in variance estimation. An alpha level of 0.05 was considered statistically significant . All analyses were conducted using the SAS statistical software package (version 9.2; SAS Institute; Cary, NC).

RESULTS

The proportions of Canadian adults who reported high self-perceived health are presented in Table 1, stratified by having a regular medical doctor or not and by other predictor variables that were considered in the univariate analyses. Overall 84.4% of respondents reported having a regular medical doctor. The proportion of individuals who reported high self-perceived health was higher in respondents who had no regular medical doctor (92.1%) than those who did (87.3%).

The trend of greater proportions of high-self perceived health being reported by the participants without a regular medical doctor than by those with a regular medical doctor was observed across all of the subgroups listed in Table 1. There was also a trend of decreasing proportion of high self-perceived health with increasing age and it was more so in those having a regular medical doctor than those without (94.2 and 94.5% in the youngest age group compared to 68.3 and 72.4% in the oldest age group, for those with and without a regular medical doctor, respectively) (Table 1). The proportion of individuals reporting high perceived health increased with increasing income, increasing level of education, in non-smokers compared to current or former smokers, and in people of "white" ethnicity/ race compared to "visible minority" and these trends were observed in both people with and without a regular doctor (Table 1); however, the proportions of high self-perceived health were higher overall in those without a regular doctor.

A stratified multivariate Poisson regression model was used to assess the independent effect of having a regular medical doctor on the proportion of high self-perceived health by age group, unadjusted and then adjusted for sex, marital status, income, education, smoking status, and cultural origin or race. Table 2 shows the PR of high self-perceived health for having a regular medical doctor in relation to not having a regular medical doctor, stratified by age. The adjusted PR (95% CI) were 0.99 (0.98, 0.99), 0.95 (0.93, 0.97), 0.91 (0.88, 0.93), and 0.93 (0.84, 1.04) for the youngest to oldest age groups (18-39, 40-69, 60-79, and ≥80 years old, respectively). No statistically significant biological interactions were found between having a regular medical doctor and other covariates.

DISCUSSION

Our analysis found that approximately 85% of Canadians reported having a regular medical doctor in 2007 to 2008, which is consistent with the CFPC statement [2]. Thus, approximately 15% of Canadians do not have a regular medical doctor. We observed a statistical interaction between age and having a doctor which indicated that age was an effect modifier of the relationship between having a regular doctor and good health. The strength of the association measure between having a regular medical doctor and health increased with age except in the oldest age group (likely due to small sample size). The estimate for the PR of good health in this age group was not statistically significant at an alpha level of 0.05. There was no significant biological interaction with age on the additive or multiplicative scales (not shown).

The proportion of high self-perceived health was greater in Canadian adults without a regular medical doctor even after controlling for covariates, contradicting the original hypothesis and the results from the literature. Our findings do not appear to be supported by the literature on physician density, which consistently demonstrates a positive association between physician density and self-perceived health [8-9]. These studies found that physician density in a geographic area may be a proxy for

Table 1. Percentage (%) of respondents aged 18 and over reporting high self-perceived health among those with and without a regular doctor, by selected demographic factors. Data was obtained from cross-sectional observations in the 2007-2008 Canadian Community Health Survey.

	Regular Medical Doctor			No Regular Medical Doctor		
	No.	Healthy	%*	No.	Healthy	%*
Age (Years)						
18-39	28,583	26,807	94.2	8,767	8,227	94.5
40-59	35,954	30,888	87.9	5,916	5,265	90.0
60-79	30,489	23,608	78.7	2,159	1,762	84.1
80 and older	7,515	5,082	68.3	355	256	72.4
Sex						
Male	43,599	36,599	87.4	10,228	9,269	92.4
Female	58,932	49,786	87.2	6,969	6,241	91.6
Marital Status						
Single or Never-Married	19,517	17,034	90.1	6,493	5,859	91.9
Married or Common-Law	59,651	51,563	88.2	8,066	7,449	93.3
Widow, Separated or Divorced	23,135	17,603	78.5	2,590	2,158	86.3
Income						
$20,000 or less	16,841	7,787	69.0	2,156	1,684	80.8
$20,000-39,999	20,166	15,720	79.2	3,280	2,875	89.9
$40,000-59,999	16,185	14,072	87.6	2,851	2,650	93.3
$60,000-79,999	12,857	11,647	90.6	2,261	2,142	95.4
$80,000 or more	25,716	24,128	94.1	4,211	4,039	96.5
Unknown	15,923	13,031	85.5	2,438	2,120	89.0
Education						
<Than Secondary School	13,551	9,264	70.1	1,959	1,513	77.5
Secondary School Graduate	11,782	9,748	84.3	1,913	1,719	90.9
Other Post-Secondary Education	5,136	4,241	84.7	1,134	1,007	89.6
Post-Secondary Graduate	65,202	57,505	90.0	10,870	10,095	94.2
Unknown	6,860	5,627	84.9	1,321	1,176	89.5
Smoking Status						
Current Smoker	17,900	14,063	81.5	5,032	4,362	88.6
Former Smoker	30,615	24,969	84.9	3,492	3,071	90.5
Non-Smoker	53,315	46,807	90.2	8,579	7,991	94.3
Cultural Origin/Race						
Visible Minority	10,970	9,240	86.6	3,278	2,876	90.6
White	87,378	73,794	87.5	13,406	12,184	92.5
Total (n=119,452)	102,303	86,205	87.3	17,149	15,466	92.1

* The proportion estimates were weighted to the Canadian population.

Table 2. Unadjusted and adjusted* prevalence ratios (PR) and 95% confidence intervals (95% CI) for high self-perceived health in relation to having a regular medical doctor, stratified by age, Canadian Community Health Survey, 2007-2008.

	Unadjusted		Adjusted*	
	PR†	95% CI‡	PR†	95% CI‡
Age (Years)				
18-39	1.00	0.99, 1.01	0.99	0.98, 0.99
40-59	0.98	0.95, 1.00	0.95	0.93, 0.97
60-79	0.94	0.91, 0.96	0.91	0.88, 0.93
80 and older	0.94	0.84, 1.06	0.93	0.84, 1.04

* Adjusted for sex, marital status, income, education, smoking status, and cultural origin or race.

† Weighted to the Canadian population.

‡ Adjusted for design effect.

overall access and availability of primary care services and that as physician density increases so does self-perceived health for that given geographic area [8-9]. Further, one Canadian study found that an additional family physician per 10,000 population has a statistically significant impact in the order of 2 to 4% on self-reported health status and other quality of care outcomes [9]. In contrast, the results of our study appear to suggest that individual measures of access to a regular physician are not associated with increases in self-perceived health. One possible explanation is that Canadians who perceive themselves to be in poor health are more likely to regularly seek-primary-medical-care. This would explain why our study found that individuals reporting having a regular doctor were less likely to report high self-perceived health. Therefore it seems that-individual-access-to a-regular doctor does not predict-health-in the same way as physician density. Our findings may suggest that individual-level utilization-of primary care physicians is associated with different factors that predict care-seeking behaviour, including health status, whereas as at the population level, primary care availability predicts health.

Three-previous-studies-on-physician-utilization-in-Canada-examined-the-relationship between need and variation in physician use [11-12]. Birch *et al.* [11] and Dunlop *et al.* [12] both found that need was positively associated (statistically significant association) with the probability and the frequency of family physician use. Blackwell *et al.* [13] found a positive association-between-need-and-utilization-of health care services. Further, a recent Canadian study found a strong association between chronic disease and healthcare use [14]. Their conclusions that perceived need for care is associated with healthcare utilization support our proposed explanation for the negative association between having a regular doctor and high self-perceived health.

Previous studies have found that both overall health and access to primary medical care vary by several demographic factors including sex, age, marital status, race and SES [1,3-5,7-10]. A Canadian study found that income education and immigrant status were both associated with self-perceived health [8] and a study on Canada and the United States found an association between SES and healthcare utilization [13]. Our results are consistent with these findings.

The result of the previous studies combined with-our findings may suggest that overall access to care in an area is predictive of health and that-increasing physician density per geographical region rather than an overall increase in the percentage of Canadians with a regular medical doctor is the best approach to improving the health of Canadians. Indeed recent data show that medical school enrolment and the number of practicing physicians have increased over the past decade in Canada, although experts state that an overall increase in the number of physicians is not necessarily the solution. Dr. Morris Barer, director of the Centre for Health Services and Policy Research at the University of British Columbia stated in a recent paper by the Medical Post that over the past decade, medical schools have increased enrolment by 70 to 80% [15]. As well, the number of physicians practising in Canada has increased by 12% while the population has increased by only 9.4% [16].

Dr. Francine Lemire, associate executive director and director of professional affairs at the CFPC was quoted in the 2012 Medical Post paper saying "…There's a sense we are reaching the number of family doctors we need but distribution continues to be an issue." [15]. The idea that a simple increase in the overall quantity of physicians in Canada is insufficient to improve health was further supported in the same paper by an associate professor of economics at l'École des Hautes Études Commerciales de Montréal (HEC Montréal), Dr. Pierre Thomas Léger who expressed that the problem in Canada is one of access to care rather than quality of care and that this problem cannot be solved by increasing the number of doctors [15]. According to the 2004 Canadian Institute for Health Information report, only 9.4% of physicians practiced in rural communities whereas 21.1% of the Canadian population live in these communities [16]. Overall, the fact that the number of physicians has increased but that there is still a disparity between urban and rural centers suggests that access to care in rural communities rather than an overall increase in the number of physicians may be a better approach to improving the health of Canadians. Thus, increasing the percent of individuals with a regular doctor may not lead to increased self-perceived health. The results of our study may be consistent with this given that we did not find a positive association between the proportion of individuals with a regular doctor and the proportion of individuals reporting high self-perceived health.

The current study-had the strengths of high statistical generalizability and high precision due to a-very-large and representative sample of the target Canadian population. The sampling design ensured representation from all provinces and territories across the country. Appropriate statistical measures were taken in order to weight the estimates to the Canadian population as well as factoring the average design effect into the variance estimates in order to provide precise estimates.

However, the current study was subject to several limitations. One limitation to the CCHS study is that the cross-sectional nature lacks the ability to show temporality and therefore is unable to show whether having a regular medical doctor preceded high self-perceived health or vice versa. For this reason it is possible that perceived health may predict access to care at an individual level and this is a plausible explanation for the discord between our findings and the findings of previous studies on physician density [8-9]. Our study was limited in the ability to control for certain known or suspected potential confounders such as chronic or other underlying health conditions, mental health status, diet, and physical activity levels due to the fact that we were only able to use the publically available CCHS dataset and were limited by the statistical model used. Given that we used a stratified Poisson regression, we were limited in the number of covariates that we could include in the model and the number of stratification variables. Province was the only publically available geographic region variable. It was tested in our initial models but was not included it in the final model because its inclusion re-

sulted in too many strata.

Another limitation of the CCHS was the non-coverage of groups who are both at risk for lower overall health and who less likely to have access to a regular medical doctor, which may have biased the PR estimates towards the null. However, we did find a significant association thus this limitation does not appear to have impacted our results. The use of self-reported measures is subject to information bias, such as recall bias and interviewer bias. Our analysis was limited by the use of self-reported health measures only. We only included having a regular medical doctor but not access to primary care through drop-in clinics thus our results may have underestimated primary-care access. The study was also subject to some selection bias (although minimized by sampling technique). Our analysis may be subject to bias from residual confounding, and in particular we were not able to include province or geographic region as a covariate. A Canadian study found region of residence was associated with the relationship between physician visits and perceived healthcare need [11], therefore this association merits further investigation.

CONCLUSION

In summary,-we-found-a-negative association between having a regular medical doctor and 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. These findings should be interpreted with caution given the limitations of this study. Future studies that use objective measures of health and that consider the effect of region of residence would be important to further investigate the relationship between individual access to care and health. As well, studies that are of longitudinal nature are needed in order to establish temporality in the relationship between access to care and health in the Canadian population.

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Developing a measurement tool to assess medical students' cultural competency

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ABSTRACT

Objectives: Given the multicultural make-up of the Canadian population, there is growing recognition of the importance of cultural competency training for medical students and healthcare providers. Studies suggest that cultural differences promote disparities in the provision of healthcare by affecting patient-physician communication, patient satisfaction, and patient adherence. This paper discusses the development of a Cultural Awareness and Sensitivity Tool (CAST), a self-administered instrument to evaluate undergraduate medical students' awareness of cross-cultural issues in healthcare and their sensitivity toward them.

Methods: Items for the CAST were generated through a review of the literature published in PubMed using keywords focusing on "cultural competence" and "medical education". All items were scored on a five-point Likert scale, with the following descriptors: strongly disagree, disagree, neutral, agree, and strongly agree. The CAST was administered to 30 undergraduate medical students at a university in Ontario via SurveyMonkey, and re-administered one week later to measure test-retest reliability. All statistical analyses were conducted using SPSS 11.0 and G String II.

Results: Twenty students (67%) responded at both time points. Only six students (30%) reported having been trained in cross-cultural issues in healthcare through course work or electives and 12 (60%) identified "South Asian" as their racial/ethnic heritage. The test-retest reliability of CAST was high at 0.931, and the internal consistency and overall reliability were moderate at 0.756 and 0.721 respectively.

Conclusions: The CAST has important implications in medical education. With improvement, it can influence curriculum development and encourage medical students to more actively undertake cultural competency training.

INTRODUCTION

As the Canadian society becomes increasingly diverse in its cultural make-up, there is growing recognition of the importance of cultural competency training for medical students and healthcare providers. The concept of cultural competence has been addressed in the nursing literature since the 1970s and has been defined as a "process, not an endpoint, in which the nurse continuously strives to achieve the ability to work within the cultural context of an individual, family, or community from a diverse cultural/ethnic background" [1,2]. A culture includes multiple dimensions such as race, ethnicity, socioeconomic status, religion, nationality, generation, and sexual orientation [3].

Numerous studies suggest that cultural differences promote disparities in the provision of healthcare by affecting patient-physician communication, patient satisfaction, and patient adherence [1,6,7]. These create barriers to healthcare accessibility, which is one of the principle tenets of the Canada Health Act [4]. In addition, the Ontario Human Rights Code asserts that every resident has the right to receive equal treatment with respect to the provision of services without discrimination on grounds such as race, colour, and sexual orientation. The College of Physicians and Surgeons of Ontario also requires healthcare providers to abide by the code, which has encouraged the integration of cultural training in medical and nursing curricula [5].

Many instruments have been previously developed in the literature to measure cultural competence. However, most of these instruments are geared toward nursing students or physicians, and assess distinct aspects of the multidimensional construct [6]. The objective of this paper is to discuss the development of a self-administered instrument to evaluate undergraduate medical students' awareness of cross-cultural issues in healthcare and their sensitivity towards them.

A model that has been utilized in the literature to guide cultural competency training in healthcare explains the construct through four main components: cultural attitude (sensitivity), cultural knowledge, cultural skill, and cultural encounter [1,2,7]. One systematic review identified 45 self-assessment tools on the topic, of which 37 (82%) were geared toward nurses and physicians. In terms of psychometric properties, the review found no information on the reliability and validity of 30 (67%) of these instruments [6]. Another validated instrument is the Inventory for Assessing the Process of Cultural Competence (IAPCC) among Health Care Professionals, a self-assessment tool with 25 items measuring awareness of cultural issues, ability to interact with diverse cultural groups, and sensitivity toward diverse beliefs and values on a four-point Likert scale. Although the reliability and validity of the IAPCC has been reported in nursing students and healthcare providers, research in undergraduate medical students is lacking [7].

The Cultural Attitudes Survey – Modified (CAS-M) was also designed for a specific population, specifically the African American, Hispanic, and Asian American racial and ethnic groups. While the CAS-M measures cultural competence attitudes, the Cultural Self-Efficacy Scale (CSES) mainly focuses on cultural skill and knowledge as opposed to addressing the broader construct [8,9]. Also, the "cultural skill" component of the CSES may not be relevant for undergraduate medical students, specifically those with limited patient contact and clinical experience.

An additional tool identified in the literature was the Cultural Competence Assessment (CCA) instrument that measures both cultural competence behaviours (including skills in clinical encounters) and attitudes (knowledge and sensitivity). Again, the reliability and validity of this instrument have been established only in healthcare providers, not in medical students [8]. This limitation was overcome by the Health Beliefs Attitudes Survey (HBAS) which was validated in first year medical students and shown to be reliable in this sample [10]. However, no other reports on the reliability of this instrument have been published. The HBAS consists of 15 items scored on a six-point Likert scale assessing attitudes toward cultural issues and the provision of good quality healthcare without any emphasis on the component of cultural knowledge [10].

Considering the limitations of the aforementioned measurement tools, the primary aim of this study was to develop the Cultural Awareness and Sensitivity Tool (CAST) specifically targeting cultural competency training in undergraduate medical students. An additional objective was to test the CAST in a sample population of medical students in order to assess its validity and reliability.

METHODS

Generation & Selection of Items

Items for the CAST were generated through a literature review focusing on previously developed cultural competency instruments on PubMed. The search strategy is presented in the online Appendix. The purpose of this review was to gain an understanding of the content of previously published questionnaires addressing cultural awareness in healthcare as a starting point for the development of items for the CAST. The review was not meant to be a comprehensive analysis of the scholarly literature and due to time and resource constraints, the search was restricted to one database.

The IAPCC was used heavily in developing the CAST because it incorporates various themes within cultural competence including awareness, sensitivity, skill, and behavioural interaction. For example, statements such as "I am knowledgeable in the area of ethnic pharmacology" and "I am aware of the specific health risks faced by people of varied cultural and ethnic backgrounds" were derived from this tool [2,3]. These statements were considered to be important measures of the domain of cultural knowledge for the sampled population.

Similarly, items from the CCA instrument that focused on adapting to varying cultural settings and interacting with diverse cultural groups comfortably were also incorporated into the CAST as measures of cultural sensitivity [8]. Statements around learning about traditional healing practices and understanding that cross-cultural barriers can lead to inaccurate histories, patient dissatisfaction with care, and miscommunications were based on published reviews [11,12].

Overall, 25 items were developed; 11 focused on the domain of cultural sensitivity while 14 were based on exploring the students' cultural awareness. Preceding the items, a section on demographics was included to qualitatively explore how the students' ethnic/racial backgrounds and prior training in cultural issues impact responses. All items were scored on a five-point Likert scale, a widely used scale in psychometric studies, with the following descriptors: strongly disagree, disagree, neutral, agree, and strongly agree.

CAST Questionnaire:

1. I feel comfortable working with people from cultural or ethnic backgrounds different from my own.
2. People from different cultures may define the concept of "healthcare" in different ways.
3. Race is the most important factor in determining a person's culture.
4. Understanding a patient's cultural background will help me provide better care as a clinician.
5. I feel comfortable evaluating situations from different cultural perspectives.
6. Learning about beliefs and values held by individuals of another cultural background is interesting for me.
7. Knowing about different cultural groups improves my ability to interact with others.
8. It is challenging for me to interact with individuals from a different cultural background than my own.
9. For a physician, a patient's cultural perspective is secondary to other issues in the provision of good quality care.
10. Cultural groups differ in the ways in which they interact with members of their own culture versus other cultures.
11. I am aware of prevailing beliefs, customs, norms, and values of other cultural groups.
12. When I am surrounded by culturally diverse individuals, I feel that my own beliefs and values are being threatened.
13. Learning about alternative/non-Western medicine and traditional healing practices is an important part of medical training.
14. Cross-cultural barriers between the patient and physician can lead to negative consequences for clinical care such as longer office visits, noncompliance, and unnecessary testing.
15. In conversations, I am attentive to nonverbal cues and culturally specific gesture.
16. Culturally influenced spirituality and religious beliefs are important aspects of a patient's decisions around their health.
17. I reflect on and examine my own cultural background, biases, and prejudices related to race and culture that may influence my behavior.
18. I respect the decisions made by my friend and colleagues when they are influenced by their cultural backgrounds even if I disagree.
19. Many aspects of culture influence a person's decisions and perceptions about health and healthcare.
20. The ease with which patients can communicate with their physicians varies across cultures.
21. I am knowledgeable in the area of ethnic pharmacology (variation in medication responses in individuals of different

ethno-cultural backgrounds).

22. I am comfortable discussing racial or cultural issues with my friends and colleagues.
23. I am aware of specific health risks faced by people of varied cultural and ethnic backgrounds.
24. I would feel uncomfortable working with a colleague who makes derogatory remarks toward individuals of a particular cultural background.
25. When I come in contact with individuals from another culture, I adapt my behavior in accordance with my understanding of their culture.

The CAST was administered to a few randomly chosen graduate students for pre-testing, which led to the re-wording of some of the statements to minimize ambiguity in their interpretation. Face and content validation were achieved through feedback from content experts in order to evaluate whether the CAST appropriately measures important domains of cultural competency.

Scoring Responses

The instrument was scored on a five-point Likert scale with each item weighted equally. In order to account for acquiescence bias (the tendency to respond positively), a few items were keyed in the negative direction [13]. For example, for the statement: "I feel comfortable working with people from cultural or ethnic backgrounds different from my own", another statement was worded in the opposite direction: "It is challenging for me to interact with individuals from a different cultural background than my own". All such negatively keyed statements were reverse scored in SPSS during data analysis.

Administration and Data Collection

The CAST was administered to 30 undergraduate medical students at an Ontario university electronically via SurveyMonkey [14]. The sampled individuals were contacted personally or through e-mail and asked to complete the questionnaire. They were assured that their responses would be kept confidential and only be reported as an aggregate. The questionnaire was re-administered one week after initial completion to assess test-retest reliability.

Statistical Analysis

All statistical analyses were conducted using SPSS 11.0 and G String II. Generalizability theory (G-theory) was used to analyze internal consistency, test-retest reliability, and overall reliability. For internal consistency, subjects (students) were the facet of differentiation, items were the facet of generalization, and time was fixed. To assess test-retest reliability, subjects were the facet of differentiation, time was the facet of generalization, and items were fixed. For overall reliability, subjects were the facet of differentiation, and items and time were facets of generalization. All factors were considered random and a crossed-design was adopted for the analysis [13].

RESULTS

Questionnaire Development

In the development phase, the wording of some statements was altered to avoid negative connotations and improve clarity based on the feedback received during pre-testing.

Description of Sample

The CAST was administered to 30 medical students at an Ontario university, of which 20 (67%) students responded at two time points seven days apart. Responses from the first wave were used for the exploratory factor analysis followed by classical test theory testing. All respondents from the first and second waves were included in the G-theory analysis. The mean age of the respondents was 24 years, and 55% (n = 11) were male. Only 6 students (30%) reported having been trained in cross-cultural issues in healthcare through course work or electives. Nine (45%) respondents were first year medical students while 8 (40%) were second years. In terms of their personal background, 13 (65%) students responded that they have spent the majority of their lives in Canada. Twelve (60%) students identified "South Asian" as their racial/ethnic heritage, while 6 (30%) and 2 (20%) identified their racial/ethnic heritage as "White" and "Other" respectively.

Item Analysis

Overall, the mean scores range from 2.7 to 4.6 on the Likert scale, suggesting that end aversion bias was not present and responses were not conservative in nature i.e. not restricted to the middle of the scale [13]. The face and content validity of the instrument was appropriate as judged during pre-testing by a content expert in cultural competence training.

Generalizability

As per G-theory, the test-retest reliability of CAST was high at 0.931, and the internal consistency and overall reliability were moderate at 0.756 and 0.721 respectively. Although the internal consistency of the CAST was moderate, this may be at the cost of losing content validity because the CAST addresses select components of cultural competency. For the purpose of drawing inferences about a population based on their scores, it may be worthwhile to focus on a wide variety of underlying domains at the cost of reducing internal consistency [13].

DISCUSSION

Since a random sample was not obtained for the study, the majority of respondents were from the same cultural group and university. As such, re-testing the CAST in a wider population base would be beneficial. Sampling a wider range of individuals (perhaps a random sample stratified by racial group or institution) would account for the influence of institution-specific medical training on cultural competence, as well as the role of one's ethnic heritage on attitudes toward culture in healthcare. The subsamples by cultural group and presence of prior training were too small to make these inferences.

While an expert was involved in the item generation and tool development phases, a formal process of quantifying the content validity of the instrument was not followed. This is a limitation that could be tackled by adopting a more structured and rigorous approach to obtaining expert opinion on individual items if more time and resources were available [13].

There is also a potential for "faking good" when completing the CAST because respondents may put forth a false-positive impression of being open to diverse cultures to avoid appearing ethnocentric. To counter this bias, respondents were assured that their responses would remain anonymous at the beginning of the questionnaire. However, social desirability has been recognized as a challenge in measuring true cross-cultural attitudes. Further research on the interplay between explicit and implicit attitudes will aid in minimizing this bias [12].

In the future, it may be interesting to explore how scores on the CAST relate to scores on a patient satisfaction survey when the students begin practicing as a measure of predictive criterion validation. Convergent validation could also be analyzed by correlating CAST scores to scores on an ethnocentrism scale since some research suggests that cultural competence and ethnocentrism are inversely related [17]. Therefore, instruments such as the CAST have important implications on medical education and training, and are stepping stones for additional research in the area. Next steps also include modifying the instrument for evaluating a cultural competency course or workshop, and assessing responsiveness through pre- and post-intervention change scores.

CONCLUSION

Measuring and understanding how cultural competence influences knowledge, attitudes, and behaviours is crucial to improving clinical competence and patient outcomes in healthcare. Since most measures of cultural competence in the literature are tailored to physicians and nurses, the CAST was developed to measure content areas (cultural awareness and sensitivity) relevant to undergraduate medical students specifically. The CAST was built based on previously published cultural competency scales and pilot-tested in a group of 20 undergraduate medical students at a Canadian university in this study. The assessment tool was found to have a high test-retest probability of 0.931, while the internal consistency and overall reliability were moderate at 0.756 and 0.721 respectively. With further improvement, the CAST can influence curriculum development and encourage medical students to be more conscious of the important role of cultural competence in the provision of good quality healthcare in an increasingly diverse Canadian population.

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Severe oligohydramnios following trastuzumab (Herceptin) use during pregnancy

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ABSTRACT

Background: Trastuzumab (Herceptin) is a monoclonal antibody used for the treatment of human epidermal growth factor receptor 2 protein (HER2)-positive breast cancer. Experience with use of this agent during pregnancy, and its possible effects on the fetus are limited.

Case: A 40 year old patient with breast cancer received a single dose of trastuzumab at 30 wks of pregnancy. This treatment was associated with severe oligohydramnios, which did not fully resolve after the drug was discontinued. Therefore the infant was delivered by emergency cesarean section at 34 wks gestation.

Conclusion: Based on a literature review, there appears to be an increased risk of oligohydramnios during the second and third trimesters associated with the use of trastuzumab. In contrast to previous reports of trastuzumab use in pregnancy, the oligohydramnios in this case did not reverse on discontinuation of the agent. Investigation of the role of HER2 in fetal renal development and amniotic fluid dynamics is needed to further our understanding of the safety of trastuzumab use in pregnancy.

INTRODUCTION

Although the majority of breast cancers occur in the menopausal and peri-menopausal age group, about 5% of breast cancers occur in pre-menopausal women [1]. Breast cancer occurs in about 1 in 3000 pregnancies every year and is one the most commonly diagnosed cancers during gestation [2]. The diagnosis of pregnancy-associated breast cancer poses a treatment dilemma for the patient and her medical team. Depending on the stage at diagnosis, adjuvant chemotherapy cannot necessarily be delayed until after delivery. Safe use of chemotherapy-especially after the first trimester-has been reported, and pregnant women with cancer can accept therapy without definite neonatal harm [3]. As advances in anticancer therapies continue, however, information about their impact on the fetus may be limited. Trastuzumab (Herceptin) is a monoclonal antibody directed against the extracellular domain of human epidermal growth factor receptor 2 (HER2) protein, which when over-expressed, causes increased cell growth and proliferation leading to a more aggressive breast cancer. A positive HER2 result on tumor histology involves immunohistochemistry, a fluorescent *in situ* hybridization (FISH) result of more than 6 HER2 gene copies per nucleus, or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2. Trastuzumab, either alone or in combination with chemotherapy, has been shown to improve outcomes in HER2-positive breast cancer [4].

Cardiac dysfunction occurs in 2% to 4% of women treated with trastuzumab [5], but information about the effects on the developing human fetus is limited. Based on the few case reports that currently exist in the literature with regards to the use of trastuzumab in pregnancy, however, there appears to be an increased risk of oligohydramnios. Oligohydramnios refers to amniotic fluid volume that is less than expected for gestational age. An adequate volume of amniotic fluid is critical to allow normal fetal movement and growth, and to cushion the fetus and umbilical cord. Oligohydramnios may inhibit these processes and can lead to fetal deformation, umbilical cord compression, and death. It is typically diagnosed by ultrasound examination and is described quantitatively as an amniotic fluid index (AFI) less than 5 cm. The AFI is measured by dividing the uterus into four imaginary quadrants. The deepest, unobstructed, vertical pocket of fluid is measured in each quadrant in centimeters. The four pocket measurements are then added to calculate the AFI. An AFI between 8-18 cm is considered normal. The volume of amniotic fluid is ultimately determined by the volume of fluid flowing into and out of the amniotic sac. By the beginning of the second trimester, fetal urine begins to enter the amniotic sac. Therefore, pathology related to the fetal renal/urinary system plays a prominent role in the etiology of oligohydramnios. We report a case of severe oligohydramnios following trastuzumab exposure during gestation, which did not resolve promptly when therapy was discontinued.

Table 1. Sonographic assessment following detection of oligohydramnios.

Estimated gestational age (wk)	Amniotic Fluid Index (cm)
32+4	Not Stated
32+6	1.3
33+2	3.0
33+5	1.8

CASE

Medical oncology perspective

A 40 year-old Caucasian woman was referred for evaluation. She noticed a lump in her left breast and was diagnosed with infiltrating ductal carcinoma at 16 weeks gestation. Biopsy revealed an estrogen receptor positive, progesterone receptor weakly positive, HER2 positive, grade 3 tumor. A left lumpectomy with clear margins was performed at 18 weeks gestation. The tumor measured 3.0 cm, and 0/3 lymph nodes were tumor-positive. While lymphovascular invasion was absent, tumor necrosis was present. Given the aggressiveness of her tumor, indicated by a high HER2 FISH ratio, the patient decided to proceed with adjuvant chemotherapy and to continue the pregnancy with expectant management. The medical oncology team agreed that there is no reason to believe that continuing the pregnancy would either adversely affect the patient's own prognosis or the health of her baby. It was also noted that while listed as a category D drug (there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk), clinical experience with trastuzumab in pregnancy is very limited and the fetal outcome data is case report based only. At 30 weeks gestation, she was treated with three cycles of epirubicin and cyclophosphamide with granulocyte colony-stimulating factor support, followed by one cycle of docetaxel (Taxotere) and 535.5 mg trastuzumab. The plan was to deliver two additional cycles of docetaxel with trastuzumab every 3 weeks, so the chemotherapy component of therapy would be finished by week 36 of pregnancy.

Obstetric perspective

The patient had a relatively unremarkable obstetric history. She was gravida (number of pregnancies) 4, preterm (num-

Table 2. Herceptin use during pregnancy [11].

	Current Case Study	Goodyer (Case 1)	Goodyer (Case 2)	Watson	Fanale	Waterston	Bader	Shrim	Sekar	Witzel	Pant
Maternal Age	40	33	38	28	29	30	38	32	28	~32	~33
Stage	III	IV	III	II	IV	II	IV	IV	IV	IV	IV
Treatment	T/D	T	T	T	T/V	T	T/P	T	T/D	T	T
Initiation	30/40	2nd trimester	Pre	Pre	27/40	Pre	25/40	Pre	23/40	Pre	Pre
Completion		29/40	6/40	20/40	34/40	1/40	28/40	24/40	27/40	NS	30/40
Antenatal complications	Oligo	None	1 of 2 viable fetal sacs	None	Oligo	None	Anhydramnios "Renal failure"	None	Anhydramnios	Oligo, Vaginal Bleeding	Oligo
Delivery	CS	CS	VD	VD	VD	VD	CS	CS	CS	CS	VD
Gestation	34	29	39	37.5	34+5	Term	32+1	37	36+2	28	32+1
Perinatal Comp.	Nil	Nil	Nil	Nil	Nil	Nil	Fetal distress	Breech	Breech	Bleeding	Nil
Fetal sex	F	F	F	F	M	F	M	F	M	F	F
Birthweight	2267 g	1220 g	2940 g	2960 g	2270 g	NS	1460 g	2600 g	2230 g	1015 g	1810 g
Neonatal	Normal	RDS	Normal	Normal	Normal	NS	Sepsis, RDS	RDS	Normal	Multiorgan Failure	Normal
Outcome	Normal	Nil significant	Normal	Normal	Normal	NS	Normal	Normal	Normal	Neonatal death	Normal
Duration of follow-up	3 months	3 years	2 years	6/12	6/12	NS	3/12	2/12	NS	21 weeks	60/12

T = Trastuzumab, V = Vinorelbine, P = Paclitaxel, D = Docetaxel, Pre = Pre-pregnancy, NS = Not stated, Oligo = Oligohydramnios, CS = Caesarean section, VD = Vaginal Delivery, RDS = Respiratory Distress Syndrome

ber of deliveries after 20 weeks but before 38 weeks) 0, abortion (number of deliveries before 20 weeks, either spontaneous or induced) 1, and living (number of living children) 2. Her most recent pregnancy was uneventful until two weeks after she received her first dose of trastuzumab. No exposure to alcohol, cigarettes, or other drugs was disclosed. At 32 weeks and 4 days gestation an ultrasound study indicated symmetric fetal growth, biometry consistent with gestational age, an estimated fetal weight of 1993 g, and severe oligohydramnios. The fetal kidneys were visualized and appeared normal in size and echogenicity. Additional exposures other than trastuzumab that may explain the oligohydramnios were excluded on a repeat history, including the use of angiotensin converting enzyme (ACE) inhibitors or non-steroidal anti-inflammatories [6, 7]. On serial ultrasound observation, non-stress tests were reactive and there were some accumulations of fluid (Table 1). However, at 33 weeks and 5 days, the AFI was still only 1.8 cm (normal 8-18 cm). The maternal fetal medicine team recommended delivery at 34 weeks secondary to the severe oligohydramnios. To induce fetal pulmonary maturation, intramuscular betamethasone (Celestone) was administered, 12 mg every 24 hours for two days. The obstetrical team decided to proceed with a repeat cesarean section. The procedure itself and postoperative course were uncomplicated. She delivered a viable female weighing 2267 g, with Apgar scores of 9 and 9 (where scores of 7-10 are considered normal). Placental pathology was unremarkable.

This case of irreversible oligiohydramnios associated with trastuzumab therapy was reported to Health Canada using the Canada Vigilance Online Adverse Reaction Reporting system [8]. The patient completed two more cycles of chemotherapy post partum. Following restaging, the plan is to continue her on docetaxel with trastuzumab every 3 weeks.

DISCUSSION

Breast cancers in pregnancy tend to be more advanced and aggressive at presentation. They are often associated with poor prognostic factors such as lymphovascular invasion, hormone receptor negativity, and over-expression of HER2 [9]. Given that treatment with trastuzumab has been shown to improve outcomes in HER2-positive breast cancer [4], its benefit in disease management warrants consideration of use during pregnancy with careful monitoring of amniotic fluid dynamics. To date, approximately 10 case reports exist in the literature regarding the use of trastuzumab in pregnancy (Table 2). There appears to be an increased risk of oligohydramnios during the second and third trimesters associated with the use of trastuzumab. In contrast to this case, the oligohydramnios was reversible on discontinuation of the agent in most cases. Of note, our patient had the most advanced maternal age. The majority of infants did not appear to suffer from significant long-term effects.

One possible mechanism for the association between Herceptin use in human pregnancy and the development of oligohydramnios is that epidermal growth factor receptors are expressed in the fetal kidney during development, which induces DNA synthesis and mitosis [10]. Therefore, blocking these receptors, such as might occur with trastuzumab, would lead to a decrease in kidney cell proliferation and thus renal dysgenesis. Further investigation of the mechanism of action of HER2 in fetal renal development may shed light on our understanding of the safety of trastuzumab therapy in pregnancy.

CONSENT

Both oral and written informed consent were obtained from the patient who also gave consent on behalf of her child for publication of this case presentation.

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La résilience des exilés

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INTRODUCTION

De par le monde, il y a aujourd'hui plus de 15 millions de réfugiés qui vivent dans des situations précaires, le plus souvent entassés dans des camps. Depuis déjà quelques années, je m'intéresse à la situation de ces personnes, particulièrement aux réfugiés nouvellement reçus au Canada. D'ailleurs, depuis l'an dernier, je m'implique dans le groupe d'intérêt consacré à la défense des droits et à la promotion de la santé des réfugiés: *Refugee Health Initiative*. J'en suis devenu le responsable pour l'année 2011-2012. Grâce à ma participation qui consiste à réaliser des entrevues médicales à des réfugiés tout juste arrivés en sol canadien, j'ai rencontré des personnes dont le parcourt sinueux et souvent dramatique m'apparut pour le moins rempli d'espoir. Ces rencontres fascinantes, ces défis communicatifs, nécessitant souvent la participation d'un traducteur, m'apprirent beaucoup sur les épreuves que doivent traverser les réfugiés, notamment la perte de leurs repères usuels, et donc, le choc culturel. Cependant, ces rencontres m'ont avant tout permis de me défaire de certaines idées reçues, principalement, de comprendre qu'il existait une relation complexe et non linéaire entre la santé mentale des réfugiés et leur vécu souvent chaotique [1]. J'appris que dans l'ordinaire contre-transfert clinique, on ne doit pas se laisser prendre au piège par un rapport de causalité qui lierait la pathologie mentale au vécu ayant mené le réfugié à l'exil. Bien sûr, il va sans dire que cette dernière affirmation surprend. Elle surprend car elle se démarque du préjugé habituel liant la migration, et toutes ses difficultés, à une prévalence supposée plus grande de maladies mentales. Ainsi, dans les prochaines lignes, j'aimerais vous montrer qu'un tel préjugé n'a pas lieu d'être, qui plus est, afin de permettre au réfugié de rebondir après l'impact traumatique l'ayant mené à l'exil, afin qu'il devienne résilient, le médecin ou l'étudiant en médecine doivent se défaire de tout fatalisme.

SANTÉ MENTALE DES RÉFUGIÉS ET RÉSILIENCE

Ainsi, la résilience telle qu'élaborée par le psychiatre français Boris Cyrulnik, c'est reconnaître que l'expérience traumatique (celle de quitter son pays en guerre, par exemple), n'a pas en soi qu'une finalité malheureuse, elle peut ne pas s'exprimer dans la pathologie, mais plutôt au travers de deux mots apparemment opposés, tel un *merveilleux malheur* [2,3]. L'oxymoron dans le vécu du migrant, et notamment dans celui du réfugié, c'est sa capacité à reconnaître la douleur de l'événement malheureux (ou encore la perte), mais aussi son caractère presque initiatique, à savoir le bonheur qui en est ressorti (le début de sa nouvelle vie sur sa terre d'accueil, ou encore un nouveau départ pour les enfants de la famille). Ainsi, bien que l'on reconnaisse plus de cas de désordre de stress post-traumatique (PTSD) (10 fois plus) chez les réfugiés vivant dans les pays développés [4], et qu'on diagnostique davantage de cas de psychose et de mutisme infantile chez leurs descendants [5], n'en demeure que la prévalence de troubles mentaux (tous troubles confondus) ne s'avère pas supérieure à la population non migrante. Qui plus est, certains enfants de populations migrantes, notamment en Grande-Bretagne, présentent généralement des taux plus bas de maladies mentales que les enfants de la population en général [5]. Cela laisse donc croire qu'il y a bel et bien eu résilience. Grâce à divers mécanismes psychologiques et sociologiques, entre autres grâce à la force de l'attachement familial, la multiplicité des interactions avec des tuteurs de résilience [6], un "*antidestin*" s'est fait jour. Ainsi, à la manière de millions d'enfants de juifs de la Shoah, mais aussi, à d'autres millions qui vivent des déchirements, des déflagrations, des abandons, à ceux qui traversent des traumatismes collectifs, des génocides ou des ethnocides, de nombreux enfants de migrants utilisent la résilience qui, tel qu'exprimé plus haut, s'avère être la capacité de rebondir après l'impact. Mais la résilience est complexe, elle ne se fait pas seule, elle se crée grâce à une multiplicité de facteurs.

LE MÉDECIN: FACTEUR DE RÉSILIENCE

Ainsi, ce que j'ai réalisé en faisant ces entrevues avec les réfugiés, c'est le difficile, mais non moins nécessaire devoir de reconnaître la blessure, mais cela, sans fatalisme. Pour faciliter la résilience, et s'illustrer tel un moteur de résilience, le médecin ou l'étudiant en médecine doit passer outre l'idée collectivement admise qu'il existe un fatalisme liant un vécu traumatique passé à un futur conditionné par le désespoir, la honte ou l'angoisse. Donc, l'une des possibilités pour faciliter la résilience, c'est certainement celle de déconstruire les mythes cliniques existant à l'égard des migrants. Qui plus est, il est primordial de poursuivre les recherches usant à la fois les outils des sciences sociales et de la médecine (notamment la psychiatrie), afin d'explorer quels déterminants de la santé facilitent la résilience chez les réfugiés. On sait déjà que l'emploi, contrairement à la population hôte, facilite la résilience et assure une meilleure santé mentale au migrant, mais pour ce qui en est de l'accessibilité aux soins de santé ou de la relation avec un médecin de famille, plusieurs recherches restent à être menées.

CONCLUSION

Bref, bien que la migration (et ses raisons) comporte son lot de difficultés, il n'en demeure pas moins que la santé mentale du migrant, et particulièrement du réfugié, et de ses enfants, n'apparaît pas plus affectée que pour la population en général. Sans doute, car, et c'est là mon hypothèse de travail, l'expérience a pu être reformulée et surtout transformée grâce à la résilience.

Laquelle est souvent facilitée par la composition familiale qui crée un refuge de solidarité et d'entraide, mais aussi par la médecine, et ses recherches, qui doivent avoir pour mandat de démystifier la résilience du réfugié, et ainsi, *dépathologiser* le vécu de l'exilé.

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Discovering promise and inspiration at Pumwani Maternity Hospital

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For my summer elective in Kenya as a first year medical student, I did not expect to save lives or change the world. I expected it to be an opportunity to learn more about disparities in health care and diseases between Canada and Kenya. I wanted to get a feel for international medical work.

The elective that my three colleagues and I signed up for was through the University of Manitoba and their partnership with the University of Nairobi. We were given a schedule that exposed us to a variety of health care facilities in the city that focused on women's health, including university-funded clinics and a public maternity hospital. Some time was spent in Sex Worker Outreach Program clinics, which encompassed field outreach in the slums and experience interviewing and examining the sex workers in clinic. Although I was exposed to a lot of women's health issues and care in these clinics, my time spent at Pumwani Maternity Hospital was where I truly became inspired to work towards improving maternal care in the developing world.

Pumwani Maternity Hospital had a patient population representative of its neighbouring slums. Built in the 1920s, it looked as though it had barely survived all those years; never renovated and poorly maintained. I openly gaped at the appalling conditions: peeling paint, water, and blood stained the walls, while torn linoleum floors, broken medical equipment, and cockroaches covered the floors. The smell of birth, feces, and unwashed bodies was enough to knock me backwards; despite the lingering scent of bleach in an attempt to mask them. I carried the smell home with me every night that week. My initial impression of Pumwani was that of a horror film; I had never been so alarmed and disgusted at health facilities in my entire life.

My first day in Labour and Delivery was discouraging to say the very least. It was one large room, subdivided into ten sections, each with six cots. A thin plastic sheet separated cots from one another and I was alarmed to discover the sheets were rarely drawn for privacy. The beds were rickety, rusted, and covered with a thin plastic mat. The few mats without women on them were still soiled from the last delivery, and not until my third day did I see one cleaned. The ward was busy with nursing students performing the majority of deliveries and supervised by midwives for complicated cases.

A scene that plays vividly over and over in my head since it happened was the first delivery I saw at Pumwani. I imagine the teenage girl felt like a caged animal as myself and the crowd of nursing students watched her struggle. She squirmed in her attempts to bear down while her feet slipped on the fluids and splashed onto the floor and all over close bystanders. The midwife made a cutting motion to her assistant to signal that the woman needed an episiotomy. This was the first time I had ever seen one performed and I struggled to stifle a gasp at the thought this would be done without any anesthesia. The moaning visceral pain of her contraction quickly transformed to a shrill sharp pain of the incision. I could almost feel her suffering and goose bumps suddenly arose all over my body. The baby's head quickly appeared, followed shortly by his body. He was blue, silent, and immobile. After a minute of oxygen (that felt like hours to me as I held my breath) he made his first little mewing cry. He was immediately taken to the Neonatal Unit, and his mother left the ward within thirty minutes of being sutured. All of this happened without the mother being informed of her baby's condition.

After this first observed delivery, I decided to take a more active role on the ward to avoid the helplessness and despair I felt that first day. Throughout the week, I was taught how to examine the dilation of the cervix, listen to the fetal heart rate with an ancient fetalscope, perform Leopold's maneuvers, and the technique of how to deliver baby and placenta. These skills were taught by nursing students younger than myself and yet infinitely more experienced. Pumwani has babies being born every couple of minutes and a severe shortage of midwives; hence I was often the first attendant to a delivery. With the knowledge

I gained from the nursing students, I felt a glimmer of hope and inspiration that I could play a small part in helping these women through their deliveries.

There were many issues I encountered at Pumwani that I had never heard of as major problems in Ottawa. The issue of understaffed and overworked midwives was a significant one. They were stretched far beyond their abilities, which often led to neglect of women in labour. Alarmingly, the mothers would sometimes deliver unassisted with the baby landing face-first into pooling bodily fluids on the mat and increasing their risks of sepsis. Moreover, issues of broken cots, torn mats, too few fetalscopes, thin sterile gloves (with double-gloving as common practice), and broken surgical equipment were constant problems in the ward.

My elective experience in Nairobi has been life-changing by inspiring me to pursue a specialty that will allow me to focus on international women's health. I was exposed to maternal care in a third world country and was able to witness the significant differences between Kenya and Canada. At first, I was overwhelmed with shock and despair by the conditions the women of Pumwani experienced as they gave birth and could feel only helplessness as I watched them struggle. As the week progressed and I learned more about obstetrics from the nursing students, I felt increasingly more inspired to work towards improving those conditions for birthing women and I still carry that inspiration with me today. The challenges surrounding maternal health I was exposed to in Nairobi will stay with me for future international women's health endeavors.

Striking a balance: *The medical student-athlete*

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INTRODUCTION

I'm a medical student-athlete. I've been training and competing for the past six and a half years in track and field, with most of those years dedicated to the long jump. Doing so has profoundly shaped me as a person (both literally and figuratively). It was suggested to me to write about my experience as a varsity athlete in medical school. My goals are to inform, promote and motivate fellow medical trainees and professionals to the seemingly incomprehensible world of pushing yourself to the extreme in both athletics and academics.

It has all been drilled in our minds that a healthy lifestyle keeps the doctor away, but this in reality can go the other way as a medical trainee (medical trainees keep the healthy lifestyle away). As future healthcare professionals, we are taught to sell the benefits of a holistic and healthy lifestyle and yet we don't necessarily lead one ourselves. I would hope that this piece helps other students and medical professionals lead a happier and healthier life by revealing both the pros and the cons of training and competing as a medical student. The topics of time management, lifestyle and stress during my ongoing medical education, will be covered.

TIME MANAGEMENT

It might (not) surprise you that the ever-present limiting factor to pursue both my athletic and academic goals, is time. To give a rough estimate of the workload, a typical week of training out of season consists of six two-hour gruelling sessions a week, while in season, four three-hour sessions plus a competition on the weekend is typical. Add in travel times and classes and there is only a limited amount of time left in the day. This is where the art of time-management comes into play. In reality, the timely organization of the sequence of training, competitions and academia for the weeks ahead is not an easy feat. It has to include optimal sleep (probably the single most difficult one to achieve), studying while taking into account how brain-dead I'll be after a particularly demanding workout, and how to make a workout fit in a day that just doesn't have enough hours. It's an ongoing mental puzzle that (hopefully) has a solution to it. The consequence of this is that there is a sort of weekly planner that gets chiselled into your mind from constantly thinking of how to fit all the pieces in. Although this might sound painful, it's a godsend for an even busier life to come in clerkship and residency.

LIFESTYLE

One thing I pride myself on is the lifestyle of a competitive athlete. Although a healthy lifestyle knows its benefits, I find that even those who prescribe it can have problems adhering to such intensive resolutions. For many, the knowledge of the health effects of exercise is not enough to motivate themselves to fit it into their daily routine. In my case, by training and competing in something I am passionate about, I have more reasons to lead a healthy lifestyle. Everything from nutrition, sleep hygiene, exercise, alcohol and drug abstinence and stress relief are ideal for optimal track and field performance. Having seen firsthand the benefits that come from simple and healthy everyday decisions, I'm a firm believer that every healthcare professional

should put a colossal emphasis on this aspect, since there is no drug in existence that can replicate its positive effects on so many aspects.

Even given difficult circumstances, such as the busy life of being a medical student and athlete, it is possible to adhere to a healthy lifestyle plan. I know many people may read this and think that they are way too busy to incorporate physical exercise as a priority in their lives, but in reality, you really don't need to buy an expensive gym membership to get active. The single biggest step is to turn off the television, stop refreshing Facebook and stop playing StarCraft so much and swap a bit of that down time with any physical activity you enjoy doing. Having resorted to many workouts in parks, gravel tracks, play structures and by other silly means, I know there are ways to make things work if the motivation is there.

If you dislike reading long texts without pictures as much as I do, perhaps Figure 1 will help you from falling asleep.

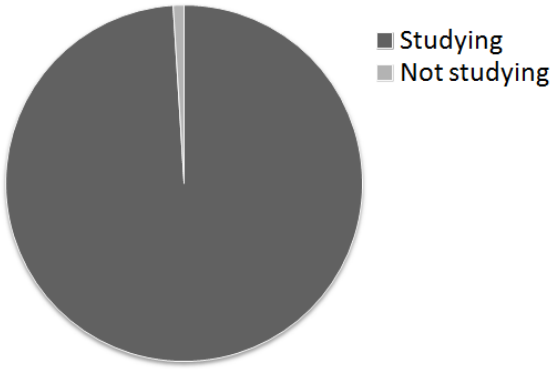

Figure 1. Society's common perception of the proportion of time spent studying while in medical school.

STRESS

The constant struggle to be at my best, both mentally and physically, comes with some frustrations though when academic activities and training sessions conflict. One thing I am often asked about is how I handle stress in my situation. Being able to train and compete in a sport I love doing has unquestionably helped me relax and has even allowed me to develop skills to excel academically. As the years pass by, I have found that I have managed to manipulate stress to become a study and performance aid rather than a hindrance to success. I quickly realized in my athletic career that a stressful situation, such as a championship, helped me excel and achieve seasonal or personal best performances. Applying this concept to my academics, studying under pressure has lost its negative connotation and has been rebranded as efficient and focused studying. This may be more philosophical than anything, but I find it futile to worry about future events that will inevitably happen regardless of whether or not I worry, knowing the adverse consequences of chronic stress. Therefore, unless the stress helps me change the outcome of that event to a better one, I try to keep it under control. I think that as a medical trainee, being placed under demanding and stressful conditions, this control becomes an asset. I like to think that this will also translate into enhanced performance under difficult conditions in the operating room as a surgeon.

CONCLUSION

If there's any message scribbled between the lines of this paper I am trying to write right now at 8:08 pm this Friday evening instead of being outside playing in the snow, it is the following: don't stop doing what you love doing, what makes you happy and what keeps you healthy when you pursue your career in medicine.

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