ANNUAL 2019-2020 ISSUE

25

years of

MCGILL JOURNAL OF MEDICINE

Special Issue: Women In Medicine by McGill Feminism in Medicine

FEATURING

Dr. Jonathan Lim

Founder of MJM

Dr. Theresa Tam

Chief Public Health Officer of Canada

VOLUME 18, ISSUE NO. 1, OCTOBER 2020

McGill
Journal of Medicine

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**Manuscripts published between August 2019 and August 2020 have been included in this issue. All manuscripts are internally peer-reviewed and, additionally, Original Research articles are externally peer-reviewed by faculty. Informed consent practices and any conflicts of interest are specified in the articles if applicable.*

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Letter from the Editors
The McGill Journal of Medicine Marks 25 Years in Print: Our Past, Our Present, and Our Future

It is with great pleasure that we write to you as The McGill Journal of Medicine marks its 25th year in operation. The journal has catalogued a quarter-century of student thought, work, and success. However, the first student-run medical journal at McGill University – The McGill Medical Journal – predated our current one, running for a half-century from 1931 – 1981. The medical student body at McGill University has been engaged in communicating scientific progress to the student, medical, and lay public for a total of 75 years. With this celebratory issue, we honor the hard work and dedication of generations of students and alumni whose shoulders we stand on today, and whose names decorate the cover of this volume.

Our Past

In our 2004 issue, Editors-in-Chief Kathy Han and Christopher Labos paid homage to The McGill Medical Journal. (1) It was founded by Clement Gray, James Gray, and Colin MacLeod in 1931, making it among the oldest student-run medical journals in the world along with the University of Toronto Medical Journal (founded in 1923). Clement, James, and Colin would go on to graduate with the Class of 1932 the subsequent year.

Colin MacLeod himself is likely to have been among McGill Medicine's most historically influential alumni. He published a seminal paper in the Journal of Experimental Medicine in 1944 that was the first to propose that DNA (not protein) was the material responsible for inheritance along with co-authors Oswald Avery and Maclyn McCarty. (2) In Nature volume 421, which celebrated the 50th anniversary of Watson and Crick's discovery of the DNA double helix, a Nature editor opined "…the fact that McCarty, Avery and MacLeod were not awarded the Nobel prize is an oversight that, to this day, still puzzles." (3) As for James and Clement Gray, we were unable to determine what became of them after they left The McGill Medical Journal and McGill.

Jonathan Lim founded The McGill Journal of Medicine in 1994, 13 years after the original journal had shut down in 1981, and the following year its first issue was released. (4) Lim elaborated on the founding of our editorial board and the realization of the journal as: "an international forum for the advancement of medical science by students." The journal's mandate was, "to provide student authors with opportunities to voice their contributions to medicine." This objective remains core to the journal's mission today. In this issue, Jonathan Lim has contributed the Letter from our Founder celebrating our 25th anniversary in operation.

The journal was widely recognized shortly after it was re-established, receiving letters of support from the likes of David Hubel (Nobel Laureate), (5) Jean Chrétien (Former Prime Minister of Canada), (6) Peter McL. Black (Harvard Professor of Neurosurgery), (7) and John van de Leuv (American College of Emergency Physicians), (8) in addition to favourable reviews by John Last (Editor, Annals RCPSC), (9) Robert Schwartz (NEJM), (10) Gale Starich and Joan Zenan (JAMA). (11) In the latter review, Starich and Zenan wrote, "MJM may prove to be an important forum for those who will be the leaders in medical science during the 21st century." Certainly, many of our past student contributors have

gone on to make significant contributions to medical science throughout their careers. In Where are they now? we explore the careers and past publications of three of our alumni, Jonathan Lim, Caralee Caplan-Shaw, and Neil Goldenberg.

Our Present

Today, The McGill Journal of Medicine has been reimagined as an open-access, peer-reviewed medical journal that exists primarily online at our website (mjm.mcgill.ca). While the original publication was structured as a two-issue periodical, we now publish on a rolling basis as our online presence allows us to be increasingly flexible for authors. In keeping with its original mandate, the work of running the journal is mediated entirely by medical and graduate students. Original articles are peer-reviewed by third-party scientists, and all material submitted to the journal is copy-edited by members of our editorial board. Without these hard-working individuals, the journal could not continue to exist.

Our hardworking staff have had a historic year. Building on the success of previous Editors-in-Chief Milani Sivapragasam and Nicholas DiStasio, we have contributed to disseminating more than 20 original written works, not to mention publishing conference abstracts from graduate departments at McGill and refreshing a number of article categories for our upcoming volume. We are looking forward to continuing that momentum into 2021 with increasing contributions from across the Faculty of Medicine and Health Science's six founding schools – Medicine and Dentistry, Nursing, Physical and Occupational Therapy, Communication Sciences and Disorders, Population and Global Health, and of course, the Biomedical Sciences.

The reality that the journal has now been in operation for 25 years is astounding and speaks to the importance of our mandate. Certainly, we editors have greatly enjoyed the privilege of providing a supportive platform from which our student body may launch its research and impart its views. If nothing else, this year's body of work is a window into the aspirations of a group that is fully engaged in the labour of progress. It will be of no surprise to see our contributors achieve much of it across their various disciplines in the years ahead.

In light of reaching the 25-year mile marker, we at the journal have also been thinking about our own progress. We are recognisant of the fact that a powerful social undercurrent is currently in the process of changing the very fabric of our society. We see this as an opportunity to re-evaluate the importance of voices that promote the thoughts and attitudes of McGill's medical student body. We know that the diversity of opinions, essays, and ideas that move us to institute positive change will be just as important in the future as the medical discoveries we are making today. McGill students will inherit many positions of influence as the torch is passed down to our generation, and our thoughts on how the social issues of our time impact both medicine and science deserve a legitimate and public platform.

Our alliances with the Post Graduate Student Society and the diverse graduate departments at McGill allow us to take advantage of the significant depth of expertise across the humanities. Therefore, we have created a separate editorial workflow for medical humanities articles submitted to the journal, and we have staffed it with individuals having expertise and interests aligned with our goal of moving into the medical humanities. It is our sincere hope that this structural change within the journal will allow us to grow into a platform that students can use to explore the myriad ways in which society and medicine are evolving together. Furthermore, we hope that it will increase our organizational ties with eminent thinkers from humanities disciplines across the university.

Our Future

The world of medical publishing is not the same today as it was when the journal was re-established in 1995.Then, online databases and search engines had only just taken their first steps toward becoming the superlative mechanism

for organizing the world's information. In the age of Google, it hardly even seems possible that a small print media outlet, one like the journal in 1995, could exist for longer than 25 days, let alone 25 years. Certainly, the open-access, online journal we have today is the result of a selective pressure that has now forced nearly every industry online. In our opinion, we must continue to adapt in order to ensure the journal's ongoing success.

What can we do to make sure The MJM thrives for the next 25 years, and how can we better serve McGill University's medical and graduate students? We believe both the journal and the students of McGill University would be best served by a high quality, student-run, open-access, peer-reviewed medical journal that has the ability to attract serious readers and contributors globally. Our founder wrote in the journal's inaugural issue that, "scientific inquiry lies at the heart of medical progress," and that belief continues to be a pillar of our organization today.

However, that goal can only be accomplished if the journal is indexed with popular medical journal databases such as MedLine and Pubmed. Although the original version of the journal was indexed with early versions of these databases, we have long since been outpaced by larger, more profitable organizations. Indexing will require meeting the challenge of modernizing our handling of publication data, our website, and reimagining our scope such that it aligns with the requirements of modern databases. In the meantime, we are happy to report that we have modernized our metadata handling such that our authors are listed and searchable on Google Scholar. Our indexing project will be the greatest challenge that the journal has yet faced as an organization, and one that our team is continually working toward.

Final Remarks

We are looking forward to a number of exciting opportunities and projects in the coming year that will strengthen our position in both scientific and humanities publishing. As the three of us officially announce another year leading the journal, we remind you that we will continue to collaborate to expand the journal's influence at McGill, while advocating on behalf of students both at McGill and elsewhere. We are incredibly proud of the work done by our team and we urge you to read their names on the masthead at the beginning of this issue. Without them, the MJM would not continue to exist, nor would it continue to thrive. They are the heart and soul of this operation.

Beyond that, we would like to express our sincere thanks to the Dean of Medicine Dr. David Eidelman, and our Board of Directors including faculty representatives from McGill University's Faculty of Medicine, Post-Graduate Student's Society, and Office of Communications, including Dr. Terry Hebert, Dr. David Ragsdale, Dr. Alina Diaconescu, Diana Colby, and Jason Clement. Their support means that we can continue to provide this unique platform for providing early career development opportunities for students. Furthermore, we thank Dr. Jonathan Lim, Dr. Caralee Caplan-Shaw, and Dr. Neil Goldenberg for their formative contributions to the journal as well as their help in producing this issue.

With that, we are tremendously excited to present this issue to you, 25 years in the making.

Sincerely,

Mack Michell Robinson, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD/PhD Candidate, 2025

Etienne Leveille
Co-Editor-in-Chief, McGill Journal of Medicine
MDCM Candidate, 2021

Jack Lam, MSc.
Managing Editor, McGill Journal of Medicine
MDCM Candidate, 2021

References

1. Han K, Labos C. Historical Footprints: MJM Past and Present. The McGill Journal of Medicine. 2004;7(2):126-7.
2. Avery OT, Macleod CM, McCarty M. Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III. The Journal of experimental medicine. 1944;79(2):137-58.
3. McCarty M. Discovering genes are made of DNA. Nature. 2003;421(6921):406.
4. Lim J. From Notion to Reality: The Creation of a New Student Medical Journal. The McGill Journal of Medicine. 1995;1(1):1-2.
5. Hubel DH. Congratulations to the MJM. The McGill Journal of Medicine. 1995;1(1):3.
6. Fuks AS, Nadine, McDonagh PD, Scot. The McGill Journal of Medicine: Student Driven. McGill in Focus: Medicine Edition. 2003:8.
7. McL. Black P. Commentary on MJM Focus (Vol. 1, No. 2): Surgery for Temporal Lobe Epilepsy. The McGill Journal of Medicine. 1996;2(1):3.
8. van de Leuv JH. A Friendly Word from the Editor of The McGill Medical Journal (1956/1957). The McGill Journal of Medicine. 1998;4(3):3.
9. Last J. Journal Review of the MJM. Annals of the Royal College of Physicians and Surgeons of Canada. 1996;29(7):424-5.
10. Schwartz RS. McGill Journal of Medicine (MJM): An international forum for the advancement of medical science by students. New England Journal of Medicine. 1997;336(12):885-6.
11. Starich GH, Zenan JS. The McGill Journal of Medicine (MJM). JAMA. 1997;278(17):1461-2.

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Special Letter from the Founder
From Reality to Legacy: Quarter Century Perspective after Founding the MJM

I feel a mixture of pride, surprise, and delight that the MJM is not just alive and kicking, but thriving after all these years since I founded the journal 25 years ago. This 25th anniversary edition provides a surreal opportunity to reflect on the formative role the MJM played in impacting my own career path in medicine and beyond.

As MJM's Editor-in-Chief from 1994 to 1995, I enjoyed reviewing content, copy-editing, and publishing the journal. But the aspects I was truly passionate about were formulating the vision and plan, building and rallying the team around a common purpose, raising the resources, and pulling it all together to achieve the launch of a high quality product in timely fashion. As a first-year medical student, I did not know what this "process" was at the time. What I did know was that whatever I decided to do in the future, I wanted it to play some role in my future profession.

After graduating from the McGill Faculty of Medicine, I went straight into general surgery residency training at the New York Hospital-Cornell Medical Center and Memorial Sloan Kettering Cancer Center. After my second year of residency, I conducted cancer research and attended graduate school at Harvard. This was where I learned that the process I found so energizing from launching the MJM was called "entrepreneurship." This newfound realization that I was an entrepreneur at heart, seeded by my earlier experience at MJM, sparked a series of events that helped launch my career as a biotechnology serial entrepreneur and investor. During the past two decades, I have had the privilege of serving as CEO of four companies that have collectively delivered seven approved therapeutic products for adult and pediatric indications in oncology, immunology, and drug delivery, benefitting thousands of patients globally.

The latest evolution of my profession is as a "venturepreneur," in which I seek to found, fund, and lead mission-driven for-profit and non-profit ventures dedicated to revitalizing people, planet, and perspective at City Hill and ARCH Venture. Looking back, I am immensely grateful for how my McGill medical education and MJM experience played pivotal roles in my early professional formation and subsequently led to such a fulfilling career journey.

I would like to take this opportunity to recognize, congratulate, and thank the successive generations of medical and science students at McGill who have helped build the MJM into what it is today – "an international, peer-reviewed publication…particularly sympathetic to contributions from students who are just beginning their careers in the medical and scientific fields."

As someone who was just beginning my career in the medical and scientific fields at the time, I can verify that the MJM's mission was accomplished in terms of impacting my own professional choices and trajectory. Achievement of this quarter century milestone reflects the diligent team effort of thousands of students over the years, bolstered by the strong support of faculty members, to establish such a solid foundation for the journal. As the MJM continues to build upon this impressive legacy, I sincerely hope that future generations of students entering the medical and scientific fields will be similarly impacted, and that society will be all the better for it.

Happy 25th anniversary, MJM!

Jonathan E. Lim, MSc, M.D., C.M. (1997)
Founding Editor
McGill Journal of Medicine

MCGILL JOURNAL OF MEDICINE

MJM

WHERE ARE THEY NOW?

The MJM has been built by student contributors over the last 25 years and continues to succeed because it offers students a steppingstone to careers in research and medicine. In this section, we have republished two original articles from the inaugural 1995 volume and included a commentary that highlights the incredible career paths of their authors. If anything, The Journal has produced incredible alumni, and the Class of 1995 is no exception: Jonathan Lim – now a successful biotechnology venturepreneur, Caralee Caplan-Shaw – a physician scientist at the forefront of pulmonary critical care, and Neil Goldenberg – a world leading pediatric thromboembolism expert. Read the commentaries at the beginning of each of their articles to find out: where are they now?

ARCHIVES

McGill Journal of Medicine

From Notion to Reality: The Creation of a New Student Medical Journal

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Publication Year
1995

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McGill Journal of Medicine

www.mjmmed.com

DR. JONATHAN LIM is a physician-turned-venturepreneur at City Hill and ARCH Venture who founds, funds and leads mission-driven for-profit and non-profit ventures dedicated to revitalizing people, planet and perspective. Dr. Lim serves as Chairman, CEO and Co-Founder of Erasca; Chairman and Co-Founder of Boundless Bio; and Board Director of Maze Therapeutics. He is an advisor to non-profit organizations such as Stanford, UC San Diego, Scripps Research and UrbanLife. From 2003 to 2018, Dr. Lim was a leader and founding investor of four biotech companies that have collectively delivered seven approved therapeutic products for adult and pediatric indications in oncology, immunology and drug delivery, benefitting thousands of patients globally. This article was originally published in the first issue of The McGill Journal of Medicine about the journal's inception at McGill University.

1 | THE NOTION

It began simply as an idea with promise. While searching for a project to pursue during the summer after my first year of medical school at McGill University, I was impressed by the wealth of opportunities available to medical students interested in research. At McGill, there was also a forum called "Student Research Day," an annual scientific meeting allowing medical students to showcase their work by presenting their results to the local healthcare community. The projects presented were of high caliber, and certainly would have been of interest to a wider audience. I was struck by the thought that a medical journal presenting solely student work would have provided the means for recognizing this work on a larger scale.

Since students may already submit their work to existing professional medical periodicals for publication, is there a need for a new journal that promotes solely student contributions to medical science? My answer is an emphatic "yes." I am convinced that students can make noteworthy contributions to medical knowledge through their participation in research activities. A single publication presenting work exclusively by students would serve notice that they can make a difference in the research community.

A student journal may also encourage individuals who are relatively new to research to submit their work

for publication for the first time, a process that might serve as an important stepping stone and incentive for further research endeavors. For aspiring student authors, the rewards of seeing one's name in print are apparent, but the process of conducting research, analyzing data, and preparing a manuscript for publication are the truly enriching aspects of the experience. A new journal focusing primarily on student authorship may also provide them with increased opportunities to receive the public recognition they deserve for pursuing independent work (1). For the student editors and publications staff, there would be additional educational benefits associated with the production of the journal.

According to a study by Taylor, it was estimated that approximately 42 hours per week are required for second year medical students at the University of Southern California to complete the assigned readings (2). Keeping pace not only with the demanding workload of the medical curriculum but also with the continuously expanding literature would be a task of Herculean proportions for potential authors and editors alike.

However, scientific inquiry lies at the heart of medical progress. We students in the health sciences have a vested interest in medical research pursuits, the reductionist or microscopic approaches to solving problems in medicine. One day, the mantle of responsibility will be placed on our collective shoulders to find cures for illnesses such as AIDS, cancer, Alzheimer's, and other chronic conditions that defy straightforward treatments. As the physicians and scientists of tomorrow, we have an obligation to remain on the forefront of current research efforts.

It is equally important for us to remain active in health policy, disease prevention and control, and other macroscopic approaches to current medical problems. The environment of uncertainty surrounding universal healthcare coverage in the United States, increasing restrictions on manpower mobility in Canada, and otherimportant issues that impact the future of medicine are of vital concern to students everywhere. We cannot afford to simply learn or practice medicine in an intellectual vacuum.

A journal would facilitate discussions regarding important medical issues and nurture student participation in both micro- and macroscopic endeavors that could potentially lead to beneficial outcomes in the medical community. For these reasons, I was inspired by the idea of starting a new student medical journal. Ideas inspire people to move in surprising new directions. Without knowing it, my colleagues and I were about to enrich our medical studies by embarking on the exciting enterprise of creating a new journal from scratch.

2 | THE FOUNDATION

In May 1994, I submitted a proposal elaborating the idea of a new medical journal for students to the Deans at the McGill Faculty of Medicine. They officially approved our organization approximately two weeks later. Thus was born the McGill Journal of Medicine (MJM), a new student medical journal.

The MJM is an independent organization run entirely by students at McGill University. Since the first general meeting in which 17 people in my class attended, our editorial board has grown to include the 52 students listed in the masthead on the inside front cover of this journal. These include first- and second-year medical students in the Faculty of Medicine, first-year students pursuing M.B.A. degrees in the Faculty of Management, and undergraduate and graduate students in the Faculties of Arts and Sciences.

We students run the entire spectrum of editorial production, from evaluating and reviewing the scientific content of manuscript submissions, to copy-editing and typesetting the final papers. On the business side, we sell advertising space and subscriptions, seek financial support in the form of donations and grants, market the journal to expand the readership and sponsorship base, solicit manuscripts, and distribute final copies of the journal to medical libraries, institutions, and individual subscribers. All of these phases of production have provided our staff with an incredible learning experience regarding the mechanisms of journal production.

As a resolute editorial board, we presented the concept of a medical journal for students to individuals and

organizations in the McGill and local communities. The McGill Computer Store, the first financial Founder of the McGill Journal of Medicine, donated a complete package of computer hardware and software sufficient for our graphics, design, and layout needs. Our other financial Founder, the Bank of Nova Scotia, along with the other companies, organizations, and individuals recognized in the Acknowledgements section of this journal, collectively contributed nearly $30,000 towards the successful establishment of the MJM.

The realization of a project of this magnitude less than one year after its inception reflects how responsive people have been to the mere idea of this publication. The students who have submitted articles for publication and have participated in the production of the journal, the faculty members who have volunteered their time to serve as referees for manuscript submissions, and the numerous individuals and organizations in the McGill and local communities who have made material and monetary donations all have contributed solely on the basis of an idea with promise. We had nothing tangible to offer them, just an idealistic concept; but this was enough to convince each and every one of them that their support for the MJM would be worthwhile. We are grateful for their generosity and faith in the idea which made the publication of this premiere issue a reality.

3 | THE REALITY

The McGill Journal of Medicine is an international forum for the advancement of medical science by students. Our objective is to provide student authors with opportunities to voice their contributions to medicine in one scholarly, biannual publication. Towards this end, we intend to publish original research and review articles relevant to the field of medicine. Our authors will represent undergraduates in bachelor's degree programs, and graduate students in master's, doctoral, or healthcare degree programs (medicine, dentistry, nursing, physical and occupational therapy, etc.).

Our intended readership will include physicians, scientists, residents, and university students in the health sciences around the world. However, among other medical scientific publications, the MJM has a unique and well-defined niche because it provides readers with a compendium of medical research accomplished exclusively by students, a feature that undoubtedly fills a void in the current arena of scientific publications.

The MJM intends to play a prominent role in recognizing and disseminating the efforts of students at institutions around the world who are making important contributions to medical science. We are grateful to the students across North America who took the initiative to submit their work for consideration in this premiere issue. The content of the final manuscripts accepted for publication reflects the broad scope of the MJM, ranging from original research articles related to clinical medicine, to articles that explore specific issues in basic science. We encourage the submission of review articles and letters because they promote the discussion of relevant issues in medicine. For the premiere issue, we are honored to have received a letter of support from one of our distinguished alumni of the McGill Faculty of Medicine, Dr. David Hubel, who received the Nobel Prize in Medicine in 1981.

There are two other features of the MJM that enhance its content. "Crossroads," a section of the journal highlighting the interplay between medicine and the humanities, presents articles that relate medicine to fields such as ethics, history, philosophy, and health policy. The other section, "MJM Focus," explores the scientific, clinical, and pathological features of a medical specialty of interest. In this issue, we focus on the medical subspecialty of "Allergy and Immunology" by presenting an invited basic science review (BSR) article written by a member of the McGill faculty, and a clinicopathological correlation (CPC) written by a resident at the Montreal General Hospital. The rationale behind this presentation is that the BSR hopefully will give readers a review of the background information necessary to understand the scientific principles underlying the clinical and pathological features of the condition described in the CPC. These sections are particularly relevant for a student audience, but will be interesting features for our readers who are established health science profession-

als. We intend to explore other medical specialties of interest in future issues of the journal, and may include profiles of the medical specialties that encounter and treat patients with similar cases to the ones presented in the CPCs.

4 | THE FUTURE

It is my pleasure to present to you, on behalf of the editorial board, this premiere issue of the McGill Journal of Medicine (MJM). We hope you will share our enthusiasm for this new publication, whether you are a student reader interested in seeing what your colleagues around the world are contributing to medical science, or are an established physician, scientist, or other practicing member of the health sciences community interested in seeing what kind of work is being accomplished by the young physicians and scientists of tomorrow. Some of our future initiatives will be submitting the MJM for indexing in reference indices, producing the journal in electronic format, and adding to the "MJM Focus" the profiles of relevant medical specialties and the residency programs that offer them.

We invite all potential authors to submit manuscripts of original, review, or Crossroads articles, and encourage readers to voice any thoughts concerning current medical issues of interest. Please keep usinformed of our progress with your feedback - this is, after all, your forum. With your continuing support and participation, our editorial board is committed to producing a quality publication. This journal began simply as an idea with promise. It is now the reality you hold in your hands.

REFERENCES

1. Ward B. Undue Credit for Supervisors [letter]. Nature 1994;368:579.

2. Taylor CR. Great Expectations: The reading habits of year II medical students. New England Journal of Medicine 1992;326:1436-1440.

ARCHIVES

McGill Journal of Medicine

The Childbed Fever Mystery and the Meaning of Medical Journalism

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Publication Year
1995

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McGill Journal of Medicine

www.mjmmed.com

DR. CARALEE CAPLAN SHAW was a regular contributor to the journal during her tenure with McGill's undergraduate medicine program from 1994-1998. After graduating from McGill, she spent a year as the inaugural editorial fellow at the Canadian Medical Association Journal and then completed her residency in internal medicine and fellowship in pulmonary and critical care medicine at Columbia University's New York-Presbyterian Hospital. She spent the next 2 years caring for patients with tuberculosis in the busy clinics of the Miami-Dade County Health Department. In 2007, she joined the faculty of the Division of Pulmonary, Critical Care and Sleep Medicine at NYU as a pulmonologist at Bellevue, the oldest public hospital in the United States. There, she began treating patients in the World Trade Center Environmental Health Center, an integrated medical and mental health program for community survivors of the September 11th attack. Her research on the long-term respiratory effects of this unprecedented environmental disaster informs clinical management of this unique population. In recent years, as director of the storied Bellevue Chest Service and the Bellevue Hospital Tuberculosis Program, her mission is to provide the best evidence-based, patient-centered care to these vulnerable patients and work toward eradicating TB through creative use of technology, education, and preventive treatment.

On the occasion of the first publication of the McGill Journal of Medicine, it seems particularly appropriate to look back into the medical past, into the early days of medical theory and practice, and into the texts that gave birth to the modern medical journal as we know it. Although the development of modern Western medicine is most often believed to have begun with Hippocrates ca. 400 B.C., Egyptian scribes compiled papyri filled with practical remedies at least 900 years earlier. Throughout most of medical history, however, medical writing remained something less than methodical, describing illnesses, procedures, and "cures" according to the dic-

tates of medical experience, with little concern for carefully designed controls and conclusive statistical analysis. But in the 19th century, a Hungarian trainee in a Viennese hospital produced a piece of medical writing that, in many ways, might be read as a harbinger of the modern medical journal. Although not the first of its kind, Ignaz Semmelweis's The Etiology, Concept and Prophylaxis of Childbed Fever is an inspiring piece of medical research and writing, a celebration of intellectual discovery and the dissemination of medical knowledge for the public good.

In his work at the maternity hospital, Semmelweis noted the high death rate of women during childbirth. Historians report that Semmelweis's research into the causes of childbed fever was sparked by his hearing "the too-frequent ringing of a little bell as the priest came to give last rites to a dying mother." (1) Semmelweis noticed further that the rate of death was higher among women who actually delivered in the hospital than among those who had given birth at home with the help of a midwife or en route to the hospital. The finding seemed paradoxical, because women who gave birth outside the hospital were often met with inconveniences and dangers unknown to the patients of the maternity clinic:

> *being delivered by a midwife, then immediately having to arise, walk down many flights of stairs to the waiting carriage, travel in all weather conditions and over horribly rough pavement to the maternity hospital, and there having to climb up another flight of stairs. For those who really gave birth on the street, the conditions would have been even more difficult. (2)*

Furthermore, Semmelweis observed that women who delivered prematurely also became ill less frequently. Similarly, no pattern or cause could be established from the positions of the women's beds in the clinic: sometimes one diseased individual would be surrounded by healthy patients; at other times, an entire row of patients would become ill. Nor could the disease be attributed to chilling when all the women along the north wall became ill, since the illness occurred just as often along the south wall and often spread to other sides ofthe room.

Combining faithful observation with thoughtful analysis, Semmelweis provides even the modern reader with a dazzling example of the scientific method at work. After having culled his information, he asks himself certain crucial questions:

> *What protected those who delivered outside the clinic from these destructive unknown endemic influences,*

if they were indeed endemic, and

> *How could these events be explained, given that the same patterns did not appear in the second clinic where one encountered the disease only sporadically? (3)*

These questions became Semmelweis's springboards for further research and observation. Additional studies revealed that women who delivered prematurely or on the street virtually never became ill: based on this observation, Semmelweis was able to rule out endemic causes. With the knowledge that deaths by childbed fever occurred less frequently at a second clinic, Semmelweis determined to discontinue deliveries from the supine position in favor of the lateral at his clinic, "so that everything would be exactly as in the second clinic." (4) Firmly within the tradition of modern scientific analysis and writing, Semmelweis establishes a controlled environment within which to conduct his research.

Semmelweis's text extends, however, beyond the limits of pure science to provide a window into the sociohistorical context relevant to the study. He begins, therefore, by revealing an important social policy affecting child-bearing practices of the time: when women arrived at the maternity hospital after having given birth in the street, admission to the clinic and the foundling home were provided free of charge. Alluding to an im-

portant sociological problem, Semmelweis explains that women often claimed, falsely, that the birth of their children had occurred unexpectedly on the way to the hospital in order to receive free care. Thus, Semmelweis draws the important distinction between the two types of "street births", births that actually occurred in the street, often under unfavorable conditions, and those that occurred, safely and hygienically, in the home. Both groups of mothers showed a lower death rate than those who delivered in the hospital, suggesting that the illness was somehow linked to the hospital itself. Thus, Semmelweis's awareness of social circumstances was instrumental to his eventual unraveling of the childbed-fever mystery.

More significant even than the awareness of social issues, however, was a different and more general kind of awareness. Frustrated by his inability to find the cause of the high occurrence of childbed fever in the clinic, and saddened by the loss of so many mothers, Semmelweis writes,

> *Everything was in question; everything seemed inexplicable; everything was doubtful. Only the large number of deaths was an unquestionable reality. (5)*

Thus, on March 2, 1847, Semmelweis departed for Venice with the hope that "the Venetian art treasures would revive [his] mind and spirits." (6) Knowing that he, in his depressed state, would be useless to both his research and his patients, Semmelweis maintained the balance and moderation recommended by Hippocrates and followed Hippocrates's early admonition that "the physician should be instructed in all subjects" (7), including the arts. The wisdom of Semmelweis's decision is then borne out by the "rejuvenated vigor" (8) with which he returns to his work and the rapid conclusion of the childbed fever story later in March.

With eyes and ears open to any new clues, Semmelweis soon discovered that Kolletschka, Professor of Forensic Medicine, had been pricked with a knife used during an autopsy. The professor contracted lymphangitis and phlebitis in the upper extremity, developed a metastasis in one eye, and eventually died of bilateral pleurisy, pericarditis, peritonitis, and meningitis. Semmelweis describes his unexpected discovery asa kind of revelation:

> *I could see clearly that the disease from which Kolletschka died was identical to that from which so many hundred maternity patients had also died. (9)*

Autopsies confirmed Semmelweis's suspicion that the women and their newborns had died of the same disease that had killed the professor. Further analysis revealed that introduction of cadaverous particles into the vascular system had caused Kolletschka's death. The Viennese medical school's emphasis on anatomical study encouraged exploration of cadavers by professors and students: apparently, soap and water were not sufficient to remove the cadaverous particles from the hands of these individuals, resulting in the infection of those women with whom they came into contact during examination and delivery.

But Semmelweis's work does not end here. Upon discovery of the cause of the deaths, Semmelweis immediately replaced the soap-and-water wash with chlorina liquida, which destroyed the cadaverous particles adhering to the hands of the doctors. Soon, in an attempt to keep medical costs down, Semmelweis helped to establish a less expensive but highly effective chlorinated lime as the new standard. Semmelweis reports the favorable quantitative effects of the new protocol:

> *In May 1847, during the second half of which chlorine washings were first introduced, 36 patients died–this was 12.24 percent of 294 deliveries. In the remaining seven months of 1847, the mortality rate was below that of the patients in the second clinic. (10)*

Semmelweis continued, throughout his life, to crusade against the careless actions of European obstetricians.

Thus, Semmelweis's illuminating text contains all the essential features–data, discussion, and conclusion–of modern medical journal writing, if in a less structured and scientifically precise form. But its narrative structure and personal reflections remind us of that which modern medical journal writing rarely does: that scientific inquiry is a passionate struggle no less inspiring than the arts of Venice; that scientific truth is inextricably bound up with social and economic truth; and that medical research, particularly in this age of rapidly proliferating ethical dilemmas, can still strive for the physical health and social good of real and suffering people. Hence, Semmelweis's obscure Etiology, Concept and Prophylaxis of Childbed Fever is more than a tiny piece in the puzzle of medical history: it is a reminder of what medical journalism has been, what it has become, and what it ought not to lose.

REFERENCES

Selections from Semmelweis and Hippocrates in Medicine: A Treasury of Art and Literature, ed. Ann G. Carmichael and Richard M. Ratzan (New York: Hugh Lauter Levin Associates, Inc., 1991).

1. Semmelweis, Ignaz, The Etiology, Concept and Prophylaxis of Childbed Fever, trans. K. Codell Carter (reprinted by permission of University of Wisconsin Press, 1983) in Medicine: A Treasury of Art and Literature 136.

2-3. Ibid. 145.

4-6. Ibid. 146.

7. Anonymous, "Admonitions of Hippocrates," trans. in Loren C. MacKinney Bulletin of the History of Medicine, 26 (1952): 20-21 (reprinted by permission of Johns Hopkins University Press) in Medicine: A Treasury of Art and Literature 54.

8-9. Semmelweis 146.

10. Ibid. 147.

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Elucidating Angiogenesis: The Role of Basement Membrane Proteolysis and Endothelial Cell Motility and Proliferation

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INTRODUCTION

The process of blood vessel neoformation from pre-existing microvasculature, known as angiogenesis, has in recent years become the focus of intense interest in diverse fields of basic scientific and clinical research. De novo blood vessel growth appears to play a vital role in early development, as well as in various physiological and pathological settings. Like vasculogenesis (the development of vascular structures from mesenchymal tissue), angiogenesis is a fundamental feature of embryonic development and organogenesis, as circulatory

branching is essential in sustaining newly developing structures and tissues. In the adult, angiogenesis is physiologically significant in its association with inflammation, wound healing, and placental formation. The redness associated with the "wheal and flare" inflammatory reaction is caused by capillary dilation (1) and neogenesis (2) at the site of tissue damage. Similarly, in a healing wound, new blood vessels arise in the developing replacement tissues as well as in the granulation tissue near necrotic regions (3). In pregnancy, organogenesis occurs with the formation of the placenta. The developing placenta requires dense capillary perfusion, which is met by rapid angiogenesis.

Angiogenesis also plays a primary role in several diseases. In addition to tumor growth and metastasis, aberrant regulation of angiogenesis is implicated in rheumatoid arthritis, in which an autoimmune inflammatory reaction directs capillary neogenesis in the joints. These capillaries may invade and destroy cartilage (4,5). Likewise, chronic inflammation is characterized by protracted angiogenesis, presumably due to continual induction of de novo vessel formation (2). In diabetic retinopathy, neovascular proliferation and macular edema lead to blindness (6). Finally, as de novo capillary production is thought to be the crucial event in tumor growth and metastasis (3), it is hoped that research into the cellular and molecular mechanisms underlying angiogenesis will yield effective cancer therapies through the inhibition and/or disruption of tumor vascularization.

Angiogenesis is both critical to, and significantly parallels, tumor metastasis. In metastasis, neoplastic cells detach from the primary tumor mass and degrade the basement membrane of an adjacent vessel prior to traveling through the vascular system. They may then extravasate at a subsequent capillary bed, invade and adhere to a secondary tissue site, and proliferate to form a new tumor mass. Angiogenesis shares some of these features, as revealed by the induction of angiogenesis by tumors implanted in rabbit corneas and chickchorioallantoic membranes, as well as by early investigations involving endothelial cell cultures (7). Based on observations in these studies, Judah Folkman, the pioneer of angiogenesis research, proposed the following chronology of events in the neovascularization process (2,4): (i) local basement membrane degradation of the parent vessel by endothelial cells (commonly an existing capillary or post-capillary venule), (ii) locomotion of endothelial cells away from the parent vessel in the direction of an angiogenic stimulus, (iii) elongation and alignment of migratory endothelial cells to form a capillary sprout, (iv) endothelial cell proliferation in the parent venule and in the capillary sprout, (v) lumen formation, (vi) anastomosis of two hollow sprouts to form a capillary loop, (vii) onset of blood flow, and (viii) production of, and pericyte incorporation into, the new basement membrane.

PRINCIPAL METHODS OF INVESTIGATION

Originally, the study of the angiogenic process was greatly limited by the lack of feasible, biologically relevant in vivo and in vitro models. However, the unveiling of the fundamental features of the neovascularization process has led to the refinement of various models and assays with which to study angiogenesis. These studies have primarily addressed three central elements of the angiogenic process: endothelial cell-mediated basement membrane degradation, endothelial cell motility, and endothelial cell proliferation.

In vitro studies of basement membrane degradation commonly employ endothelial cells cultured on a substrate designed to simulate the extracellular matrix. The substrates include gels composed of collagen, fibrin, or Matrigel, a laminin-rich gel recently developed from reconstituted basement membrane proteins (8). These in vitro models of angiogenesis involve endothelial cell attachment to the extracellular matrix, proteolytic invasion of the matrix in response to exogenous angiogenic inducers, endothelial cell alignment, and formation of capillary-like tubes. Tumor cell cultures have also been used as part of in vitro assays of angiogenesis (9).

These models have also been used, often with the administration of presumed angiogenic modulatory factors, to study endothelial cell migration and proliferation. In vivo research on cell migration and proliferation has utilized the rabbit cornea and chick embryo

chorioallantoic membranes. In the first model, protein-polymer pellets implanted into the rabbit cornea serve as a sustained release system for angiogenic factors; the degree of neovascularization is subsequently quantified (4,10). Alternatively, the degree to which angiogenesis inhibitors (also called "anti-angiogenic" or "angiostatic" substances) prevent the neovascularization normally induced by a tumor implant can be determined. The vascular chorioallantoic membrane of the chick embryo provides a more rapid assay based on a similar methodology (4,11). In this system, the embryo is incubated without its shells for several days, after which time tumors or sustained-release discs are implanted into the chorioallantoic membrane. An additional in vivo system has recently been developed in which Matrigel, supplemented with heparin and fibroblast growth factor (FGF), is injected subcutaneously (12). The basement membrane proteins reconstitute a gel that is intensely vascularized within a few days, upon which the effects of angiogenic modulators can be assessed. Lastly, several tumor models can serve as in vivo assays of angiogenesis. These include tumors grown through one of several mechanisms: direct tumor transplantation into animals (4), subcutaneous injection of human tumor cell suspensions into athymic mice (13), and expression of oncogenes in transgenic mice (14).

ROLE OF BASEMENT MEMBRANE PROTEOLYSIS

Endothelial cells line the interior of blood vessels and are ensheathed by a basement membrane, a specialized form of the extracellular matrix comprised of collagen, glycoproteins such as fibronectin and laminin, and heparan sulfate proteoglycans. A crucial early step in the neovascularization process is the dissolution of the basement membrane at the site of endothelial outgrowth from the parent vessel, which facilitates cell migration and stromal invasion. The phenomenon of cell invasiveness is not unique to angiogenesis, but isalso an essential component of both tumor metastasis and embryonic morphogenesis. Examples of the latter include primary and secondary mesenchymal cell invasion of the blastocoel in sea urchin gastrulae, the invasion of somites by migrating neural crest cells in vertebrate embryos, and fibroblast invasion of the developing cornea (15).

While the migration of single cells could presumably occur without matrix degradation, endothelial cell invasion, which involves penetration by multicellular tubes, cannot. Endothelial cells are normally noninvasive in vitro, forming a monolayer on a collagen matrix. In this respect, they differ markedly from other mesenchyme-derived cells, such as fibroblasts, leukocytes, and smooth muscle cells, that actively move through collagen substrate (16,17). Investigations of the cellular and molecular mechanisms responsible for endothelial cell invasion represent a major focus of angiogenesis research throughout the last decade.

One of the earliest studies of the cellular and molecular mechanisms of angiogenesis addressed the degradation of major basement membrane structural components (i.e., collagen types IV and V) by migrating endothelial cells (18). In an in vitro assay, endothelial cells responded to a chemoattractant located on the opposite side of a filter containing collagen substrate. The investigators isolated metalloproteinases that degrade type IV or V collagens from membrane extracts of the migrating endothelial cells, demonstrating that endothelial cells express cell membrane-associated proteases specific for basement membrane collagens.

Studies on the effects of corticosteroids on angiogenesis have raised important issues regarding the role of proteolysis. Both cortisone and hydrocortisone, when administered with heparin or a heparin fragment, inhibited neovascularization in the chick embryo chorioallantoic membrane, the rabbit cornea, and selected mouse tumors (19). By contrast, treatment with heparin alone promoted tumor angiogenesis, while independent treatment with cortisone elicited little or no effect on angiogenesis. Furthermore, the angiostatic action of the administered corticosteroids was found to be independent of their glucocorticoid and mineralocorticoid activities (20,21). Steroids whose only observed function is the inhibition of neovascularization include the dihydro- and tetrahydrosteroid metabolites of cortisone, which may act physiologically to maintain angiosta-

sis (19). Although the mechanism of corticosteroid-induced inhibition of neovascularization is unknown, it has been observed that corticosteroid and heparin co-administration induces basement membrane dissolution along capillaries that regress in response to such treatment (22). This seemingly paradoxical finding that basement membrane dissolution may inhibit rather than promote angiogenesis suggests a complex role for proteolysis in angiogenesis. While specific basement membrane proteolysis by endothelial cells invading the subendothelial matrix is integral to the expansion of a vascular network, it is likely that more generalized dissolution of the basement membrane and extracellular matrix (as elicited, for example, by corticosteroid and heparin co-administration) effectively removes the substrate within which endothelial cells are able to migrate and proliferate, and thus inhibits angiogenesis.

Because endothelial cells are not usually invasive, the elaboration of proteases involved in basement membrane degradation is believed to be tightly regulated (23). Numerous studies have sought to identify factors capable of inducing endothelial invasion in vitro. An important early investigation used bovine microvascular endothelial cells cultured on a collagen gel (24). Treatment of the endothelial cells with the tumor promoter phorbol myristate acetate (PMA), which dramatically increases capillary endothelial cell production of collagenase and plasminogen activator, induced invasive activity and subsequent capillary-like tube formation. This effect was prevented by treatment with the metalloproteinase inhibitor 1,10- phenanthroline, a finding which supports the notion that endothelial cell invasiveness is a metalloproteinasedependent process. It is possible that PMA mimics the normal effects of angiogenic factors in vivo.

Pepper et al. modeled angiogenesis in vitro by wounding a confluent monolayer of bovine microvascular endothelial cells grown on gelatin substrate and then overlaying it with a casein-agar mixture containing plasminogen (25). Cell migration from the wound edge coincided with increased urokinase-type plasminogen activator (uPA) cell-surface expression, which returned to normal levels upon cessation of movement.

Plasminogen activators produced by endothelial cells convert plasminogen to plasmin, a serine protease capable of directly degrading extracellular matrix components such as laminin and fibronectin. Plasmin may also act as an activator of the zymogen forms of secreted collagen-specific proteases, including type IV collagenase, which is essential for basement membrane degradation. This study thus substantiates previous findings implicating plasminogen activator in invasive proteolysis (24). To what extent this wounded monolayer model relates to angiogenesis during embryonic development and organogenesis, however, remains in question.

A crucial investigation involving bovine capillary endothelial cell growth on the human amnion basement membrane provided further insight into the role of basement membrane invasion during angiogenesis (26). Treatment of either the basement membrane or the underlying stromal aspect of the amnion with basic fibroblast growth factor (bFGF, also designated FGF-2) induced endothelial cell invasion in a dose-dependent manner. Several substances inhibited the invasion process, including transforming growth factor-beta (TGF-ß), inhibitors of plasminogen activators, anti-tissue plasminogen activator (tPA) antibody, a metalloproteinase inhibitor, and antibodies to type IV and interstitial collagenases. The results of this study are significant in their suggestion that angiogenesis involves degradation of both the perivascular basement membrane and the stroma of the tissue to be vascularized. This indicates that these processes are mediated by both direct and plasminogen-mediated protease activity.

Another significant discovery regarding the control of basement membrane proteolysis during angiogenesis arose from an in vitro model in which bovine microvascular endothelial cells cultured on fibrin gels were treated with various angiogenic factors (27). Prompted by a seemingly counterintuitive earlier report that the angiogenesis inducer bFGF stimulates the production of plasminogen activator inhibitor-1 (PAI-1) by endothelial cells (28), Pepper et al. showed that the angiogenic agents TGF-ß1 and PMA also induce PAI-1 (27). Interestingly, they observed that TGF-ß1 inhibited lumen formation in tube-like structures that had been induced

by bFGF. Considerable progress toward elucidating the mechanism for this phenomenon was made by measuring the ratio of uPA:PAI-1 mRNA levels as an indicator of proteolytic balance. In response to bFGF, the balance is shifted toward enhanced proteolysis; that is, more uPA is induced than PAI-1. By contrast, TGF-ß1 tilts the balance toward inhibition of proteolysis through greater induction of PAI-1 than uPA. As shown in Table 1, TGF-ß also modulates angiogenesis through inhibition of endothelial cell motility and proliferation (29). The cytostatic effect of TGF-ß1 is likely attributable to the induction of cell cycle arrest via the inhibition of a number of steps involved in cyclin-dependent kinase gene (cdk) activation, thus preventing the phosphorylation of the Rb gene in late G1 phase (30). These observed inhibitory effects of TGF-ß on proteolysis and endothelial cell motility and proliferation are further complicated by the finding that, in vivo, TGF-ß1 can elicit monocyte-mediated induction of angiogenesis (31). TGF-ß1 may thus have two opposing activities in vivo: direct-acting inhibition and monocyte-mediated induction of angiogenesis.

Matrix metalloproteinase enzymes and their specific inhibitors from another enzyme-inhibitor system modulating basement membrane degradation during angiogenesis. The tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) bind several members of the metalloproteinase family, including active interstitial collagenase and latent and active type IV collagenases, (23,32). The suggestion that TIMPs inhibit the protease activity of active metalloproteinases and/or prevent stromelysin-mediated activation of latent metalloproteinases provided the conceptual basis for further in vitro investigations of angiogenesis using these inhibitors (32). TIMP-1 and general inhibitors of both serine- and metalloproteinases have demonstrated antiangiogenic activity in the in vitro human amniotic membrane model (25). Furthermore, the balance between type IV collagenases and TIMPs was recognized as a key determinant of basement membrane proteolysis during endothelial tube formation on a collagen substrate (33).

Research on laminin, a major basement membrane glycoprotein, has revealed an additional layer of complexity in the modulation of basement membrane proteolysis during angiogenesis. In vitro studies demonstrate that laminin, previously known to promote cell migration by haptotaxis, contains both anangiogenic and an antiangiogenic peptide unit (34). The angiogenic peptide increases collagenase IV activity and plasminogen activator activation, and is located on a chain of the laminin molecule whose expression varies during development (8). Therefore, it is possible that laminin plays a role in the induction of angiogenesis during embryonic development and organogenesis, while inhibiting the process in more mature tissues. Furthermore, future research may reveal that, in some pathological forms of angiogenesis, mutations in the genetic regulator(s) of the embryonically-expressed laminin chain gene promote the expression of this protein in mature tissues. A strong analogy is evident between this hypothetical mechanism underlying certain angiogenic phenomena and the concept of proto-oncogene activation during tumorigenesis.

ENDOTHELIAL CELL MOTILITY AND PROLIFERATION

A pervasive feature among a number of angiogenic agents is their ability to stimulate endothelial cells at three levels: proteolysis, motility, and proliferation (23). As discussed above, proteolysis of matrix components by endothelial cells is required for egress from the parent vessel, as well as for capillary sprout penetration into, and lateral expansion within, the extracellular matrix. Motility is involved in both endothelial cell chemotaxis toward angiogenic stimuli and endothelial cell alignment to form a capillary sprout. Lastly, endothelial cell proliferation is essential in order to populate the expanding neovascular network.

Tumors grown in laboratory animals yielded the first isolated angiogenic factors (4,35). The advent of endothelial cell cultures provided a further impetus for the isolation of angiogenic factors, particularly endothelial cell growth factors. With the discovery that many of these factors bind strongly to heparin, the application of heparin affinity chromatography facilitated the purification of endothelial cell growth factors from a variety

Factors	Origin	EC Receptor	Signal Transduction	EC Motility	EC Proliferation
FGF-1,-2	ECM	FGF-R, HSPG-R	TK	+	+
TGF-alpha	diverse cells	EGF-R	TK	unknown	+
TGF-beta	diverse cells	TGF-R	Se/ThK	-	-
VEGF	diverse cells	VEGF-R (flk-1)	TK	unknown	+
PDGF	diverse cells	PDGF-R	TK	+	+
PAF	diverse cells	PAF-R	G-protein/PI	+	no effect
TSP-1	diverse cells, ECM			-	-
Heparin	ECM, mast cells	*	unknown	-	+
NO	EC	unknown	unknown	+	+
IL-2	macrophages, T cells	IL-2R	TK	unknown	+

TABLE 1 In vitro endothelial cell responses to putative angiogenic factors *EC: endothelial cells; FGF-1,-2: fibroblast growth factor-1, -2; ECM: extracellular matrix; FGF-R: fibroblast growth factor receptor; HSPG-R: heparan sulfate proteoglycan receptor; TK: tyrosine kinase; (+): induction; (-): inhibition; TGF-alpha: transforming growth factor-alpha; EGF-R: epidermal growth factor receptor; Se/ThK: serine/threonine kinase; VEGF: vascular endothelial growth factor; VEGF-R: vascular endothelial growth factor receptor; PDGF: platelet-derived growth factor; PDGF-R: platelet-derived growth factor receptor; PAF: platelet-activating factor; PAF-R: platelet-activating factor receptor; PI: phosphoinositide pathway; TSP-1: thrombospondin-1; (*): no known EC receptor (influence ECs by indirect mechanisms; see text for details); NO: nitric oxide; IL-2: interleukin-2; IL-2R: interleukin-2 receptor.*

of non-neoplastic tissues, including the retina, hypothalamus, brain, and cartilage (4).

Angiogenic factors can be classified according to a variety of characteristics, including the effect on endothelial cells, the mechanism of action, and the molecular form. Many of the angiogenic agents that induce endothelial cell motility are believed to be chemotactic factors, while agents that induce proliferation generally belong to the growth factor family (2). Among the substances acting principally to induce either endothelial cell motility or proliferation, many target endothelial cells directly, while others are thought to act indirectly, their effects mediated by other host cells. Furthermore, angiogenic agents can exist either in secreted form or, in the case of such molecules as epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-a), as membrane-bound glycoproteins (13). Bound angiogenic molecules are cleaved from the endothelial cell membrane to yield a soluble mitogen or chemotactic factor. Table 1 shows the biological activities of the major angiogenic factors associated with endothelial cell motility and proliferation.

Two of the earliest factors isolated were endothelial cell growth factor (ECGF) from the hypothalamus and fibroblast growth factor (FGF) from the brain; these molecules are now understood to be structurally related (2). ECGF, as originally described, is a precursor to what has become known as acidic fibroblast growth factor (aFGF, or FGF-1), while the brain-derived FGF has since been redesignated as basic FGF (bFGF, or FGF-2).

FGFs are highly potent angiogenic factors, and are commonly used to initiate blood vessel development in in vitro models in which the effects of subsequently administered modulators of angiogenesis are to be studied. FGF-1 and -2 are bound to low-affinity heparan sulfate sites in the extracellular matrix, and must be released by heparitinase or matrix-degrading proteases, such as plasminogen activator, in order to bind to high-affinity cellular receptors and thereby exert their biological effects (2,36,37). As shown in Table 1, FGFs function dually as direct-acting endothelial cell mitogens and chemotactic factors (2).

Vascular endothelial growth factor (VEGF, also referred to as vascular permeability factor, or VPF) is another heparin-binding endothelial cell growth factor known to possess angiogenic activity in vivo (38,39). Astructural homolog of platelet-derived growth factor (PDGF), VEGF was first isolated as a tumor-derived vascular permeability factor, and exists in one of four different molecular species arising by alternative mRNA splicing (38). Two of these are soluble proteins, whereas the other two are bound to cell-surface or basement membrane proteoglycans containing heparan. As indicated in Table 1, VEGF acts directly on endothelial cells to induce cell proliferation (38-41) and migration (5,42). The precise mechanism, although unknown, is thought to involve tyrosine kinase receptor-mediated activation of phospholipase C, leading to a transient rise in intracellular calcium concentration (43). Investigations have shown that VEGF may be induced by hypoxia to promote angiogenesis in ischemic tissues (40). It is possible that the low oxygen tension in embryonic tissues and developing organs likewise induces VEGF to promote neovascularization of these regions.

Several angiogenic processes are associated with the menstrual cycle. The extensive neovascularization that occurs in the periphery of developing ovarian follicles, and the microvascular expansion into neighboring lutein cells that accompanies the development of corpora lutea, may both depend on VEGF (44). The expression of VEGF mRNA by perivascular cells has been documented in female mice during the neovascularization of ovarian follicles and the corpus luteum, and during the expansion of the endometrial vasculature (45). Moreover, VEGF can be expressed in numerous steroidogenic and/or steroid-responsive cell types, including theca, lutein, granulosa, endometrial stroma, decidua, and adrenal cortical cells; in some cases, VEGF expression is restricted to a particular phase of the ovarian cycle (46).

In addition to the mitogenic role of VEGF in angiogenesis, a complementary angiogenic function of this molecule has recently been proposed that implicates VEGF in the induction of microvascular hyperpermeability. Endothelial permeability results in extravasation of plasma proteins into the extracellular space. This leads to the deposition of a fibrin gel that serves as a provisional matrix fostering the ingrowth of new blood vessels. In various physiological and pathological processes, microvascular hyperpermeability and plasma-derived matrix deposition correlate with the onset of angiogenesis (46). It is therefore possible that microvascular hyperpermeability is a crucial feature of angiogenesis, and that VEGF, as a unique inducer of vessel permeability, may be a ubiquitous player in the neovascularization process. In this regard, VEGF is thought to interact with other angiogenic factors, as evidenced by its regulation tissue factor (TF) expression and its role in mediating, at least partially, the effects of FGF-2, TGF-*, tumor necrosis factor, histamine, and other agents (43,46).

Platelet-derived growth factor (PDGF) may also act as an endogenous modulator of angiogenesis. The expression of PDGF mRNA by microvascular endothelial cells is increased by pro-inflammatory factors such as TGF-ß and thrombin, and is decreased by agents that elevate cAMP (47). In conventional two-dimensional culture, endothelial cells proliferate and express alpha and beta chains of the PDGF receptor. However, in three-dimensional culture, capillary-like tube formation and the corresponding induction of a nonproliferative, differentiated endothelial cell phenotype is associated with downregulation of PDGF receptors (48). This is reflected in Table 1, which shows that PDGF induces endothelial cell proliferation. As evidenced by the differential expression of PDGF receptors in the progression of endothelial cell proliferation to sprout development and subsequent tube formation, the plasticity of the endothelial cell phenotype is an important feature of the angiogenic process.

Platelet-activating factor (PAF), a phospholipid mediator of inflammation, is produced by stimulated monocytes/macrophages, neutrophils, basophils, and platelets, and is also elaborated by cultured endothelial cells after stimulation by a variety inflammatory mediators, such as histamine and TNF-* (49). Therefore, the angiogenic response to histamine and TNF-* may, at least in part, be mediated by PAF. Additionally, an autocrine mechanism for PAF may be suggested by the ev-

idence that endothelial cells both produce PAF and express PAF-specific receptors. At physiological concentrations, PAF induces endothelial cell migration, but not proliferation (50). PAF exhibits a range of other biological effects, including the enhancement of vascular permeability, which may have implications in angiogenesis similar to those discussed above for VEGF.

The potential role of tissue factor (TF, also known as thromboplastin) in angiogenesis was recently studied by transfecting sarcoma cells with sense and antisense constructs of the TF gene (51). Tumor cells overexpressing TF established larger and more vascular tumors than both antisense transfectants (which underexpressed TF) and untransfected tumor cell controls. The degree of TF expression by tumor cells was positively correlated with the endothelial cell mitogenic response. Furthermore, tumor cell TF expression varied directly with the transcription of VEGF and inversely with that of thrombospondin-2 (TSP-2). TF, the principal molecule of the extrinsic coagulation pathway, is expressed by a variety of tumors, and is hypothesized to mediate the enhanced procoagulant activity common among cancer patients (52). However, the proposed induction of angiogenesis by TF, and its consequent significance in tumor growth, are most likely independent of its interaction in the coagulation cascade (51). The extent to which TF may promote angiogenesis in physiological and nonneoplastic pathological states is currently unknown.

Thrombospondin-1 (TSP-1) is a perivascular extracellular matrix glycoprotein secreted by platelets, endothelial cells, and a variety of other cells; it stabilizes platelet aggregates in thrombi and wounds (53,54). Five unique members of the thrombospondin family have been identified to date; among them, only TSP-1 and -2 contain domains likely to influence angiogenesis (54). Loss of p53 in fibroblasts cultured from patients with Li-Fraumeni syndrome leads to reduced expression of TSP-1 and concomitant expression of the angiogenic phenotype (55). This is explained by the observation that, as shown in Table 1, TSP-1 inhibits in vitro endothelial cell migration and proliferation toward angiogenic agents (56). TSP-1 also inhibits neovascularization in vivo (54). In a recent study, however, human peripheral blood monocytes (which are recognized as proangiogenic by the rat cornea assay) were found to produce TSP-1, an angiogenic inhibitor (57). This paradoxical finding draws attention to the fact that macrophages produce both angiogenic and antiangiogenic agents, and to the likelihood that the net biological effect may reflect a balance in the modulators produced. Clearly, it is difficult to interpret angiogenic responses through the analysis of only a single angiogenic mediator.

As presented in Table 1, heparin produced by activated mast cells potentiates angiogenesis by stimulating endothelial cell locomotion (58). Additional evidence suggests that heparin induces endothelial cell proliferation and motility indirectly by increasing the binding of FGFs to their endothelial receptors, as well as by protecting FGFs from inactivation (2). Heparan sulfate proteoglycans are the major glycosaminoglycans on the surface of endothelial cells and in the subendothelial basement membrane (59). Through their strong affinity for many endothelial cell growth factors, heparin-like molecules on the endothelial cell surface may assist in the angiogenic process by serving to concentrate the growth factors in the immediate vicinity of the vascular endothelium (4).

Heparin is prototypical of those angiogenic factors that act by indirect pathways and thus, despite their in vivo angiogenic activity, may not demonstrate an effect on vascular endothelial cells in vitro. Several indirect pathways are possible. The factors may, for example, mobilize monocytes and activate them to secrete endothelial cell mitogens and/or chemotactic factors. Alternatively, indirect angiogenic factors may cause the release of matrix-bound or intracellularly-stored, direct-acting angiogenic factors.

Nitric oxide (NO), also known as endothelial-derived relaxation factor (EDRF), has recently been added to the growing list of angiogenic modulators. In both in vitro endothelial cell cultures and in vivo in the rat cornea, capillary endothelial cell migration and proliferation was induced in a dose-dependent manner by exogenous NO generators and by endogenous NO production elicited by substance P (60). As is true for PAF, endothelial cells both produce and respond to NO.

A large variety of other angiogenic modulators are currently undergoing early investigation. For example, TIMP-1 and -2 have been shown to inhibit tumor invasion and angiogenesis in vitro by inhibiting metalloproteinase activity and thereby blocking tumor and endothelial cell motility (61). Quite interestingly, it has been shown recently that TIMP-2 can inhibit bFGF-induced endothelial cell proliferation by an as yetundefined mechanism that is independent of metalloproteinase inhibition (32). Similarly, somatostatin analogs such as octreotide acetate have been shown to inhibit angiogenesis in vitro, and although the precise mechanism is unclear, it is thought to involve direct endothelial cell activation and to be G protein-, calciumand cAMP-dependent (62,63). In addition, an internal fragment of prolactin (PRL) potently inhibits angiogenesis modeled in vitro by bFGF-induced proliferation of cultured endothelial cells (64). Native PRL, however, appears to have no effect, raising the possibility that some modulators of neovascularization arise by specific proteolysis of circulating, angiogenically-inactive molecules. Recombinant ribonuclease (RNase) inhibitor has also been implicated as a modulator of angiogenesis, inhibiting the angiogenic response to bFGF in the mouse cornea (65). Subcutaneous implantation of RNase inhibitor-releasing disks beneath intradermally-inoculated mammary tumor cells showed significant inhibition of tumor growth. Furthermore, the novel angiogenesis inhibitor angiostatin, which is homologous to an internal segment of plasminogen, appears in the serum in the presence of a primary tumor and markedly suppresses angiogenesis in distant metastases (66). Lastly, numerous macrophage secretory products, including several mentioned previously, have been shown to mediate angiogenesis (67).

Given the great diversity of angiogenic factors and their pluralistic modes of action and biological activities, physiological mechanisms to prevent rampant capillary neoformation must be equally complex. Indeed, under most normal conditions, capillary endothelial cells remain quiescent. The regulatory mechanisms responsible for this quiescence plausibly involve both intracellular controls, such as growth factor sequestration, and extracellular controls, including inhibitors such as TGF-ß.

CLINICAL APPLICATIONS

A flurry of activity in the field of angiogenesis research is currently underway as its expanding clinical contexts are continuously being discovered. In particular, a potential role of angiogenic modulation has been suggested in diabetic retinopathy, rheumatoid arthritis, cardiovascular disease, certain vasculopathies, tissue grafting and organ transplantation, and in various solid tumors, such as Kaposi's sarcoma. The visionthreatening vascular proliferation in diabetic retinopathy has been postulated to stem from the stimulation of choroidal endothelial cells by VEGF and FGF-2 elaborated by retinal pigment epithelial cells (68). By contrast, the release of angiogenic inhibitors by retinal pigment epithelial cells has been proposed as the physiological mechanism underlying avascularity in the retina (69).

The administration of the AGM-1470 (TNP-470) derivative of fumagillin, an angiogenesis inhibitor obtained from Aspergillus fumigatus, has proven effective in preventing neovascularization of joint synovia in rat models of rheumatoid arthritis (70). Synovial fluid VEGF levels have been shown by immunoassay to be significantly higher in rheumatoid arthritis patients than in those with other arthritides (5). Immunohistologic studies have demonstrated p55 and p70 IL-2 receptors in the vasculature of rheumatoid joints (71), suggesting possible molecular targets for future therapies.

In another application of angiogenesis research, direct gene transfer of an expression vector for FGF-1 into porcine arteries shows promise for the neovascularization and proposed resolution of early atherosclerotic lesions (72). Other studies have demonstrated that angiogenic growth factor-laden fibrin glue, implanted between the aorta and left ventricular myocardium, induced site-directed neovascular development (73). Related studies have shown enhanced de novo epicardial small vessel growth in rabbits receiving intrapericardial infusions of FGF-2, especially in those animals having left ventricular hypertrophy (74). This provides exciting

prospects for intervention in cardiac diseases in which myocardial oxygen supply is compromised and/or demand is increased. It is quite conceivable that the induction of new collateral vessel formation may delay or halt the progression of coronary artery disease to myocardial infarction, as well as the advancement of ventricular hypertrophy to heart failure.

With respect to vasculopathies, clinical trials are being performed in the treatment of high-risk hemangiomasof infancy through long-term daily administration of inteferon-*-2*, which has anti-angiogenic properties (75). In addition, in the chronic inflammatory condition of systemic vasculitis, increased levels of angiogenic haptoglobin in patient sera have been implicated in the hyperproliferation of vessels, possibly in response to ischemia of involved tissues (76).

Angiogenic modulation has also been applied to peptic ulcer disease. As a peptic ulcer is essentially a form of wound, one would expect its healing to depend upon microvascular ingrowth. Indeed, the induction of angiogenesis in duodenal ulcer beds via oral administration of acid-resistant FGF-2 in rats has successfully accelerated healing of the ulcers, and is currently undergoing Phase I clinical trials (77,78).

Recent investigation of pancreatic islet iso- and xenografting in the hamster have demonstrated that endothelial cells of host muscle tissue origin are responsible for revascularization of the grafts (79). Since graft endothelial cell-dependent antigen recognition by host immune cells, a host-versus-graft reaction, is thought to play an important role in most graft rejections, this result prompts the hypothesis that graft survival could be enhanced if the selective inhibition of neovascularization in graft tissue and promotion of angiogenesis in host tissue is achieved.

Perhaps the most important clinical applications to emerge from angiogenic research lie in cancer therapy. Phase I trials using carboxy-amino-triazole (CAT), an anti-angiogenic agent, are in progress for the treatment of cancer patients with various tumor types (80). A fumagillin analog that has demonstrated tumoristatic activity against Lewis lung carcinoma and B12 melanoma is also presently undergoing clinical trials. IFN-*, which suppresses angiogenesis in vivo, has been approved by the U.S. Food and Drug Administration for the treatment of Kaposi's sarcoma in AIDS patients (81). Cultured Kaposi's sarcoma cells exhibit PAF production and release, and possess high-affinity, membrane-associated PAF receptors (82), providing molecular targets that could be exploited in alternative therapy of this neoplasm. In addition, antisense oligonucleotides directed against FGF-2 mRNA have significantly inhibited proliferation of Kaposi's sarcoma cells derived from AIDS patients and suppressed the demonstrated angiogenic activity of these cells (83).

Furthermore, angiogenesis is also being used in tumor grading, the density of vascularization positively correlating with the risk of tumor progression (84). The use of microvessel quantitation, as well as immunohistochemical staining for endothelial cell markers, in the pathological evaluation of neoplasms promises to become more prevalent in the future.

CONCLUSION

Advances in the elucidation of angiogenesis in recent years stem primarily from the investigation of three critical features of the neovascularization process, namely endothelial cell proliferation, motility, and basement membrane proteolysis. Although considerable progress has been made with respect to the characterization of angiogenic factors that mediate these processes, much remains to be discovered concerning angiogenic regulatory mechanisms.

In this regard, it appears that the primary difference between tumor angiogenesis and normal neovascularization lies not in the elaboration of distinct endothelial cell growth factors, but rather in the modulation of their expression and activity. Whereas tumors most often express angiogenic agents continuously, many normal tissues seem to contain endothelial factors that are only expressed under tight regulation. The diverse activities and modes of action of the numerous angiogenic modulators greatly complicate our understanding of the regulatory mechanisms involved in neovascularization.

In the final analysis, when dealing with such a com-

plex phenomenon as angiogenesis, the sharp distinction between angiogenic factors direct versus indirect, protease-activating versus chemotactic or mitogenic, and even inducing versus inhibiting is quite likely an oversimplification. Some angiogenic factors exert both direct and indirect effects, while others function dually as mitogens and activators of proteolysis. Still other angiogenic factors act as inducers in some contexts and inhibitors in others. Further research into angiogenesis may show that, like tumor cell release of VEGF, the expression of angiogenic factors responds to signals from the cellular microenvironment. Future discoveries may indeed reveal that the temporally coordinated activities of a number of key angiogenic regulators are responsible for the predominance of neovascularization during embryogenesis and various physiological and pathological processes, including tumor metastasis.

REFERENCES

1. Benjamini E, Leskowitz S. Immunology: a short course, 2nd ed. New York: Wiley-Liss, Inc.; 1991

2. Folkman J, Klagsbrun M. Angiogenic factors. Science 235: 442-447, 1991.

3. Folkman J. What is the evidence that tumors are angiogenesis dependent? Journal of the National Cancer Institute 82: 4-6; 1990.

4. Folkman J. Toward an understanding of angiogenesis: search and discovery. Perspectives in Biology and Medicine 29(1): 10-36; 1985.

5. Koch AE, et al. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. Journal of Immunology 152(8): 4149-4156; 1994.

6. Murphy RP. Management of diabetic retinopathy. American Family Physician 51(4): 785-96; 1995.

7. Ausprunk DH, Folkman J. Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. Microvascular Research 14: 53-65; 1977.

8. Kleinman HK, et al. The laminins: a family of basement membrane glycoproteins important in cell differentiation and tumor metastases. Vitamins and Hormones 47: 161-184; 1993.

9. Yanase T, et al. Inhibitory effect of angiogenesis inhibitor TNP-470 on tumor growth and metastasis of human cell lines in vitro and in vivo. Cancer Research 53: 2566-2570; 1993.

10. Gimbrone MA Jr., Cotrans RS, Folkman J. Human vascular endothelial cells in culture: growth and DNA synthesis. Journal of Cell Biology 60: 673-680; 1974.

11. Ausprunk DH, Knighton DR, Folkman J. Vascularization of normal and neoplastic tissues grafted into the chick chorioallantois. American Journal of Pathology 79: 597-618; 1975.

12. Passaniti A, et al. A simple, quantitative method for assessing angiogenesis and antiangiogenic agents using reconsitituted basement membrane, heparin, and fibroblast growth factor. Laboratory Investigation 67: 519-28; 1992.

13. Gleave ME, et al. Epidermal growth factor receptor-mediated autocrine and paracrine stimulation of human transitional cell carcinoma. Cancer Research 53: 5300-5307; 1993.

14. Folkman J, et al. Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 339: 58-61, 1989.

15. Browder LW, Erickson CA, Jeffery WR. Developmental Biology, 3rd ed. Philadelphia, PA: Saunders College Publishing; 1991.

16. Schor SL. Cell proliferation and migration on collagen substrate in vitro. Journal of Cell Science 41: 159- 175; 1980.

17. Delvos U, et al. Interaction of vascular wall cells with collagen gels. Laboratory Investigations 46: 61-72; 1982.

18. Kalebic T, et al. Basement membrane collagen: degradation by migrating endothelial cells. Science 221: 281-283; 1982.

19. Folkman J, et al. Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone. Science 221: 719; 1983.

20. Crum R, Szabo S, Folkman J. A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment. Science 230: 1375; 1985.

21. Crum R, Folkman J. Anti-angiogenesis by steroids without glucocorticoid or mineralocorticoid activity in the presence of heparin. Journal of Cell Biology 99: 158a; 1984.

22. Ingber DE, Madri JA, Folkman J. Anti-angiogenesis by angiostatic steroids in the presence of heparin: induction of basement membrane dissolution. Journal of Cell Biology 101: 105a; 1985.

23. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. Cell 64: 327-336; 1991.

24. Montesano R, Orci L. Tumor-promoting phorbol esters induce angiogenesis in vitro. Cell 42: 469-477; 1985.

25. Pepper MS, et al. Urokinase-type plasminogen activator is induced in migrating capillary endothelial cells. Journal of Cell Biology 105: 2535-2541; 1987.

26. Mignatti P, et al. In vitro angiogenesis on the human amniotic membrane: requirement for basic fibroblast growth factor-induced proteinases. Journal of Cell Biology 108: 671-682; 1989.

27. Pepper MS, et al. Transforming growth factor-beta 1 modulates basic fibroblast growth factor-induced proteolytic and angiogenic properties of endothelial cells in vitro. Journal of Cell Biology 111: 743-755; 1990.

28. Saksela O, Moscatelli D, Rifkin DB. The opposing effects of basic fibroblast growth factor and transforming growth factor beta on the regulation of plasminogen activator activity in capillary endothelial cells. Journal of Cell Biology 105: 957-963; 1987.

29. Muller G, et al. Inhibitory action of transforming growth factor beta on endothelial cells. Proceedings of the National Academy of

Sciences USA 84: 5600-5604; 1987.

30. Lin HY, Moustakas A. Cellular and Molecular Biology 40(3): 337-349; 1994.

31. Weisman DM, et al. Transforming growth factor-beta is chemotactic for human monocytes and induces their expression of angiogenic activity. Biochemical and Biophysical Research Communications 157: 793- 800; 1988.

32. Murphy AN, Unsworth EJ, Stetler-Stevenson WG. Tissue inhibitor of metalloproteinase-2 inhibits bFGFinduced human microvascular endothelial cell proliferation. Journal of Cellular Physiology 157(2): 351-358;1993.

33. Schnapper HW, et al. Type IV collagenases and TIMPs modulate endothelial cell morphogenesis in vitro. Journal of Cellular Physiology 156: 235-246; 1993.

34. Grant DS, et al. Two different laminin domains mediate the differentiation of human endothelial cells into capillary-like structures in vitro. Cell 58: 933-943; 1989.

35. Azizkhan J, et al. Stimulation of increased capillary endothelial cell motility by chondrosarcoma cellderived factors. Cancer Research 43(7): 3281-3286; 1983.

36. Bashkin P, et al. Basic fibroblast growth factor binds to subendothelial extracellular matrix and is released by heparitinase and heparin-like molecules. Biochemistry 28: 1737-1743; 1989.

37. Friesel RE, Maciag T. Molecular mechanisms of angiogenesis: fibroblast growth factor signal transduction. FASEB 9(10): 919-925; 1995.

38. Kim KJ, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 362: 841-844; 1993.

39. Plate KH, et al. Vascular endothelial growth factor is a potential tumor angiogenesis factor in human gliomas in vivo. Nature 359: 845-848; 1992.

40. Shweiki D, et al. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 359: 843-845; 1992.

41. Connolly DT, et al. Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. Journal of Clinical Investigation 84: 1470-1478; 1989.

42. Favard C, et al. Purification and biological properties of vasculotropin, a new angiogenic cytokine. Biology of the Cell 73(1): 1-6; 1991.

43. Connolly DT. Vascular permeability factor: a unique regulator of blood vessel function. Journal of Cell Biochemistry 47(3): 219-23; 1991.

44. Findlay JK. Angiogenesis in reproductive tissues. Journal of Endocrinology 111: 357-366; 1986.

45. Shweiki D, et al. Patterns of expression of vascular endothelial growth factor (VEGF) and VEGF receptors in mice suggest a role in hormonally regulated angiogenesis. Journal of Clinical Investigation 91(5): 2235-2243; 1993.

46. Dvorak HF, et al. Vacular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. American Journal of Pathology 146(5): 1029-1039; 1995.

47. Kavanaugh WM, et al. Transcriptional regulation of the A and B chain genes of platelet-derived growth factor in microvascular endothelial cells. Journal of Biological Chemistry 263: 8470-8472; 1988.

48. Marx M, Perlmutter RA, Madri JA. Modulation of platelet-derived growth factor receptor expression in microvascular endothelial cells during in vitro angiogenesis. Journal of Clinical Investigation 93(1): 131-139; 1994.

49. Camussi G, et al. The release of platelet-activating factor from human endothelial cells in culture. Journalof Immunology 131: 2397-2403; 1983.

50. Camussi G, et al. Platelet-activating factor directly stimulates in vitro migration of endothelial cells and promotes in vivo angiogenesis by a heparin-dependent mechanism. Journal of Immunology 154(12): 6492- 6501; 1995.

51. Zhang Y, et al. Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice. Journal of Clinical Investigation 94(3): 1320-1327; 1994.

52. Murray, JC. Coagulation and cancer. British Journal of Cancer 64: 422-424; 1991.

53. Tolsma S, et al. Peptides derived from two separate domains of the matrix protein thrombospondin-1 have anti-angiogenic activity. Journal of Cell Biology 122: 497-511; 1993.

54. Good DJ, et al. A tumor suppressor-dependent inhibitor of angiogenesis is immunologically and functionally indistinguishable from a fragment of thrombospondin. Proceedings of the National Academy of Sciences USA 87: 6624-6628; 1990.

55. Dameron KM, et al. Control of angiogenesis in fibroblasts by p53 regulation of thrombospondin-1. Science 265: 1582-1584; 1994.

56. Taraboletti G, et al. Platelet thrombospondin modulates endothelial cell adhesion, motility, and growth: a potential angiogenesis regulatory factor. Journal of Cell Biology 111: 765-772; 1990.

57. DiPietro LA, Polverini PJ. Angiogenic macrophages produce the angiogenic inhibitor thrombospondin 1. American Journal of Pathology 143(3): 678-684; 1993.

58. Azizkhan RG, et al. Mast cell heparin stimulates migration of capillary endothelial cells in vitro. Journal of Experimental Medicine 152(4): 931-944; 1980.

59. Buonassisi V, Root M. Enzymatic degradation of heparin-related mucopolysaccharides from the surface of endothelial cell cultures. Biochimica et Biophysica Acta 385(1): 1-10; 1975.

60. Ziche M, et al. Nitric oxide mediates angiogenesis in vivo and endothelial cell growth and migration in vitro promoted by substance P. Journal of Clinical Investigation 94(5): 2036-2044; 1994.

61. Ray JM, Stetler-Stevenson WG. The role of matrix metalloproteinases and their inhibitors in tumor invasion, metastasis and angiogenesis. European Respiratory Journal 7: 2062-2072; 1994.

62. Wolfering EA, et al. Somatostatin analogues inhibit angiogenesis in the chick chorioallantoic membrane. Journal of Surgical Research 50: 245-251; 1991.
63. Patel PC, et al. Postreceptor signal transduction mechanisms involved in octreotide-induced inhibition of angiogenesis. Surgery 116(6): 1148-1152; 1994.
64. Clapp C, et al. The 16-kilodalton N-terminal fragment of human prolactin is a potent inhibitor of angiogenesis. Endocrinology 133: 1292-1299; 1993.
65. Polakowski IJ, et al. A ribonuclease inhibitor expresses anti-angiogenic properties and leads to reduced tumor growth in mice. American Journal of Pathology 143(2): 507-517; 1993.
66. Oreilly MS, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastasesby a Lewis lung carcinoma. Cell 79: 315-328; 1994.
67. Sunderköpter C, et al. Macrophage and angiogenesis. Journal of Leukocyte Biology 55: 410-422; 1994.
68. Sakamoto T, et al. Vessel formation by choroidal endothelial cells in vitro is modulated by retinal pigment epithelial cells. Archives of Ophthalmology 113(4): 512-520; 1995.
69. Glaser B, et al. Retinal pigment epithelial cells release inhibitors of neovascularization. Ophthalmology 94: 780; 1983.
70. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature Medicine 1(1): 27-31; 1995.
71. Cozzolino F, et al. Interferon-alpha and interleukin 2 synergistically enhance basic fibroblast growth factor synthesis and induce release, promoting endothelial cell growth. Journal of Clinical Investigation 91(6): 2504-2512; 1993.
72. Nabel EG, et al. Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo. Nature 362: 844-846; 1993.
73. Fasol R, et al. Experimental use of a modified fibrin glue to induce site-directed angiogenesis from the aorta to the heart. Journal of Thoracic and Cardiovascular Surgery 107(6): 1432-1439; 1994.
74. Landau C, Jacobs AK, Haudenschild, CC. Intrapericardial basic fibroblast growth factor induces myocardial angiogenesis in a rabbit model of chronic ischemia. American Heart Journal 129(5): 924-931; 1995.
75. Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alpha-2a therapy for life-threatening hemangiomas of infancy. New England Journal of Medicine 326: 1456-1463; 1992 (and corrections New England Journal of Medicine 330: 300; 1994).
76. Cid MC, et al. Identification of haptoglobin as an angiogenic factor in sera from patients with systemic vasculitis. Journal of Clinical Investigation 91(3): 977-985; 1993.
77. Hull MA, Cullen DJE, Hawkey CJ. Basic fibroblast growth factor in gastric ulceration: mucosal levels and therapeutic potential. Gastroenterology 106: A97; 1994.
78. Wolfe MM, et al. Safety and efficacy of an angiogenic peptide, basic fibroblast growth factor (bFGF) in the treatment of gastroduodenal ulcers: a preliminary report. Gastroenterology 106: A212; 1994.
79. Vajkoczy P, et al. Histogenesis and ultrastructure of pancreatic islet graft microvasculature. Evidence for graft revascularization by endothelial cells of host origin. American Journal of Pathology 146(6): 1397-1405; 1995.
80. Kohn E, et al. Phase I trial of signal transduction inhibitor, CAI. Proceedings of the American Association of Cancer Research 35: 244; 1994.
81. Logan A. Angiogenesis. Lancet 341: 1467-1468; 1993.
82. Bussolino F, et al. Platelet activating factor produced in vitro by Kaposi's sarcoma cells induces and sustains in vivo angiogenesis. Journal of Clinical Investigation 96(2): 940-952; 1995.
83. Ensoli B, et al. Block of AIDS-Kaposi's sarcoma (KS) cell growth, angiogenesis, and lesion formation in nude mice by antisense oligonucleotide targeting basic fibroblast growth factor. A novel strategy for the therapy of KS. Journal of Clinical Investigation 94(5): 1736-1746; 1994.
84. Hollingsworth HC, et al. Tumor angiogenesis in advanced stage ovarian carcinoma. American Journal of Pathology 147(1): 33-41; 1995.

WOMEN IN MEDICINE

Women in Medicine: Foreword

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WOMEN IN MEDICINE is a reflective series celebrating and recognizing the influential work of female doctors. The McGill Journal of Medicine collaborated to produce the series, written by female medical student authors who are members of the McGill Feminism in Medicine group in the McGill Faculty of Medicine and Health Sciences. This by women, about women series sought to highlight inspirational stories of leading female physicians, based on one-on-one interviews between the authors and their subjects, exploring such topics as medicine, career development, gender, and family. The series covers inspirational figures such as Dr. Lysanne Campeau, Dr. May Cohen, Dr. Louise Pilote, Dr. Liane Feldman, Dr. Danielle Martin, and Dr. Theresa Tam

KEYWORDS
medicine, feminism, gender equality

Dr. Caralee Caplan-Shaw, MD

The most important advice I can give to the students reading this special issue—to the next generation of medical women—is to remember that there is more than one path to leadership for women in medicine.

When I graduated from medical school at McGill, I applied to residency programs in internal medicine but decided to withdraw from the match in order to spend a year as the inaugural editorial fellow at the Canadian Medical Association Journal. I had been an English major in college, and at the CMAJ, I found a way to combine my interests in medicine, writing, and public health by launching the journal's first public health column.

Later that year, my medical school study buddy Jason flew up to Ottawa from New York to pop the question. Suddenly I was scrambling to reapply to residency pro-

grams in New York and was fortunate to land a spot at Columbia. By the time I had completed my residency and my pulmonary-critical care fellowship, our daughter Natalie was 15 months old, and I was 3 months pregnant with our son Gabriel. I still remember lying on the floor of our empty apartment, exhausted and nauseated, after packing up for our move to Miami, where Jason would start his fellowship in cardiothoracic surgery.

On arrival, I began my job search. I had become the primary breadwinner overnight, would soon have 2 children under 2 with no family around to help, and a husband who was working so hard that he hadn't found time to go to the benefits office to sign up for health insurance. Working nights and weekends was clearly not an option for me under the circumstances, but I ultimately wanted to build a successful career in academic medicine.

Rather than join a private practice or an academic center like most of my co-fellows, I chose to work in the busy TB clinics of the Miami Dade health department. Little did I know that my decision would lead me to find a mentor, gain clinical expertise in a disease of great public health importance, become an early adopter of telehealth to care for TB patients across the state, answer complex TB questions on a regional hotline, and work on creative projects in physician and patient education.

The journey ultimately led me back to New York City and Bellevue Hospital, where I care for patients with respiratory problems after exposure to World Trade Center dust and fumes, and I have found my calling as Director of the Bellevue Chest Service and the Bellevue Hospital TB Program. Here, our youngest was born, and I have managed—with a village of family and friends—to balance family life with inpatient and outpatient clinical care, quality improvement projects, and scientific publications. Recently, Jason and I were forced to meet the challenges of being on the front lines of the Covid crisis as a 2-physician family. And what has become increasingly important to me is helping the young women in our division navigate life after fellowship.

Sometimes, in medicine as in life, what feels like a detour can be one of many paths to fulfillment. More women are rising to leadership positions, but our institutions still have a long way to go. And every woman who expects more for herself — who takes risks, asks for that raise or promotion, and follows her own unique path — lifts not only herself but all the women hoping to rise up behind her. In this section, find inspiration among the stories of women who've risen to meet the challenges placed in front of them, whether by life or career, and found balance and success at the top of their fields.

Women in Medicine: Dr. Lysanne Campeau

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ABSTRACT

Dr. Lysanne Campeau (M.D., C.M., Ph.D., F.R.C.S.C.) is an Assistant Professor of Urology at McGill University's Jewish General Hospital. Through her flamboyant career in medicine, her research accomplishments, and her advocacy work for gender equality in medicine, she is a model of ambition, dedication, and passion. Dr. Campeau completed medical school as well as her urology residency at McGill University. She is the first woman to complete her entire residency at McGill University in this specific field. Dr. Campeau then went on to complete a clinical fellowship in Female Pelvic Medicine and Reconstructive Surgery at New York University, as well as a Ph.D. in Physiology and Pharmacology at Wake Forest Institute for Regenerative Medicine. She then came back to work as a urologist at the Jewish General Hospital and a clinical researcher at the Lady Davis Institute. Her research interests lie in female pelvic medicine, voiding dysfunction, and urogenital reconstruction. In addition to her clinical and academic duties, Dr. Campeau is involved in teaching urology residents as well as in some volunteer endeavours in the community. A resilient person, Dr. Campeau builds on her experience of gender discrimination in medicine to advocate for equality in her field. She also aims to raise awareness on the topic of incontinence, which is often taboo among the public. Through awareness campaigns as well as her innovative research in the field, Dr. Campeau works to develop new treatments and improve outcomes for patients who suffer from this condition. Dr. Campeau is a positive leader and role model for aspiring female physicians to whom she advises to cultivate adaptiveness, integrity, and honesty in order to navigate the challenging journey that is medicine.

KEYWORDS

Urology, female pelvic medicine, urogenital reconstruction, incontinence, gender equality, feminism

Dr. Lysanne Campeau, M.D.C.M., Ph.D., F.R.C.S.C. Assistant Professor of Urology, McGill University

Very few physicians exemplify the ambition, dedication, and passion for medicine as well as Dr. Lysanne Campeau (M.D.C.M., Ph.D., F.R.C.S.C.), an Assistant Professor of Urology at McGill University's Jewish General Hospital.

Born into a French-speaking family in Montreal's West Island, Dr. Campeau showed fascination and curiosity for physiology and biomechanics at a very early age. "I remember being very young and looking at my hands, wondering how they could move the way they did," she recalls. Her scientific mind and her love of learning were encouraged by parents, especially given that they did not instill any stereotypical gender roles on her. Growing up with two brothers, Dr. Campeau remembers always feeling on equal grounds with them. She played the same sports as them and never felt any lesser despite the times. With this unfettered interest, she was offered a scholarship to the private Collège André-Grasset where she completed her CEGEP diploma. By that time, she knew she wanted to pursue a career in a health-related field.

McGill University was an obvious first choice for Dr. Campeau when came the time to apply to medical school; the university's openness to the world as well as its reputation for excellence greatly appealed to her. Once in medical school, a classmate suggested she would enjoy doing an elective in urology, which she did. At the time, there were no women on staff and a single female resident, making her a self-dubbed "rare species." Her affirmative personality and irreproachable work ethics were quickly noticed, and she received support from both residents and staff as she began to get involved in the field.

After graduating from medical school in 2005, Dr. Campeau entered her urology residency at McGill. Although she describes it as a very challenging time of her life involving hard work and long hours, Dr. Campeau enjoyed residency. She was passionate about the work and enjoyed the team aspect of surgery. She nonetheless faced certain gender-based obstacles during these years. She remembers having challenging encounters with more junior residents that did not always accept being led by a woman. "This was a different time," she states, "and these people were a product of their time. To me, this kind of interaction was not surprising; it was simply the norm."

When asked what specific challenges female residents can expect currently, Dr. Campeau explained that women have to maintain a certain attitude to succeed in medicine. In her opinion, being adaptive is key, as it allows you to approach and interact with a person in a way that is tailored to this specific relationship dynamic. "I don't interact with male colleagues the same way I do with other professionals I work with," she describes. She also specifies that aside from a few specific occasions, she mostly felt equal to her male counterparts as a resident trainee. Dr. Campeau graduated from residency in 2010, becoming the first woman to complete her entire urology residency at McGill University. Having considered gynecology before choosing urology, Dr. Campeau chose to join these two fields of interest and went on to complete a fellowship in Female Pelvic Medicine and Reconstructive Surgery at New York University. With her eye toward academics, she sought opportunities to combine research to her clinical fellowship and was soon offered a scholarship to complete her Ph.D. in Physiology and Pharmacology at the Wake Forest Institute for Regenerative Medicine. This resulted in Dr. Campeau obtaining board certification from the American Board of Urology as well as in her specialty of Female Pelvic Medicine and Reconstructive Surgery, on top of her Canadian Royal College Certification in Urology.

Her positive experience as a resident at McGill and the constructive relationships she fostered with her colleagues during her residency brought Dr. Campeau back to Montreal to work at the Jewish General Hospital as a staff. She also became a clinical researcher at the Lady Davis Institute, leading innovative research on the topics of female pelvic medicine, voiding dysfunction, and urogenital reconstruction.

After several years working in this domain, she enjoys

being able to develop long-term relationships with her patients. She also appreciates the breadth of practice that urology offers; she remembers being astonished as a resident at the variety of different surgeries she could perform within a single day – from microsurgery to open abdominal interventions to robotic surgery. She also values the possibility of offering her patients behavioral, medical, and surgical treatment, with the option of surgery being used as a last resort when other treatments have failed. This brings her satisfaction in knowing she is making a difference for patients who are truly suffering. "Incontinence is not a sexy subject. It is often a taboo subject among the public," says Dr. Campeau. "But it affects vulnerable individuals whose voices aren't necessarily heard, so it's important to bring this topic to light." For this purpose, Dr. Campeau has volunteered her time for The Canadian Continence Foundation's campaign on overactive bladder in collaboration with Châtelaine, appearing in a promotional video(1) encouraging people to seek treatment for this condition.

When asked if she considers herself a feminist, Dr. Campeau answers affirmatively without hesitation. She notices that people often misunderstand the term, interpreting it as women being superior to men, when in truth it refers to gender equality. In her opinion, because there remains a considerable amount of inequities and discrimination towards women in the society we live in, being a feminist and speaking out on these issues is crucial. She adds that her husband and her sometimes reflect on this together as well when thinking of their two daughters and how they will move through the world. Dr. Campeau engages in feminist advocacy in her work as Assistant Professor of Urology and site director for residency training at the Jewish General Hospital. As the coordinator of the residents' monthly journal club, she includes an article pertaining to gender disparities within the medical field almost every month. Whether it be in the vocabulary used by staff to evaluate residents or the words used when writing a research proposal, she explains that there still exists a noticeable difference in the way men and women are portrayed and portray themselves in medicine. She once had a research mentor tell her she didn't brag about herself enough when writing her research proposals. "Now I try to think, 'how would I write about the importance of my research to convince the research panel, if I were a man?'"

Dr. Campeau also recalls moments in her career when she experienced these disparities. There were times when she was mistaken for a nurse, or had a patient address her male junior resident when she was the chief resident who performed the patient's surgery. She also feels that as a female physician, she is held to a higher standard when it comes to appearing professionally dressed, for example. She reiterates, however, that people holding these admittedly outdated beliefs are products of their generation. Dr. Campeau's impressive career and countless academic and clinical achievements at a young age are a testament to her ability to brush off these events, remain focused on her goals, and devote her energy to providing the best care for all her patients. "I can see that the newer generation of female residents experiences less and less this pressure to achieve the double standard, and it's encouraging," she says. After being the only woman on staff in urology at the JGH for 5 years, Dr. Campeau was recently joined by Dr. Mélanie Aubé-Peterkine and is thrilled to see that women are carving out a place for themselves in this field. Dr. Campeau is also a member of the Society for Women in Urology, which provides a space to discuss and share the realities, challenges, and positive experiences of being a female physician in the field.

To aspiring female physicians, residents, and students, Dr. Campeau advises to remain adaptive in every situation they encounter, stressing that this is a skill that is useful during training and in practice afterwards. She also states the importance of believing in one's convictions and not letting other people's opinions push you to make one decision or another. To her, integrity and honesty remain key qualities that will result in positive outcomes throughout one's life. She also explains that one's professional reputation begins to shape itself from the first moments of medical school, thereby highlighting the importance of maintaining constructive and agreeable working relationships: "As I was reading books on childhood education when becoming a new mother, I came across this Maya Angelou quote: 'People will for-

get what you said, people will forget what you did, but people will never forget how you made them feel.' I believe this is true in medicine as well; being the first author or obtaining a prestigious scholarship are remarkable achievements we as doctors should strive for, but not at the cost of doing dishonest things, stepping on other people, or making others feel bad."

REFERENCES

1. M. L. P. C. O. M. 19 décembre. (2019, December 19). Gérer la vessie hyperactive. Retrieved March 17, 2020, from https://fr.chatelaine.com/commandite/gerer-la-vessie-hyperactive/

Women in Medicine: Dr. May Cohen, aka "The Gender Lady"

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Dr. May Cohen

ABSTRACT

Some of the greatest strides seen in Canadian women's health and in gender equity in medicine can be attributed to Dr. May Cohen: an unyielding activist who dedicated her life's work to advocacy. From spearheading the development of the first Women's Health Office at McMaster University to serving as President of the Federation of Medical Women in Canada, her career is a testament to what can be achieved with a strong social conscience and unwavering determination.

KEYWORDS

May Cohen, Gender Equity, Abortion Rights, Medicine

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Dr. May Cohen, aka "The Gender Lady"

Some of the greatest strides seen in Canadian women's health and in gender equity in medicine can be attributed to Dr. May Cohen: an unyielding activist who dedicated her life's work to advocacy. From spearheading the development of the first Women's Health Office at McMaster University to serving as President of the Federation of Medical Women in Canada, her career is a testament to what can be achieved with a strong social conscience and unwavering determination.

Even early on in her life, one could see that Dr. May Cohen had a strong sense of resolve. Born in Montreal and raised in Toronto, she wanted to become a doctor from an early age. In one interview, Dr. Cohen recalled the moment she shared her desire to become a physician with her eighth grade teacher, who told her that "women do not become doctors." (1) Fortunately, she

didn't let that dissuade her, and eventually she went on to attend the University of Toronto's Medical School as one of only fourteen women in the class. (1)

Dr. Cohen's resolve persisted as a young woman pursuing medical training before women in medicine were commonplace. In an interview on White Coat, Black Art, Dr. Cohen was asked what it was like as a medical student at a time when women formed merely 10% of the class. (2) She recalled the first day the dean came in to welcome the fresh-faced cohort: "He informed us that we would have to wear a tie and shave everyday. All we could do as the few women was look at our own legs." (2) Similarly, she recalled that her anatomy professor would always greet the class with "Good morning, Gentlemen." On one occasion, she decided to sit in the front row along with the other women in the class to make a statement. His greeting, however, remained the same. At the time, she wasn't yet sensitized to the discrimination and later stated she was simply happy to be amongst the chosen ten percent. (2) In 1955, Dr. Cohen went on to graduate at the top of her class–a reflection of the tenacity and perseverance that underlined the rest of her career and life.

As Dr. Cohen moved into the early part of her career, she began to take an interest in social issues that intersected with women's health. When Dr. Cohen first started practicing as a family physician in Toronto, abortion was illegal in Canada. (2) She remembered several instances where patients came to her seeking abortion services; fortunately, most of them at the time had the financial resources to travel to England, where abortion was legal. One of the most striking moments, however, was when one of her own patients was admitted to the emergency department and subsequently died from the complications of an illegal abortion. (2) For her, the young woman's death became symbolic of a larger problem, as she understood the fundamental connection between women's autonomy over their bodies and their health.

Dr. Cohen took on a more active role in advocating for women's medical rights as Canadian political landscapes shifted. In 1969, a significant change in the abortion law was passed under Trudeau's Liberal government making abortion permissible under certain circumstances. Under these laws, abortion would be legal to perform in a hospital if a committee of three physicians determined that continuing the pregnancy would endanger the mother's life or health. (3) While this was certainly a huge step forward, Dr. Cohen quickly realized that loopholes existed within the new law. Firstly, not every hospital was obliged to have an abortion committee and secondly, as 'health' and 'life' were not clearly defined in the law, it allowed greater room for interpretation resulting in some committees being more restrictive than others. (2) At the time the change was highly contentious, and many pro-choice physicians and abortion providers were targeted in violent hate crimes. (2,3) Despite the risk to herself, Dr. Cohen joined the abortion decision committee at Branson Hospital in Toronto and tirelessly fought for access to legal and safe abortion for women across Canada. She strongly believed that "if someone is forced to carry a pregnancy they don't want, that is a risk to their health." (2) Since those early days, she has continued to figure prominently in the medicolegal debate on abortion laws and women's right to choose.

In addition to her advocacy work on abortion, Dr. Cohen played an active role in promoting an understanding of women's specific health needs across the country. 'Year of the Woman' was declared in 1975 and the government funded several women's health initiatives. (1) As part of one project, Dr. Cohen was invited to lead a workshop on women's health in Shelburne, Nova Scotia. While she visited, she was disappointed to realize that women living in the area did not have access to routine breast exams or pap smears. "There was no concept of 'women's health' and 'men's health' at the time, and [Dr. Cohen] believed that if you were a good doctor then you were a good doctor to both." (1) Her experience in Nova Scotia led her to question whether women's health needs were being appropriately met elsewhere in Canada. (2) A few years later, while on sabbatical in Australia, Dr. Cohen learned of an ongoing study investigating women's specific health needs in each state, which motivated her to organize a similar effort in Canada. (1,2) This eventually led to her to co-found the Women's

Health Office at McMaster University in 1991, which would become the nucleus of the women's health initiative in Canada. (1)

The first of its kind in any Canadian medical school, the Women's Health Office sought to educate and raise awareness of diseases that affected women differently, whether in prevalence, prognosis or therapy. (4) "When I went to medical school, the medical paradigm was that of the 70 kg male, who was white," she mentioned in one interview. "Everything in terms of dosage of drugs, in terms of prognosis, was based on that paradigm." (2) The Office strived to change this by organizing lectures on women's health to all members of the Faculty of Health Sciences, and by acting as a resource to university and community-based groups launching their own women's health initiatives. Dr. Cohen's persistence in pushing for the inclusion of women's health in the medical school curriculum eventually led to the creation of the Women's Health Inter School Curriculum Committee, a partnership spanning across five Ontario medical schools. (4) In establishing institutional recognition of women's health issues, Dr. Cohen challenged the male-centric paradigm in medicine and transformed the educational landscape for all health students in Canada.

Throughout her career, Dr. Cohen has focused on promoting an evidence-based understanding of women's issues both in health and in healthcare. As a researcher, Dr. Cohen has promoted women's health issues in areas such as breast cancer and domestic abuse. Within healthcare itself, Dr. Cohen has also played an important role in understanding the factors that have restricted equal access to the workplace. Issues of gender equality, discrimination, abuse, gender differences in practice, and the effect of having children on professional life are all areas in which Dr. Cohen has taken an active interest. (5,6,7) In her article titled Cracking the glass ceiling, she states: "We know the difference that women leaders make in professional education, research and women's health care. However, we must be more rigorous in defining and understanding the factors that influence the impact that women make, including their leadership style." (8) By shedding light on such issues, Dr. Cohen has helped pave the way for the many female physicians who followed after her.

Dr. May Cohen is now retired, but her legacy continues to impact the medical community. In light of her longstanding advocacy for gender equality in medicine, she was inducted to the Canadian Medical Hall of Fame in 2016. In 2017, she was named an Officer to the Order of Canada for her "exemplary leadership in the establishment and growth of the field of women's health in Canada". (4) In 2019, the world premiere of "The Gender Lady: The Fabulous May Cohen," an award-winning documentary chronicling her inspirational life, aired at the Toronto Jewish Film Festival. When asked about the documentary, she said, "I want to send the message that physicians have a social responsibility, and that is what I tried to do during my career in promoting women and women's health. These were all issues of social importance that went beyond what was good for only myself." (9) Through the many accomplishments in her life and career, Dr. May Cohen has certainly exemplified the pursuit of social justice, and is a role model for current and future physicians alike.

REFERENCES

1. Faculty of Medicine, University of Toronto. Women's Health Trailblazer: Dr. May Cohen, MD'55. [Online]. Available from: https://medicine.utoronto.ca/alumni/womens-health-trailblazer-dr-may-cohen-md55.

2. White Coat Black Art. [Online]. Available from: https://www.cbc.ca/player/play/1539433539961/.

3. Abortion rights: significant moments in Canadian history. [Online].; 2009. Available from: https://www.cbc.ca/news/canada/abortion-rights-significant-moments-in-canadian-history-1.787212.

4. Federation of Medical Women of Canada. [Online]. Available from: https://fmwc.ca/dr-may-cohen-named-as-an-officer-to-the-order-of-canada/.

5. Cook DJ,GLE,CMea. Discrimination and abuse experienced by general internists in Canada. J Gen Intern Med. 1995;(10): 565-572.

6. Woodward CA WAFBCM. Time spent on professional activities and unwaged domestic work. Is it different for male and female primary care physicians who have children at home? Can Fam Physician. 1996;(42): 1928-1935.

7. Cohen M FBWCGC. Gender differences in practice patterns of Ontario family physicians. Journal of the American Medical Women's Association. 1991; 2(46): 49-54.

8. Cohen M. Women's issues–Cracking the glass ceiling Cmaj 157.12 (1997): 1713-1714. CMAJ 157.12. 1997;: 1713-1714.

9. Depko T. Daily News. [Online]. Available from: https://dailynews.mcmaster.ca/articles/may-cohen-documentary-to-premiere-at-the-toronto-jewish-film-festival/.

Women in Medicine: Dr. Louise Pilote

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ABSTRACT

Always driven by a desire to understand, Dr. Louise Pilote (MDCM, MPH, PhD, FRCPC) can accurately be described as a lifelong learner. As the former Director of the Division of General Internal Medicine at McGill University, this clinician scientist is a Professor of Medicine at McGill and holds a James McGill chair. Her research interests include cardiovascular disease, specifically in women, as well as health service outcomes. Pilote's most recent endeavor focuses on the impact of gender on health outcomes on a globalized scale. Now a mother of five, Pilote shares her experience with integrating professional and personal life. She also discusses the intersection of medicine and feminism, while providing advice for the next wave of clinician researchers.

KEYWORDS
Internal medicine, feminism, gender equality

Dr. Louise Pilote, MDCM, MPH, PhD, FRCPC

For many physicians, the pathway towards medicine is marked by a familial role model or an early childhood aspiration. Coming from a sizeable family with seventy first cousins - none of whom were doctors - Dr. Louise Pilote (MDCM, MPH, PhD, FRCPC) jokes that she actually decided to become a physician after a year and a half of medical school. Believe it or not, the catalyst for Pilote's medical career can be traced back to a serendipitous bus stop encounter with two medical students in Sherbrooke. Always interested in both science and people, at the time Pilote was a keen CEGEP student who was applying broadly to journalism, physical education, nursing, and medicine. While on the bus,

she sparked up a conversation with the two medical students, and in doing so, was encouraged to enter the field she would grow to greatly impact. There is no denying that Pilote's career has been motivated by an intrinsic pursuit of knowledge - with a Masters of Public Health from Harvard, PhD in epidemiology from Berkeley, and post-doctoral fellowships in cardiology, health services research, and clinical epidemiology – all following her internal medicine residency at McGill. More recently, Pilote has gained recognition for her pioneering research on the impact of gender roles in disease, with the globalized research project GOING-FWD (Gender Outcomes INternational Group: to Further Well-being Development). If Pilote's academic and professional career were not impressive enough, now might be the time to mention that this clinician researcher has five children.

As medical students gain exposure and progress through their formative clerkship rotations, it is common to envision various futures. After a summer dissection program during her medical education at McGill, Pilote thought she was destined to become a surgeon. Following this, she discovered her love of the thought process inherent to internal medicine and was set to be an internist. Subsequently during her pediatrics rotation, Pilote's love for children and thinking amalgamated so perfectly, that she eventually ranked this specialty as her first choice. At the time, there was a two-week period between medical students submitting their rankings for residencies and programs releasing their respective rankings of students. It was during this period that Pilote was able to reflect and realize that although she loved pediatrics, a career treating sick children would be too emotionally difficult for her. She made the decision to call the program director of pediatrics and ask him to rank her last, in the hopes of beginning a residency in her second choice: internal medicine. According to the celebrated internist Pilote, she has never regretted her decision.

During her residency in internal medicine, Pilote sought out research exploring the intersection of medicine and society. In doing so, she readily admits that she would read the abstract, skip the methods section, and go straight to the discussion. Pilote, always motivated by a desire to understand, felt she could not truly appreciate the study design and statistical methods of these papers. And thus, she sought out the opportunity to expand her knowledge base and began her Masters of Public Health at Harvard. It was here, during her formative education in epidemiology, that Pilote's interest in global health took fruition. This interest was solidified following her masters, where Pilote spent a year in Ethiopia during Mengistu's dictatorship with a nine o'clock curfew. There, she taught the fundamentals of public health and epidemiology to local doctors, and worked together to develop action plans. Wanting to further develop her own capacity to conduct research, Pilote's next step was the Robert Wood Johnson Clinical Scholars Program - a post-doctoral fellowship in clinical epidemiology at Stanford. Here, her broad research endeavors included investigating the prevalence of tuberculosis infection in the homeless of San Francisco and comparing cardiology outcomes between Canada and the United States. Now a bona fide researcher in the making, Pilote chose to extend her stay in California and completed a PhD in epidemiology at Berkeley.

Initially, Pilote's research focused on health service outcomes, specifically the safety and efficacy of cardiac procedures and drugs. Roughly two decades ago, Pilote started wondering whether these types of outcomes differed for men and women. Around the same time, research began to emerge demonstrating differences, such as women receiving less cardiac care, and Pilote questioned – why? This served as the foundation for many of Pilote's research endeavors, which highlight women and vascular disease throughout the lifespan. Across Canada, there was a call for proposal to form a team of researchers focused on sex and gender, which Pilote gladly answered. One thing led to another, and the project GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond - PRemature Acute Coronary SYndrome) emerged. The term gender became very political, and Pilote recounts that of all the research she had done in her life, this is what she became known for. For her, it was like the community at large was telling her this research was important, and that it needed to be understood. In terms

of sex and gender differences, Pilote feels the balance has been pushed towards precision medicine - with a harsh focus on genetic and biological factors. In her opinion, by integrating gender-related factors - like roles, relations, and institutionalized gender - the pendulum shifts to incorporate BOTH biology and society in understanding disease. A true epidemiologist at heart, Pilote further sought to understand the impact of society itself on disease and disease outcome. This led to globalizing the research, with GOING-FWD. This personalized medicine project is funded by the Canadian Institutes of Health and Research (CIHR) as well as GENDER-NET, and includes a network of five countries (Austria, Canada, Cyprus, Spain, and Sweden). In essence, the aim of the research is to understand the impact of sex and gender on health outcomes, within a host of non-communicable diseases. In doing so, the goal is to personalize medicine and improve patient outcomes by tailoring disease prevention, presentation, severity, and even response to intervention, based on sex and gender.

Being raised with four brothers, Pilote says she always knew she wanted to have a big family. In her early thirties, she and her husband decided to start a family. Now with five children, the obvious question ensues: how does a professional woman balance life with a big family? There's no magic answer, but Pilote emphasizes, "you find a way of making it work." Whether it was nursing in the shower or presenting at a conference with her newborn snuggly secured to her chest, Pilote certainly made it work. She also stresses the importance having a supportive partner, and having help at home if needed. For Pilote, "if you don't have a well-organized situation at home, as a mother, you worry all day - if it's well organized, you leave in the morning [for work] with peace of mind and you can be present during the day." Pilote's children range in age from 16-23 years old, and it is obvious when she speaks of them that she is a very proud mother.

When asked her position on the intersection of feminism and science, Pilote replied, "as a feminist, I want to be a woman who does good science – that's my way of living my feminism." And there is no doubt that Pilote lives her feminism through research, as emphasized by her involvement in everything from women's cardiovascular health, to GENESIS-PRAXY, to GOING-FWD. In terms of women's career paths and development, Pilote acknowledges there are inherent structural issues, but also stresses the importance of identifying limitations as external versus self-imposed. She elaborates, "no one has said to me you cannot do this because you're a woman, but I have told myself I cannot do this because I'm a woman." As the former Director of the Division of General Internal Medicine at McGill University and a tenured James McGill Professor of Medicine since 2008, Pilote has certainly held powerful positions. However, she recognizes she may not have sought certain leadership positions because of her "traditional" roles and priorities. She proposes a paradigm shift: it is time to change leadership models – why should just one person sit at the helm? Pilote advises that leadership structures must change to incorporate women and their many roles, to promote research and career advancement.

With such a diverse background, it comes as no surprise that Pilote aims to inspire the next wave of clinician researchers to keep their minds open to discovery and creativity. She cautions not to rigidly pick one focus, as you never know which research endeavor will take off. As evidenced by Pilote's own research career, the community at large often serves to reinforce what is important, relevant, and needed. For future physicians, Pilote counsels to "always remember that society gave you such a privileged opportunity to help, always keep that in mind". This statement is currently echoed by Pilote's own dedication to her field, as she selflessly works at the frontline of the COVID-19 pandemic.

Women in Medicine: Dr. Liane Feldman

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ABSTRACT

Dr. Liane Feldman MDCM, FACS, FRCS has been making waves in the world of surgery through her accomplishments, innovative research, and mentorship for over 30 years. From her beginnings in the Cognitive Science department at Brown University to her current position as Edward W. Archibald Professor, Dr. Feldman discusses her path to becoming the first woman Surgeon-In-Chief of the MUHC.

KEYWORDS
General surgery, Women in Medicine

Born and raised in Montreal, Dr. Liane Feldman dreamed of becoming a physician as far back as she can remember. Both her father's career as a psychiatrist, as well as the extraordinary depiction of wartime doctors on television's *M*A*S*H*, fueled her journey towards becoming the McGill University Health Centre's (MUHC) current Surgeon-in-Chief. Dr. Feldman is the youngest person, and the first woman to hold this position at McGill University, making her success both unprecedented and historic.

However, Feldman's path to surgery was not a straight arrow. She first pursued an undergraduate degree in Cognitive Science at Brown University, which introduced her to the world of neuroscience and linguistics. Upon entering medical school at McGill University, she was leaning towards a medical specialty or neurology, given her background. As a medical student, Feldman loved all the different fields in which she was rotating. However, a spark was lit during her last block of the curriculum: General Surgery. She felt a connection

with the hands-on nature of the specialty, the team atmosphere, and most importantly, she felt at home in the operating room (OR).

With mentors in General Surgery, such as Dr. Gerald Fried and Dr. Lawrence Rosenberg, the choice between internal medicine and surgery was easy–"I liked the idea of being able to take care of the total aspect of the patient," says Feldman. She thrived on treating the sickest patients and challenged herself to learn how to handle any situation. In other words, whether it was managing trauma resuscitations, critically ill patients, or essentially curing patients of their cancer, the versatility of the program spoke to Feldman's personality. "Things that I found stressful were the sorts of things I wanted to master," she says.

She went on to complete her residency in General Surgery at McGill. The landscape of the program, while male-dominated at the time of her training, has changed significantly over the years–there are now more women in the field. Nevertheless, Feldman had a number of female role models in surgery at McGill, including her program director, Dr. Judith Trudel. She saw them balance important careers and family life, including pregnancy. In Feldman's day, leading women challenged the field to achieve equal representation in medical school, residency classes (even in surgical fields), and amongst professors. Today, the focus has shifted to the leadership positions in our medical institutions. When we look at these positions, why are women so underrepresented?

Being married to a corporate lawyer broadened Feldman's perspective on this issue, which she views as societal and not only specific to medicine. Recognizing the problem is the initial step, but trying to identify the barriers is another: why is the gender disparity so apparent in positions of power? Feldman replies: "I think that's a great question. I think it's subtle." Feldman feels that acknowledging our inherent limitations is essential to increasing the number of women in leadership positions. Family life and clinical work will always take priority, because "they are very in your face," she says. To be a competitive contender for leadership positions, much additional work has to be done such as leading research programs, being involved in specialty societies, speaking at conferences and building an international reputation. Feldman emphasizes that none of this is possible without mentorship and the support from colleagues, family, and friends, as well as the importance of inspiring role models.

Feldman is motivated by the increased awareness around gender equity in medicine, but maintains that it is not just about women. It is about inviting less traditional voices, including all underrepresented minorities, in general, to the conversation. In her opinion, this is the key to making medicine better: "We want to attract the best people, we want to keep them engaged, [and] we want to keep them productive, so that the profession benefits and our patients benefit; so [that] we innovate and move forward."

Innovation cannot occur without research. Dr. Feldman is heavily involved in improving patient care, as well as the quality and efficiency of various surgeries. Her most recent feat involved designing the "Enhanced Recovery After Surgery" program, also known as ERAS, as part of each patient's perioperative pathway at MUHC. This program aims to improve patient outcome by reducing the post-operative hospital stay, significantly mitigating complications such as infection. Additional projects include surgical education in minimally invasive techniques as well as working on various strategies to improve surgeons' performance in the operating room using video-based assessments. An ambitious endeavor, she admits, as surgeons are often trained to adopt traditional attitudes towards the practice, including their surgical techniques. In following with her strive for challenge, she aims, through these projects, for a change in culture.

Dr. Feldman is thriving in her new position and sees it as an opportunity to work with every team member involved in surgical patients' care including nurses, anesthesiologists, as well as administrators. She admits that her new set of responsibilities can be stressful at times, but does she enjoy it? "Absolutely!" she says.

The arrival of COVID-19 has added an additional layer of complexity to her new position. Feldman describes this period as a true "trial by fire," but the pandemic is a perfect burning platform to expose the "weak

points" of the healthcare system and force necessary change. Feldman is convinced that COVID-19 will ultimately make the department and the hospital stronger. In the General Surgery department, elective surgeries were cancelled to increase bed availability for COVID patients. Feldman also participated in COVID-19 ward duties, and maintains that the Herculean efforts undertaken by the staff in the face of the pandemic were remarkable. When it comes to urgent surgeries, her team formed a committee, including a clinical ethicist, with the objective of creating protocols to establish OR priority. Feldman is proud of the team's ability to provide continued care to patients requiring immediate attention, even in the face of an unfortunately ever-lengthening waitlist.

It was a pleasure and a privilege to chat with Dr. Feldman; her immense passion for surgery is palpable. As a kid, she dreamed of helping people. She mentions that she occasionally needs to pinch herself to make sure she is awake. She recognizes that being a surgeon comes with many implications for family and lifestyle, in addition to the added weight of the responsibility of the job. "Being a surgeon can be devastating sometimes [...] we feel a great responsibility when complications happen and things don't go well." Despite these challenges, Feldman describes that the importance of a surgeon's impact on a patient's life is indisputable and ultimately, she has no regrets. She encourages young women to pursue what captivates their imagination and sparks their curiosity to persevere over the long run. As words of wisdom, Feldman encourages young women (and anybody, really) to follow their heart.

As my final question to Dr. Feldman, I asked what aspect of her career has given her the most sense of accomplishment: "Mentorship. Teaching generations of surgeons to become the best they can be is what I'm most proud of."

Women in Medicine: Dr. Danielle Martin

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ABSTRACT

Dr. Danielle Martin is an Associate Professor at the University of Toronto and Executive Vice President and Chief Medical Executive at Women's College Hospital in Toronto, where she is also a practicing family physician. Her career epitomizes an idea that is often discussed in medical training, but rarely manifests in practice: physicians are both advocates for individual patients and stewards of public health equity at a systems level. Dr. Martin has dedicated her career to improving and strengthening Canada's universal health care system. She is a public leader in the ongoing debate about health care privatization and founded the organization Canadian Doctors for Medicare. Notably, Dr. Martin spoke about Canadian health care and advocated for single-payer health care in a widely publicized US Senate hearing led by Senator Bernie Sanders. She has also published a book titled, Better Now: Six Big Ideas to Improve Health Care for All Canadians, which breaks down complex health policy into six actionable steps in order to improve the health care system for all Canadians. She continuously advocates for public involvement in health policy through research and public outreach and is a role model for young physicians aspiring to leadership roles in health and health care policy, while simultaneously pursuing a career in clinical practice. In fact, doing both provides a unique framework for improving the individual wellbeing and health of Canadians.Dr. Martin believes that advocacy is a skill that requires practice and training; she advises young trainees that the time to start is now.

KEYWORDS
women, leadership, feminism, public health

Dr. Danielle Martin, MD, MPP, CCFP, FCFP, Associate Professor at the University of Toronto Department of Medicine and author of the book, "Better Now: Six Big Ideas to Improve Health Care for All Canadians"

"Being sick is bad enough without worrying about having to pay for your care. Medicare is a work in progress, but it's a work worthy of our greatest efforts. It represents a promise to be the kind of country we can be proud of." Fulfilling the promise of universal access to free healthcare services has provided the impetus for Dr. Danielle Martin's career as a practicing family physician, hospital administrator at Toronto's Women College Hospital, associate professor at the University of Toronto, and author of the book *Better Now: Six Big Ideas to Improve Health Care for All Canadians*.

Dr Martin's life-long commitment to improving health care for all Canadians was first inspired by her own family's experience. Her grandparents arrived in Montreal as new immigrants long before Canada's creation of an accessible, single-payer medical system. Soon after their arrival, the family had to contend with her grandfather's illness and eventual death at the age of fifty-four. Their subsequent journey through a private-payer health care system created mounting healthcare bills and crippling debt. Her strong sense of social justice was further motivated by her upbringing in downtown Toronto, where she grew up alongside family and friends from diverse backgrounds.

Dr. Martin was the first person in her family to become a physician – although the decision to pursue medicine came relatively late in her academic career. She completed her undergraduate degree in Biochemistry at McGill University under the assumption that she would pursue a career in science. Somewhat ironically, a decision to join the McGill Debating Union "turned out to be at least as formative as her formal education." Martin says that time spent interacting and socializing with political science and philosophy students taught her how to construct and articulate a well-reasoned argument. These skills would ultimately serve her well in her role as a major player in the ongoing, national health care debate on how to reform and improve our existing single-payer system. Post-degree, Dr Martin's interest in policy led her to Ontario, where she eventually found herself working in health care policy. She learned how governmental decisions were made and the importance of physician advocacy in this process. At that point, Martin realized her passion for health care and systemic improvement, and she decided she should pursue a career in medicine.

Dr. Martin's advocacy work directed at strengthening Canada's single-payer system started early in her career. After completing her undergraduate medical degree at Western in London, Ontario, Dr. Martin then returned to Toronto for her residency at St. Michael's Hospital where "inner city medicine and advocacy were core to the philosophy of the education program." This philosophy suited her— "I was a system-oriented person before I was a clinician, and I have always thought about my clinical work through that lens." Dr. Martin's early work as a clinician in rural and remote communities also provided important learning opportunities–at that point in her career, she was speaking out about the promise of public healthcare and the need to revitalize our system.

These early work experiences prepared Dr Martin for her current roles as both a public health advocate and a leader at Women's College Hospital, where she works as the Executive Vice President and Chief Medical Executive, as well as an academic family physician. A number of extraordinary mentors also played a vital role in getting her to her current position, including her mother who modeled a successful life balance of career and family. Dr. Martin shares credit with her other mentors who supported her in establishing the Canadian Doctors for Medicare (CDM) organization in 2006, encouraged her to pursue a master's degree in public policy, and offered Martin her first leadership roles. She appreciates that many of her mentors, who were leaders themselves, were able to invest time and create space for her in their systems. This ability to create "system space" taught Dr. Martin an invaluable lesson: "systems are critical, but they are not built for individuals." Martin believes that

systems need to be built with flexibility and filled with adaptable leaders, so that even those who do not fit the mould can still be successful. This resonates in Martin's core philosophy of Canadian health care: "We need to build a system that is flexible and meets the needs of all Canadians, regardless of what they can bring to the table."

This philosophy on systems thinking certainly came to the foreground in 2014, when Dr. Martin received a phone call that would change the course of her career: US Senator Bernie Sanders found Dr. Martin through the CDM, which is now a nationwide organization that advocates for the strengthening and improvement of universal publicly funded healthcare in Canada. Senator Sanders asked Dr. Martin to speak at a Senate hearing about what the American health care system could learn from other countries about universal health care coverage and cost control. The five minutes that Dr. Martin had to discuss what the US could learn from Canada landed her on the front pages of Canadian and international news and transformed her career such that public engagement and education became central to her work.

As a result of this US senate hearing, Dr. Martin's role became increasingly public facing, eventually culminating with her book, *Better Now: Six Big Ideas to Improve Health Care for All Canadians. Better Now* was published in 2017 as Dr. Martin's response to the lack of real change taking place in an environment where too much of the conversation about health system improvement was happening cyclically and amongst the same people. The book was written to ignite a passion for change in the Canadian public, especially amongst those who are concerned about our healthcare system, but who are not normally involved in the decision-making process. Dr. Martin describes her "ideas" as the "greatest hits" that would have the biggest impact on improving health care.

Since *Better Now* was published, there has been some progress towards a better healthcare system. However, the current COVID-19 pandemic has shone an intense light on the existing shortfalls of our health and social services, reinforcing the need for the policies that Dr. Martin spent her career advocating for. Across the country, thousands of people have lost jobs and the security, healthcare and social benefits that accompany them. As Dr. Martin points out and addresses in her book, the "CERB (Canada Emergency Response Benefit) that has been put in place during the pandemic is similar in principle to the notion of the Basic Income Guarantee"–a policy that recognizes the huge role that social and economic circumstances play in determining the health of populations. Indeed, COVID-19 underscores the need for action to reduce the inequities in our healthcare system that predate the pandemic and are only now being exacerbated. Also, the pandemic will inevitably result in longer wait times for many elective procedures that have been cancelled. This highlights another "big idea" described in Dr. Martin's book regarding the reorganization of healthcare delivery to reduce wait times and improve the quality of care being delivered. As she has famously said, "Sometimes it's not actually about the amount of resources that you have but rather about how you organize people in order to use your queues most effectively [...] when you try to address wait times, you should do it in a way that benefits everyone, not just people who can afford to pay."

Dr. Martin acknowledges her many forms of privilege–her status as a white, English-speaking person and physician–but says she still experienced push-back at times during her career and felt that her views were taken less seriously than those of her colleagues as a result of being a woman, a family doctor, and a public-facing researcher. She has worked to address this by being "explicit in her values and the evidence issues she cares about, relying on those things that are harder for people to discount." Dr. Martin recognizes that we still have a long way to go in order to address equity in leadership in medicine–not just across the gender spectrum but also in diversity in race, ethnicity, and belief. "Gender equity is important, but it isn't enough if it isn't inclusive," she says and adds that she hopes to see positive change arise from the work being done across the country to address anti-Indigenous and anti-Black racism in medicine and beyond.

Dr. Martin has worked tirelessly to advocate for good healthcare that is accessible to all, and her career illus-

trates the necessity of assuming a bifocal lens. To create real change in medicine that benefits everyone, one needs to see patients both as individuals, as well as how they fit into a larger system working to improve the health of all people. Dr Martin urges young physicians aspiring to be policymakers and hoping to make changes in our health system that the time is *now*–"You can be an advocate now, your voice matters. The sooner you get on the issues you care about, the more skills you will amass. Advocacy is a skill set and it requires that you train just as you do for your clinical work."

Women in Medicine: Dr. Theresa Tam

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ABSTRACT

Canada's Chief Public Health Officer, Dr. Theresa Tam (BMBS (UK), FRCPC) attended medical school in the United Kingdom before immigrating to Canada where she trained in pediatrics and specialized in infectious disease. She has maintained a *'pourquoi pas'* attitude throughout her career that has helped her realize her vocation in public health, gain experience in the healthcare field—both around the globe and on Canadian soil—and advance into prominent leadership positions. Today, as Canada's Chief Public Health Officer, known colloquially as Canada's Top Doctor, Dr. Tam has been thrust into the spotlight as a result of the COVID-19 pandemic. This article outlines her exciting career trajectory and explores the challenges she faces while informing Canadians of guidelines for staying healthy during the pandemic.

KEYWORDS
public health, COVID-19, pandemic, gender equality, feminism

Early life and career

Born in British Hong Kong, Dr. Theresa Tam emigrated with her parents at a young age to the United Kingdom (UK), where she attended a small all-girls boarding school. While she was passionate about the humanities, arts, and science alike, she had a particular affinity for biology. This was in part because Dr. Tam felt supported and inspired by her biology teacher, Mrs. Bradley, who she regards uniquely as "in her own rights and fame, an expert in ferns." Dr. Tam was one of the first students in her school's history to become a physician. "It was an unusual choice," she said, "but I thought [...] why not have a go?"

Interestingly, Dr. Tam was not always on track to be-

come a high-profile agent of public health; in fact, she initially hoped to become a general surgeon. As Dr. Tam explained, students in the UK medical school system at the time were required to complete a three-year undergraduate degree combined with research, followed by a two-year pre-residency internship in a specific field. (1) Dr. Tam chose to study biochemistry with a research focus on carcinogenesis. She then opted for general surgery and internal medicine for her internship. When her family moved to Alberta, Dr. Tam planned on applying for a surgery residency, however, she knew acceptance would be unlikely as a foreign medical graduate. Instead, she applied for a residency in pediatrics and considers herself fortunate to have been accepted to attend the University of Alberta. Following her residency, she completed a fellowship in pediatric infectious disease at the British Columbia Children's Hospital—a path that ultimately changed the course of her career.

Vocational change

Prior to her fellowship, Dr. Tam had little exposure to public health. In the infectious disease program, her mentors, who were experts in vaccinology, exposed her to their work at The Vaccination Evaluation Center and the many clinical trials in which they were involved. This piqued her interest such that she recalls she "actually shifted from a more research and clinical interest into [...] public health." She promptly joined the Canadian Field Epidemiology program, where one of the first outbreaks she tackled was a highly virulent strain of influenza. While she had a hand in treating many subsequent outbreaks around the globe, she retained a particular affinity for that disease. As Dr. Tam stated, "influenza really never left my career; it became my favourite virus, as it were."

Owing to the strong expertise she had accumulated, Dr. Tam was able to accept a position at the Public Health Agency of Canada (PHAC). At the time, she was already working as an attending pediatric infectious disease specialist at the Children's Hospital of Eastern Ontario. The workload of two full-time jobs was heavy and unsustainable, and Dr. Tam knew "[she] just couldn't do both." She loved working at the bedside of patients in the Emergency Department and the Pediatric Intensive Care Unit, making it difficult to hang up her stethoscope and leave her clinical duties behind; nevertheless, she chose to pursue her vocation in public health. Within the PHAC, Dr. Tam continued to advance into leadership roles, becoming Deputy Chief Public Health Officer, Assistant Deputy Minister for Infectious Disease Prevention and Control (2), and in 2017, Chief Public Health Officer (CPHO), the position which she currently holds.

Career development

Dr. Tam credits her success partly to her peers who pushed her out of her comfort zone, while admitting that "it doesn't usually take too much convincing, and I [...] take on the next challenge." In fact, Dr. Tam explained that she never aspired to any position, including her current one. "The bottom line is there was really no planning," she explained, "given my career trajectory, I kind of feel like I was building up to this job." The ease with which Dr. Tam accepts new challenges led her to the trenches of many global health initiatives, including Polio eradication in Bangladesh. (3) Dr. Tam proudly stated that she was "the first non-American team member of the Stop Transmission of Polio Program" of the Centers for Disease Control and Prevention. Leading up to her role as CPHO, she was at the forefront of the Canadian responses to multiple communicable disease outbreaks, including H1N1 and SARS, and acted as an international expert to the World Health Organization. (2) In 2006, while acting as the Director of the Immunization and Respiratory Infections Division and Co-Chair of the Pandemic Influenza Committee, she helped update the Canadian Pandemic Influenza Plan for the Health Sector. (4) This report was written after the SARS pandemic, which hit Toronto in 2003, and has been updated several times since, now including advice based on the H1N1 outbreak in 2009. (5)

In addition to protecting Canadians against disease outbreaks, Dr. Tam has made it her goal to champion the reduction of health disparities in key populations

in Canada. She has met Canadians face to face in order to better understand their plights, investigate disparity in public health outcomes, and gain a more intimate and informed perspective on the stigmatization and discrimination that exists within Canada. Dr. Tam's commitment to listening to the public, exemplified through her discussions with Indigenous communities and people suffering from addiction during the opioid crisis, has allowed her to make informed policy recommendations to people who have the power to take action and create change. She remarked that as CPHO, she has the "very direct and very frequent opportunity to discuss important public health issues with the decision-makers of the country and around the world." This places her in an ideal position to incite systemic change.

Fighting for equity

Since she was appointed, Dr. Tam has been striving to make Canada's healthcare system more equitable and inclusive. "When I became the [CPHO]," she reflected, "my vision was to do whatever I can to champion a more inclusive society, a more inclusive health system, be a voice of inclusion. And so, health equity is very much run through horizontally in everything that I do [and] gender equity is a part of that whole picture." In fact, in her 2019 CPHO Report of the State of Public Health, titled 'Addressing Stigma: Towards a More Inclusive Health System,' (6) Dr. Tam outlined suggestions for improving gender equity within the healthcare system. She stated, "Just like any system, quite frankly, [there exists] gender stereotyping, inequities at certain levels of leadership, [and] harassment in different ways. [...] We have to admit to the fact that there is stigma and discrimination in the health system." Recognizing that medicine used to be quite male dominated, she explained that things are trending towards equality. Now, men are outnumbered by women in terms of both medical students and practicing physicians, and we are seeing more women in leadership roles. In fact, until very recently, the health of Canadians was managed at the federal level by three women: Dr. Tam as the CPHO, Patty Hajdu as the Minister of Health, and Tina Namiesniowski as the President of the PHAC (who recently stepped down in late September, being replaced by Iain Stewart). (7, 8) When asked if she considers herself a feminist, Dr. Tam stated she envisions the future of feminism as "really creating the kind of society in the world where all people have the support or the chance to realize their full potential, which actually is the underlying objective of health equity."

Pandemic response

While undoubtedly qualified to be CPHO during a viral pandemic, Dr. Tam does not take this role lightly. In her Report on the State of Public Health in Canada in 2019, (6) Dr. Tam referred to the post-social media world as "the age of misinformation and disinformation," which complicates her role of communicating public health decisions to the public. During the current pandemic, she states, "it's quite difficult actually to manage the communications, and people can slice and dice and put their own perspectives on what you just said, whether it's actually in line with your intent." To combat this, she has strived to maintain cohesion in the general advice given to the public despite any jurisdictional differences. Moreover, Dr. Tam has been criticized for her early response to the pandemic, in particular for underestimating the spread and impact that COVID-19 would have both nationally and internationally, and for cautioning the use of masks. She explained that her advice was evidence-based in the context of rapidly evolving information and a paucity of data early on. "It is challenging trying to communicate the fact that there are things that we know, things that we don't know, and the fact that we may have to change our public health advice at the time," Tam explained. She finds herself reflecting on the decision-making process and wondering, 'is this the best way to position something?', 'how can I do better in terms of getting consensus on a certain area?'" While it may seem to the public like Dr. Tam is holding Canada's weight on her shoulders, she is not solely responsible for decisions made as part of the COVID response. "The decision-makers are our elected officials," she explained, "the people who have the actual public health authority

to act are at a different level of government." So, while Dr. Tam is "an advisor, [...] a champion, a leader, [and] a convener," she does not have the final say in COVID-related decisions.

Despite this sharing of responsibility, Dr. Tam admits the COVID response has taken its toll on her and on others in public health. As her role in this crisis has become more demanding, she has relied upon a network of family, friends, and colleagues. Her parents have remained healthy and supportive throughout the pandemic, and her nieces and nephews have continued to inspire her as they always have. "I am [...] Auntie Theresa to many," she said proudly. Dr. Tam recognizes the importance of balance in her life and as such, she tries to make time for her hobbies: she enjoys running and fancies herself "somewhat of an ornithologist." In light of the second wave being well under way, maintaining a sense of normalcy remains as important as ever.

We have come to know Dr. Tam as a result of her role as CPHO during the coronavirus pandemic, but she had been quietly advocating for improved public health long before COVID hit. Although she found her vocation relatively late in her career during her fellowship, she has no regrets, only aspirations. "I really want to finish my career seeing polio actually eradicated," she said. When asked to offer advice to those interested in a career in public health, Dr. Tam offered the following insight: "it is very exciting if you like complexity, if you like a job where the population is your patient. Even though you can't see instantaneous outcomes, it's all worth it in the end. [...] The future is prevention, and there needs to be a massive investment in public health, of which the people who work in public health is the biggest investment." Dr. Tam ended the interview by saying "go with the flow; don't sweat it too much," which is advice that seems to have served her well throughout her career and will surely continue to do so.

REFERENCES

1. University of Nottingham Medical School: History [Internet]. Nottingham: The University of Nottingham; [Date unknown] [cited 2020 Oct 5]. Available from: https://www.nottingham.ac.uk/manuscriptsandspecialcollections/collectionsindepth/university/university-collection/university-of-nottingham-medical-school.aspx.
2. Dr Theresa Tam, BMBS (UK), FRCPC [Internet]. Geneva: World Health Organization; [Date unknown] [updated 2020; cited 2020 Oct 5]. Available from: https://www.who.int/about/who_reform/emergency-capacities/oversight-committee/theresa-tam/en/.
3. Global Immunization: STOP [Internet]. Atlanta: Centers for Disease Control and Prevention; [Date unknown] [updated 2020 Apr 24; cited 2020 Oct 5]. [Available from: https://www.cdc.gov/globalhealth/immunization/stop/index.htm.
4. Tam, T., Grimsrud, K. The Canadian Pandemic Influenza Plan for the Health Sector [Internet]. Toronto: Longwoods Publishing Corporation; 2006 [cited 2020 Oct 5]. Available from: https://www.longwoods.com/articles/images/Canada_Pandemic_Influenza.pdf
5. Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector [Internet]. Ottawa: Government of Canada; 2018 [cited 2020 Oct 5]. Available from: https://www.canada.ca/en/public-health/services/flu-influenza/canadian-pandemic-influenza-preparedness-planning-guidance-health-sector/table-of-contents.htmlpre.
6. Tam, T. Addressing Stigma: Towards a More Inclusive Health System [Internet]. Ottawa: Government of Canada; 2019 [cited 2020 Oct 5]. Available from: https://www.canada.ca/en/public-health/corporate/publications/chief-public-health-officer-reports-state-public-health-canada/addressing-stigma-toward-more-inclusive-health-system.html.
7. Public Health Agency of Canada [Internet]. Ottawa: Government of Canada; 2020 [updated 2020 Mar 7; cited 2020 Aug 20]. Available from: https://www.canada.ca/en/public-health.html.
8. President of the Public Health Agency of Canada: President Iain Stewart's biography [Internet]. Ottawa: Government of Canada; 2020 [updated 2020 Sept 28; cited 2020 Oct 5]. Available from: https://www.canada.ca/en/public-health/corporate/organizational-structure/president.html.

ORIGINAL RESEARCH

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Impact of a family medicine-based transitional care intervention on readmission and length of stay: a pilot study

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ABSTRACT

Transitional care interventions, often led by hospital specialists, have mixed impact on reducing readmissions. Interventions led by family physicians may be more promising. The objective of this study was to evaluate the impact of a family-medicine-based intervention in reducing the incidence of emergency department (ED) visits, hospital readmissions and the length of stay (LOS) of older patients. A quasi-experimental pilot-study was conducted at a Family Medicine Group (FMG) in Montreal. Thirty-five patients discharged from the FMG-affiliated hospital between July 2014-2015 were compared to 68 historical controls discharged from the same hospital one year prior. Inclusion criteria were: 65+ years, rostered at FMG, high-risk of readmission; and discharged to home/senior residence. Patients' charts were reviewed to determine a composite outcome of all-cause rates of acute hospital use (ED visit/hospital readmissions) and LOS at 30, 60, 90 and 180-days post-discharge. We found no statistically significant differences in acute hospital use rates between groups. LOS was statistically significantly shorter at 90- and 180-days for patients compared to controls: Incidence Rate Ratio (95% Confidence Interval) at 90-days: 0.66 (0.64-0.69) and at 180-days: 0.49 (0.43-0.55). Our study provides support to the impact of a family-medicine-based transitional care intervention in reducing the LOS of vulnerable older patients readmitted to hospital.

KEYWORDS

Transitional care; vulnerable populations; family practice

1 | INTRODUCTION

Older patients transitioning from the hospital to home are at risk of having complicated care transitions, with more readmissions, longer stays, and even death (1). These poor health outcomes result from poor coordination and communication during these transitions (2, 3). In response to this situation, transitional care interventions, which are defined as a "set of actions designed to ensure the coordination and continuity of healthcare as patients transfer between different locations or different levels of care within the same location" have been implemented (1). These interventions may have a positive impact on reducing hospital readmissions (4, 5) and mortality in older patients after hospital discharge (6), but some interventions have not shown success.

Multiple hypotheses have been suggested in the literature as to why some transitional care intervention are more effective than others in reducing readmissions, mortality and length of stay (LOS) when readmitted. First, it is not yet known in which settings transitional care interventions could provide better results (7). In fact, a systematic review concluded that there is no evidence to support the implementation of hospital-based transitional care interventions (8). It is possible that a family medicine-based transitional care intervention would be more successful to reduce older patients' service use (9). Indeed, a transitional care intervention based in a primary care team, more specifically led by a Virtual Ward (VW) physician and a VW nurse (acting as a case-manager) from the primary care team where the admitted patient is registered, would ensure that the usual care providers are involved early on and throughout the transition by improving communication between the usual family physician and the hospital. Better communication between the usual family physician and the hospital could help reduce short-term readmissions (10). The usual family physician is equipped with longitudinal and comprehensive understanding of the patients' needs and is trained in managing community-based chronic diseases, offering a significant benefit to the care provided by an unfamiliar hospital internist. Other components for a successful transitional care intervention to reduce short-term readmissions include a home visit within three days after discharge (10) and should begin at the pre-hospital discharge (11).

Therefore, we designed a family medicine-based transitional care intervention, in an attempt to increase and strengthen the engagement of usual care providers working in the same primary care team. The main objective of this pilot study was to evaluate the impact of our family medicine-based transitional care intervention (described in the methods below) on ED visits or hospital readmission rates and LOS of older patients at risk for readmission. A more detailed description of the family medicine-based transitional care intervention is described in our companion paper (12). We hypothesized that patients in the intervention group would have fewer ED visits, fewer hospital readmission rates and shorter LOS than patients in the control group.

2 | METHODS

2.1 | Design and Setting

A quasi-experimental pilot study with an independent historical control group was used to determine the impact of the intervention on hospital readmission rates and LOS.

A participatory approach was used to root the primary care practice-based study in action and make it meaningful for clinicians, patients and caregivers (13). Participatory approach is an approach of conducting research by actively involving all relevant stakeholders, in this case clinicians, patients and caregivers, throughout the research project (13). Indeed, patients and caregivers were involved in the development of the clinical intervention and the care process indicators. This study was initiated by a family physician and nurse from the Herzl Family Practice Center, at the Jewish General Hospital (JGH), in Montreal, Canada. The Herzl Family Practice Center is a McGill University-affiliated primary care interdisciplinary team located in Montreal, Quebec. In addition, the clinic is attached to a hospital where patients can be hospitalized in a family medicine ward and cared for by doctors who also work at the primary

care clinic. This project was a practice-based initiative (14), in that it was the VW clinicians who contacted the McGill University researchers to evaluate their transitional care intervention. Together, clinicians and researchers served on a "steering committee", who managed the course of the research project, on a weekly basis throughout the study.

| Intervention

We built upon the VW model (5, 15-17), in which an interdisciplinary team, usually located in a hospital, coordinates care, meets daily, facilitates communication between the hospital and the usual providers, and offers a single point of contact for the patients. In contrast to basing a team within the hospital setting and the intervention at the primary care setting, our design was expected to strengthen communication with the usual care providers and their involvement. Furthermore, the patients' discharge plan was initiated during hospitalization.

The intervention was divided in three clinical modules to facilitate its potential implementation in other clinics. Module 1 was composed of the selection process and hospital discharge plan. A designated VW nurse (case manager) from the Herzl Family Practice Center visited the family medicine ward daily and selected patients based on their LACE index (18), which identifies patients at risk for readmission or death within thirty days of discharge. The LACE index was chosen because it is well used and validated (18) and to be in line with the other Canadian Virtual Ward intervention, based in hospital (15). The index is based on four indicators: LOS of the index admission, acuity of the admission, co-morbidity index, and number of ED visits within the last 6 months. LOS of index admission was estimated as the discharge plan was prepared. As per recommended, patients who scored equal or higher than 10 on the LACE index, indicative of a high risk of readmission, during their daily visits to the family medicine ward were approached and the intervention was explained (18). The VW nurse scheduled follow-up appointments with the patients' usual family physicians, residents, and nurses at the Herzl Family Practice Center and elaborated the discharge plan. The caregivers, when available, were involved throughout the period the patients were admitted into the VW. The discharge plan occurred while the patients were still hospitalized.

Module 2 was composed of case management. The VW nurse provided post hospital discharge follow-ups by phone (the initial follow-up was done within 72 hours post hospital discharge), assessed the patients and caregivers' needs and symptoms, shared educational information, reviewed the patients' medications, and confirmed follow-up appointments with patients and caregivers and the usual family physicians, residents, and nurses at the Herzl Family Practice Center. The VW nurse was available to the patients and caregivers by phone five days a week. The VW nurse also initiated communication with community services, such as home care services, and organized home visits by the usual family physicians, residents, and other health professionals if needed.

Module 3 was composed of weekly multidisciplinary rounds. Weekly meetings with the usual family physician, resident, the VW nurse and VW physician, social worker, and pharmacist were organized to review each VW patient's medical history, medication list, and medical and social issues. Adjustments in diagnosis or treatment were made, and patient, caregiver, usual family physician, community pharmacist, and home care services were notified. Finally, a discharge plan from the VW was organized when the situation became stable. These three modules are described in our companion paper (12). The intervention started on July 1st, 2014 with internal funding from the director of the Herzl Family Practice Clinic.

2.2 | Participants

The VW group consisted of all patients admitted in the family medicine ward at the JGH, between July 1st, 2014 and June 30th, 2015. Inclusion criteria were: having a family physician at the Herzl Family Practice Center, being 65 years old and over, being at risk for readmission

(LACE 10), and being discharged to home or senior residence. All patients admitted to the ward who met the criteria were contacted by the VW nurse and, upon their consent, were offered to be included in the intervention group.

A historical control group consisted of all patients discharged from the same ward between July 1st, 2013 and June 30th, 2014. The same inclusion criteria were used. All patients admitted to the family medicine ward and satisfying the criteria were included in the control group except for patients who participated in the intervention group to ensure independent groups. Consent from the control group was not required.

The study and consent forms were approved by the Research Ethics Office of the JGH.

| Data Collection and Outcomes

A retrospective chart review of the Electronic Medical Records (EMR) of patients in VW and historical control groups was used to measure the primary outcomes: a composite outcome (ED visits and/or hospital readmissions) and LOS. Both outcomes were measured at 30, 60, 90 and 180 days post discharge. For each patient readmitted, LOS was calculated as the cumulative number of days for all hospital readmissions, where an ED visit counted as one day, and any LOS started the day of admission to ED and ended the day of hospital discharge.

2.3 | Analysis

Descriptive analyses were performed on patients' characteristics and study outcomes. Care process descriptions were examined over the length of stay in the VW program for the intervention group. Unadjusted proportion of patients with at least one readmission and average LOS were calculated. Poisson regressions, controlling for exposure time, were performed for readmission at each time point. Given that at least 12 VW patients (34%) were not readmitted during the study period, zero-inflated Poisson regressions, controlling for exposure time, were performed for LOS at each time point. We were not able to adjust for age, sex, and LACE score given the limited sample size. However, sensitivity analyses were performed adjusting for age, sex, and LACE scores for each outcome. The care processes of the intervention were refined as the study progressed, therefore the number of care processes performed at the beginning of the intervention were not fully implemented and this could create a "ramp-up" effect, whereby the impact of the intervention would be stronger in patients recruited later on. Therefore, we verified the potential existence of a ramp-up effect, and its impact on our results by performing another set of sensitivity analyses. Ramp-up effect was calculated as the number of days between the start of the intervention and the patient recruitment in the intervention. Finally, to evaluate the potential adverse effect of the intervention on mortality, we performed Kaplan-Meier survival analyses, using Log rank statistics to compare the groups on mortality rates at 90 and 180 days. All analyses were performed with Statistical Package for the Social Sciences (SPSS; IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp).

3 | RESULTS

Fifty VW patients and 89 control patients were examined for eligibility. Of these, 15 VW patients and 21 control patients were excluded due to transfer to long-term care or rehabilitation services, or refusal. A total of 35 patients in the VW and 68 in the control group were included in the study (Figure 1).

The demographics for the 35 VW patients and 68 controls are in Table 1. Overall, no clinically meaningful differences at inclusion were observed in terms of age, sex distribution, LACE score, or discharge destination. On average, the LOS in the VW intervention group was 48.1 17.2 days, during which the VW team provided transitional care as described in the intervention. The proportion of patients who were contacted by the VW nurse within 72 hours post discharge was 54.3%; this proportion climbed to 80% if we considered a 4-day

timeframe. More details describing the diverse care processes provided to the VW group is given in Table 2.

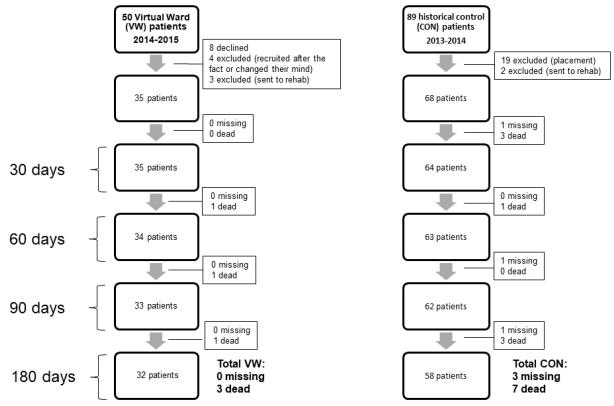

FIGURE 1

	VW* (n=35)	CON* (n=68)
Age at inclusion, in years *mean (SD)*	82.3 (8.5)	83.5 (8.2)
LACE score *mean (SD)*	12.6 (2.9)	12.7 (1.9)
L score*	2.9 (1.2)	5.0 (1.3)
A score*	3.0 (0.0)	3.0 (0.4)
C score*	3.2 (1.6)	3.8 (1.4)
E score*	1.4 (1.5)	0.9 (1.2)
Sex (M:F, % of F*)	14:21 (60%)	24:44 (65%)
Discharge destination		
Home *n (%)*	27 (77%)	57 (84%)
Senior Residence *n (%)*	8 (23%)	11 (16%)

TABLE 1 Demographics of the intervention patients and the historical group patients **VW = Family medicine-based Virtual Ward intervention; CON = Historical control patients; L = Length of stay; A = Acuity; C = Comorbidity; E = Emergency room visit; M = Male; F = Female*

Over the 180-day of follow-up period, readmissions varied from 23% to 66% in the VW group and from 33% to 60% in the control group. Over the same period, the LOS decreased from 3.9 at 30 days to 1.3 days at 180 days in the VW group and from 9.1 days at 30 days to 2.3 days at 180 days in the control group. Change in

Care processes	Statistics
Number of days in the VW* *mean (SD)*	48.1 (17.2)
Number of patients for whom a med-reconciliation form was completed *n(%)*	35 (100%)
Number of patients contacted by VW nurse within 72 hours post discharge *n(%)*	19 (54.3%))
A score*Number of patients contacted by VW nurse within 4 days post discharge *n(%)*	28 (80%)
Number of patients for whom the home-based services were contacted by VW nurse at least once *n(%)*	28 (80%)
Number of contact with the home-based services per patient *mean (SD)*	6.5 (4.8)
Number of prescription adjustments made *mean (SD)*	2.5 (1.8)
Number of patients with no adjustment *n(%)*	1 (3%)
Number of patients with 1 adjustment *n (%)*	11 (31%)
Number of patients with 2 to 8 adjustments *n (%)*	23 (66%)

TABLE 2 Descriptive statistics on the care processes given to the patients registered in the family medicine-based transitional care intervention
VW = Family medicine-based Virtual Ward intervention

ED visits/hospital readmission rates varied from +6% to -10% between the VW and control group. LOS in the VW group was 0.4 days to 1 day per 30 days of post discharge follow-up period shorter than the control group (Table 3).

After adjusting for exposure time and zero-inflation, we found no statistically significant differences in the incidence of readmission rates between VW and the control at 30 days (Incidence Rate Ratio [IRR[=0.66, 95% Confidence Interval [95%CI]=0.29-1.47), 60 days (IRR=0.75, 95%CI=09.40-1.44), 90 days (IRR=0.93, 95%CI=0.52-1.66), and at 180 days (IRR=1.07, 95%CI=0.65-1.76) (Figure 2). The LOS was found to be statistically significantly shorter at 90 (IRR=0.66, 95%CI=0.64-0.69) and 180 days (IRR=0.49, 95%CI=0.43-0.55) for VW patients compared to controls. However, no difference in LOS was detected at 30 days (IRR=1.16, 95%CI=0.95-1.42) and 60 days (IRR=1.04, 95%CI=0.89-1.23) (Figure 2). Sensitivity analyses adjusting for age, sex, and LACE found no clin-

ically meaningful differences in the IRRs (Tables 4 and 5).

		30 days	60 days	90 days	180 days
Readmissions, n (%)	VW*	8 (23%)	12 (35%)	15 (45%)	21 (66%)
	CON*	20 (33%)	29 (46%)	30 (48%)	35 (60%)
LOS*, mean number of days per 30 days (SD)	VW*	2.9 (9.3)	2.7 (7.2)	1.7 (5.5)	1.3 (6.1)
	CON*	4.2 (9.1)	3.4 (7.3)	3.3 (7.0)	2.3 (4.6)

TABLE 3 Unadjusted percentages of living patients with at least one readmission and average length of stay **Family medicine based Virtual Ward intervention;CON = Historical control patients; LOS = Length of stay*

There was no indication of a ramp-up effect on the rate of readmissions in VW patients at any time point (data not shown). There were statistically significant ramp-up effects on the LOS at 30, 90 and 180 days. The IRR (95% CI) was 0.997 (0.995-0.999) at 30 days, 0.999 (0.997-1.000) at 60 days, 0.997 (0.995-0.998) at 90 days, and 0.998 (0.997-0.999) at 180 days. In other words, for every additional day since the start of intervention, an additional 0.1% to 0.3% reduction in the LOS was found. This was deemed as not clinically meaningful. No difference in mortality was observed between the VW group (3 patients or 8.6%) and the control group (7 patients or 10.3%) at 180 days (Log Rank (Mantel-Cox) Chi-Square=0.10, df=1, p=0.75).

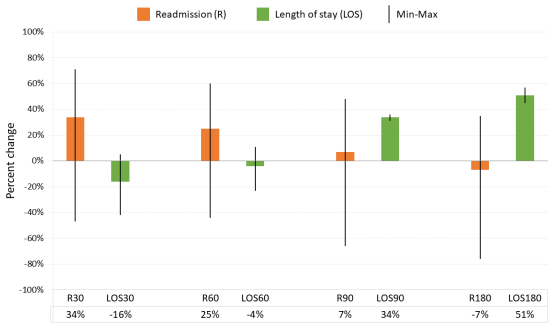

FIGURE 2

	IRR*	95% CI* min	95% CI* max
LOS30*			
VW* vs CON*	1.20	0.97	1.48
Age	0.99	0.98	1.00
Women vs Men	1.05	0.85	1.30
LACE* score	0.91	0.87	0.96
LOS60*			
VW* vs CON*	0.99	0.84	1.17
Age	1.02	1.01	1.03
Women vs Men	1.18	1.00	1.39
LACE* score	0.92	0.88	0.95
LOS90*			
VW* vs CON*	0.66	0.57	0.76
Age	1.03	1.02	1.04
Women vs Men	1.31	1.15	1.51
LACE* score	0.98	0.95	1.01
LOS180*			
VW* vs CON*	0.49	0.43	0.55
Age	1.01	1.00	1.01
Women vs Men	1.21	1.09	1.35
LACE* score	1.00	0.98	1.03

TABLE 4 Incidence Rate Ratios for all-cause cumulative Length of stay at 30, 60, 90 and 180 days adjusting for age, sex and LACE score and controlling for exposure time.

**VW = Family medicine-based Virtual Ward patients; CON = Historical control patients; IRR = Incidence Rate Ratios; CI = Confidence Intervals; min = minimum; max = maximum; LOS30 = length of stay at 30 days; LACE = Length of stay (L), Acuity (A), Comorbidity (C), Emergency room visit (E); LOS60 = length of stay at 60 days; LOS90 = length of stay at 90 days; LOS180 = length of stay at 180 days.*

4 | DISCUSSION

Our family medicine-based VW intervention showed a statistically significant effect on reducing LOS at 90 90 (IRR=0.66, 95%CI=0.64-0.69) and 180 days (IRR=0.49, 95%CI=0.43-0.55) for older patients at risk of readmission , but it did not have an effect on the hospital readmission rates at any time point.

It is likely that the reduction of cumulative LOS was due to the hospital staff becoming aware of the VW

	IRR*	95% CI* min	95% CI* max
Read30*			
VW* vs CON*	0.679	0.303	1.520
Age	1.034	0.987	1.085
Women vs Men	0.990	0.445	2.151
LACE* score	1.077	0.906	1.280
Read60*			
VW* vs CON*	0.758	0.397	1.446
Age	0.999	0.963	1.037
Women vs Men	0.971	0.485	1.735
LACE* score	1.101	0.960	1.263
Read90*			
VW* vs CON*	0.931	0.519	1.671
Age	1.004	0.970	1.039
Women vs Men	1.004	0.556	1.815
LACE* score	1.038	0.909	1.186
Read180*			
VW* vs CON*	1.071	0.647	1.774
Age	1.002	0.972	1.033
Women vs Men	1.056	0.630	1.768
LACE* score	1.051	0.938	1.177

TABLE 5 Sensitivity analyses of Incidence Rate Ratios for readmission at 30, 60, 90 and 180 days adjusting for age, sex and LACE score and controlling for exposure time.

** VW = Family medicine-based Virtual Ward patients; CON = Historical control patients; IRR = Incidence Rate Ratios; CI = Confidence Intervals; min = minimum; max = maximum; Read30 = readmissions at 30 days; LACE = Length of stay (L), Acuity (A), Comorbidity (C), Emergency room*

team's presence and the hospital staff's increasing confidence in the family medicine-based VW ability to ensure adequate transitional care, thus discharging patients sooner. Indeed, the link between the hospital and the Herzl Family Practice centre, which is based within the hospital, might have been strong enough to warrant earlier discharge.

The lack of impact on reducing readmissions rate, ER visits or hospitalizations, does not seem to be due to a ramp-up effect as it was clinically non-significant. However, it could be due to the lack of an integrated health care network, which has not yet been implemented in Quebec. Indeed, the link between community services and the Family Medicine Groups in Quebec is weak (19-21). Nurses from home care services may not have been aware of the family medicine-based VW intervention and sent patients to ED directly, rather than contacting the VW nurse. Unfortunately, we did not assess whether discharge instructions were followed by home care services. Similarly, patients may have preferred to by-pass, or simply forgotten to call the VW nurse when a new symptom appeared. Reinforcing the link between Family Medicine Groups, such as the Herzl Family Practice centre, and home care services in the future of the VW might help decrease readmissions to hospitals. For instance, inviting a home care services representative to the multidisciplinary rounds would be an important step toward increasing this communication.

Despite promising results, our study has some limitations. First, the small sample size limits the generalizability of our results. Indeed, our study was limited by the one-year internal funding from the director of the clinic for a VW nurse and the number of patients admitted during that period. Our historical control group prevented us from considering secular trends. Nonetheless, steps were taken to minimise bias in interpreting our findings by performing multiple sensitivity analyses. While unequal group sizes may have a small effect on the precision of the estimate within each group, this design was preferred over equal group sizes as it allowed us to maximize the overall sample size and therefore power to detect an effect of the intervention in our study outcomes. The care process information collected may have benefitted from some additions, such as the assiduity of usual family physicians to multidisciplinary meetings and number of successful contacts between patients and VW nurse, irrespective of who initiates the call. Additionally, chart data might be incomplete, and we might not have captured readmissions outside of the JGH hospital. This is not likely in our population, as older patients tend to go to the same hospital (22) and hospitals reorient patients when they are already known by another hospital. Finally, due to the lack of power, we could not fully explore the effects of age, sex, and LACE score on hospital readmission rates and LOS, despite having found significant effects of these variables in sensitivity anal-

yses. These variables should be considered in a larger study. Similarly, future studies may benefit into looking at ED visit and hospitalizations separately.

This participatory research project emerged from clinicians who contacted researchers interested in evaluating a transitional care intervention for older patients. Together, they developed the research questions and methods, considering usefulness and feasibility relevant to the practice. This is important, as practice-based research is thought to bridge the gap between research and practice, and make healthcare innovations more relevant to clinicians and patients (14). This intervention should be applied in more family medicine groups, while allowing adaptations of the intervention to different clinical contexts. The results of this study will be used by the clinical team to further refine the intervention. The results are promising and future studies should use a stronger design, such as a randomised controlled trial, for greater confidence in the effect of this complex intervention.

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REFERENCES

1. Coleman EA, Boult C. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc. 2003;51(4):556-7.

2. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc. 2004;52(5):675-84.

3. Aminzadeh F, Dalziel WB. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. Ann Emerg Med. 2002;39(3):238-47.

4. Lewis G. Predictive modeling in action: how 'virtual wards' help high-risk patients receive hospital care at home. Issues in International Health Policy, Commonwealth Fund pub 2010;1430(94):1-16.

5. Lewis G, Georghiou T, Steventon A, Viathianathan R, Chitnis X, Billings J, et al. Impact of 'virtual wards' on hospital use: a research study using propensity matched controls and a cost analysis. Final report. National Institute for Health Research Service Delivery and Organisation programme. Southampton: National Institute for Health Research; 2013.

6. Le Berre M, Maimon G, Sourial N, Guériton M, Vedel I. Impact of transitional care services for chronically ill older patients: a systematic evidence review. J Am Geriatr Soc. 2017;65(7):1597-608.

7. Rennke S, Nguyen OK, Shoeb MH, Magan Y, Wachter RM, Ranji SR. Hospital-initiated transitional care interventions as a patient safety strategy: A systematic review. Ann Intern Med. 2013;158(5_{Part_2}) : 433 – 40.

8. Kansagara D, Chiovaro JC, Kagen D, Jencks S, Rhyne K, O'Neil M, et al. VA Evidence-based Synthesis Program Reports. Transitions of Care from Hospital to Home: An Overview of Systematic Reviews and Recommendations for Improving Transitional Care in the Veterans Health Administration. Washington (DC): Department of Veterans Affairs (US); 2015.

9. Lewis G, Vaithianathan R, Wright L, Brice MR, Lovell P, Rankin S, et al. Integrating care for high-risk patients in England using the virtual ward model: lessons in the process of care integration from three case sites. Int J Integr Care. 2013;13:e046.

10. Verhaegh KJ, MacNeil-Vroomen JL, Eslami S, Geerlings SE, de Rooij SE, Buurman BM. Transitional care interventions prevent hospital readmissions for adults with chronic illnesses. Health Aff (Millwood). 2014;33(9):1531-9.

11. Low LL, Tan SY, Ng MJ, Tay WY, Ng LB, Balasubramaniam K, et al. Applying the Integrated Practice Unit Concept to a Modified Virtual Ward Model of Care for Patients at Highest Risk of Readmission: A Randomized Controlled Trial. PLoS One. 2017;12(1):e0168757.

12. Dhalla IA, O'Brien T, Morra D, Thorpe KE, Wong BM, Mehta R, et al. Effect of a postdischarge virtual ward on readmission or death for high-risk patients: a randomized clinical trial. JAMA. 2014;312(13):1305-12.

13. Lewis G. Case study: virtual wards at Croydon primary care trust. London: The King's Fund. 2006.

14. Deacon M. Caring for people in the 'virtual ward': the practical ramifications for acute nursing work. J Psychiatr Ment Health Nurs. 2003;10(4):465-71.

15. Jagosh J, Macaulay AC, Pluye P, Salsberg J, Bush PL, Henderson J, et al. Uncovering the benefits of participatory research: implications of a realist review for health research and practice. Milbank Q. 2012;90(2):311-46.

16. van Walraven C, Dhalla IA, Bell C, Etchells E, Stiell IG, Zarnke K, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. CMAJ. 2010;182(6):551-7.

17. Lewis C, Moore Z, Doyle F, Martin A, Patton D, Nugent LE. A community virtual ward model to support older persons with complex health care and social care needs. Clin Interv Aging. 2017;12:985.

18. Bourgeois FC, Olson KL, Mandl KD. Patients treated at multiple acute health care facilities: Quantifying information fragmentation. Arch Intern Med. 2010;170(22):1989-95.

19. Gagnon J, Gonzalez Reyes A, Vedel I, Ladores M, Vriniotis G, Arsenault-Lapierre G, et al., editors. Insights following the implementation of a family medicine based virtual ward. 44th NAPCRG annual meeting; 2016 November, 12-16; Colorado Springs, USA.

ORIGINAL RESEARCH
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The Family Medicine-Based Virtual Ward: Qualitative Description of the Implementation Process

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ABSTRACT

Purpose: Numerous transitional care interventions have been proposed to improve care transitions from hospital to home and reduce avoidable hospital readmissions among chronically ill older patients. The virtual ward (VW) is an intervention that aims to reduce this risk by providing follow-up care for patients discharged from the hospital. In 2015, a family medicine-based VW was implemented at the Jewish General Hospital, in Montreal, Canada. This intervention involves care coordination and follow-up by the multidisciplinary primary health care team. This study provides a description of the family medicine-based VW and its implementation to guide health care providers seeking to adapt this intervention to their own setting. **Methods**: A retrospective qualitative study was conducted. Data was obtained from semi-structured group interviews with the VW team and health professionals from two other hospitals, and from informal discussions with members of the VW team. An inductive narrative approach was used for data analysis. **Results**: The design of the family medicine-based VW was informed by a systematic review of transitional care interventions. The team adapted the VW to utilize existing processes and identified three distinct modules that implementers should consider: discharge planning, case management, and weekly multidisciplinary rounds. The following were identified as key factors in the implementation process: 1) funding, 2) home care, 3) communication, 4) standardization of protocols, 5) quality improvement, and 6) positive reception. **Conclusions**: The family medicine-based VW addresses the care of frequent health system users and compensates for gaps in communication and coordination. This research may be useful in informing family medicine-based VW implementation initiatives by providing contextual detail about the family medicine-based VW, its implementation process, and factors that facilitated its implementation in a Montreal hospital.

1 | INTRODUCTION

It is estimated that approximately 20% of patients discharged from the hospital are readmitted within thirty days (1). The risk of readmission is increased for older patients with multiple chronic illness (2-4). A large portion of readmissions may be prevented with improved communication and continuity of care during the transition (5). Multiple post-hospitalization transitional care interventions have been proposed to address these gaps (6). One transitional care intervention that has been successful in the United Kingdom and that has recently been implemented in select hospitals in Canada and the United States is the virtual ward (VW) (7-10).

The VW provides transitional care to inpatients identified as being at increased risk of emergency department (ED) visits or hospital readmission (11). The VW builds on the hospital-at-home model (12) by providing care in the patients' homes for conditions that would otherwise require in-patient care. In contrast to hospital-at-home programs, which are a substitute for hospital admission, VWs provide a combination of early discharge and transitional care for admitted patients.

A recent systematic review of transitional care interventions found that the risk of complications and readmissions was reduced and patient satisfaction was increased when there was greater continuity of care, involvement of multidisciplinary teams, and closer follow-up (7). Also, further reduction in risk is expected when the VW is anchored in primary care, since family physicians would be more implicated in discharge and follow-up (9). It is therefore recommended that transitional care interventions incorporate the above elements.

The Herzl Family Practice Centre ("the Herzl"), a Montreal Family Medicine Group (FMG) affiliated with a large, urban hospital (the Jewish General Hospital – JGH), developed and piloted a family medicine-based VW. The family medicine-based VW was implemented at the JGH with the aim of reducing the number of avoidable readmissions. More specifically, the intervention was developed to 1) target older, more vulnerable patients at high risk of ED visit or hospital readmission (9, 13), 2) begin hospital discharge planning while patients are still in the acute care setting (14), 3) and provide better continuity of care by coordinating with the patients' family physician (9).

VWs are an increasingly popular way of providing patient-centered follow-up care after hospital discharge (15). Knowledge about its implementation process and how VW components may be adapted to different needs and resource availabilities is expected to help improve the success of implementation initiatives. However, existing research provides insufficient detail about the intervention, context, and implementation process to inform VWs' transferability to other settings, in Quebec and internationally. The objectives of this research were, therefore, to: 1) provide a description of the JGH family medicine-based VW, and 2) provide a description of the processes surrounding its implementation at the JGH.

2 | METHODS

2.1 | Study Design

This research followed a qualitative descriptive study design (16). A participatory research approach (17) was followed, consisting of a collaboration between researchers and clinician stakeholders to generate more meaningful knowledge and more readily effect change (17, 18). The research team comprised: the VW physician, VW nurse case manager, a research coordinator, and three researchers. All members contributed to defining the objectives, data collection, data analysis, and dissemination of results (19).

2.2 | Data Collection

Data collection took place between 2015 and 2017. Data was obtained from: 1) a group interview (2016) with members of the JGH VW team; 2) two group interviews (2016), each conducted with at least two members of the JGH VW as well as members of a different hospital (Site 2 and Site 3) with an embedded FMG; and 3) individual informal interviews with the members of the JGH VW clinical and administrative staff. The

participating members of the JGH VW team were: the VW family physician, the VW nurse manager, the VW nurse case manager, the VW medical resident, a pharmacist, a social worker, and an administrative coordinator. Site 2 is another urban Montreal hospital, and Site 3 is located on an Indigenous reserve, within proximity of Montreal. The participants from Site 2 were: the Family Medicine Unit medical director, the Family Medicine Unit assistant director, the Family Medicine Unit department head, and the head of service nurse clinician assistant. The participants from Site 3 were: the director of nursing, the home care nurse manager, and a family physician. The group interview guide was developed using the Diffusion of Innovations framework (20) with additional questions added by the research team to address conditions of implementation more relevant to the VW program. The group interviews were audio recorded and transcribed, and notes were taken by 3 researchers during the discussions. For the informal interviews, notes were taken during the discussions (over 50 hours of research team meetings between 2015 and 2017).

2.3 | Analysis

A narrative approach (21, 22) was used to analyze interview transcripts and meeting notes to develop a description of the family medicine VW and its implementation at the JGH. An inductive thematic analysis (23) was performed to draw out key conditions that facilitated its implementation. Data were coded, for preliminary themes pertaining to these facilitating conditions, in parallel by two researchers using NVivo (version 12). Disagreements between coders about how data were categorized were discussed until consensus was reached. The emergent themes were then discussed, validated, and interpreted with the research team.

2.4 | Ethics

Ethics approval was obtained from the McGill University Faculty of Medicine Institutional Review Board. All members of the research team and all participants in the group interviews provided written consent prior to participating.

3 | RESULTS

3.1 | Description of the family medicine-based virtual ward

Hospitalized patients with an elevated risk of ED visit or future hospitalization are recruited for admission to the family medicine-based VW program. The program combines community-based follow-up care with principles of hospital care, which involves an interprofessional team, regular team meetings, and a single point of contact for patients. It was conceived as an extension of an existing home care program, to which a nurse case manager was added. The core VW clinical team at the Herzl comprised: a VW family physician, a nurse manager, a VW nurse case manager, a VW nurse practitioner, a VW resident, a social worker, and a pharmacist. The entire team participated in weekly multidisciplinary rounds and home care planning. The roles of each VW team member were clearly defined. The nurse manager at the Herzl played a key role in establishing the program, refining protocols, and leading the quality improvement process. The VW nurse case manager provided care coordination among the members of the virtual-ward multidisciplinary team, the patients' usual family physicians, home care services from community health centres (Centre local de services communautaires - CLSC), and patients/caregivers. She also functioned as the primary point of contact for the patients and their family after discharge and monitored the patients' progress closely, mainly through telephone evaluations. The VW nurse practitioner conducted physical evaluations and adjusted treatment plans in collaboration with the VW medical resident and VW family physician. The pharmacist oversaw medication adjustments and made recommendations for optimal pharmacological management. The social worker played an important role in evaluating patients' social and family environment, ensuring that patients and caregivers have adequate resources for home recovery. The VW family physician and/or res-

ident admitted patients to the VW, reviewed the case, performed home visits to assess the patient's recovery, regularly assessed patients' needs, provided guidance to the VW nurse case manager, and adjusted medications when needed. For instance, if a patient presented signs of acute heart failure exacerbation, the VW physician could adjust the medication accordingly and inform the VW case manager to provide closer follow-up. Finally, an administrative coordinator provided administrative support and scheduled appointments.

The family medicine-based VW program comprised three distinct modules: 1) selection process and discharge planning; 2) case management and close monitoring after discharge; and 3) weekly multidisciplinary rounds.

| Module 1: Selection Process and Discharge planning

The VW nurse case manager conducted daily rounds of the hospital family medicine units to identify potential candidates for the program. She evaluated the patient's risk of ED visit and readmission using the LACE index (13), which generated an ED visit and readmission risk score through a combination of the following variables: length of stay, acuteness of their condition, comorbidity, and ED visits in the last 6 months. Eligible patients satisfied the following criteria: 1) registered to a family physician practicing in the FMG; 2) planned for discharge to their home or to a semi-autonomous residence in the coming days; and 3) achieved a LACE score of 10 or greater, indicating a high risk of ED visit or readmission. The most common conditions of patients admitted to the VW included heart failure, chronic obstructive pulmonary disease, gastro-intestinal bleeding, dementia, and diabetes complications (type 1 or type 2).

Potential candidates were provided with an explanation of the program and consent for admission was obtained. Patients discharged to convalescence or rehabilitation, palliative care, residential centres, or long-term care were not admitted under the program. However, patients discharged to an interim centre were advised to contact the VW upon returning home for potential admission to the program.

Upon discharge of the patient, the VW nurse case manager also verified the presence of a medication reconciliation, notified the patient' usual primary care physician of his/her program enrollment, and verified that the patient has scheduled follow-up appointments with his/her usual family physician.

| Module 2: Case management

The second module comprised: the work of the VW nurse case manager leading up to and following patients' discharge from the hospital. The nurse case manager provided comprehensive discharge planning and coordination, ensuring that adequate community resources were in place for the patient at discharge and potential gaps in the transition were eliminated. She provided direct follow-up with patients/caregivers to provide greater continuity throughout the transition period, in addition to typical case management.

After patient discharge, the nurse case manager continued to provide monitoring, support, and information regarding self-care to patients/caregivers, mainly through regular telephone contacts. More precisely, a first telephone contact occurred within the first 48 to 72 hours post-discharge to provide a general patient assessment (i.e. symptoms, quality of life, the quality of healthcare services they receive, etc.). In addition, discharge instructions, future medical appointments, and treatments were reviewed.

During the first month, the VW nurse case manager made daily to weekly phone calls to reassess the patient, adjust medications as needed, and educate optimal management of the patient's condition. These contacts allowed the nurse to identify and manage minor problems, potentially preventing an ED visit. The VW nurse case manager kept the VW family physician/resident informed of the patient's health status and asked for their input into the patient's care plan. The patient's condition was also regularly discussed during weekly multidisciplinary meetings (see below).

Two follow-up, face-to-face visits were scheduled with a health care professional (the VW physi-

cian/resident or the VW nurse case manager), at home or in clinic, according to the patient's mobility. The first of these follow-ups was scheduled within the first 7 days following discharge (a 45 to 60-minute consultation), and the second about a month after discharge. Additional follow-ups were scheduled as needed, depending on the patient's condition.

| Module 3: Multidisciplinary rounds

The third module consisted of weekly multidisciplinary meetings conducted by the VW team to discuss the enrolled patients. These meetings involved the VW physician and resident, the VW nurse case manager, pharmacist, social worker, nurse practitioner, and (when possible, via telephone) the patient's family physician and a home care services (CLSC) representative. The team discussed concerns affecting the patient's health and well-being, from the perspective of their respective disciplines. They discussed changes in diagnosis or treatment, and the VW nurse case manager then notified the patient/caregiver, the usual family doctor, community pharmacy and home care services. After a minimum of six weeks, if the patient was deemed stable, the team organized the patient's discharge to regular care.

3.2 | Implementation Process

The VW team explained that, at the JGH, as with most hospitals in Quebec, family physicians and primary health care (PHC) teams are not typically notified when their patients are hospitalized or discharged, despite often being able to provide vital input about the patients' medical histories and appropriate post-discharge care. Typically, upon discharge, patient care may be transferred to CLSC home care services, or, in many cases, patients return home without a clear care plan. Thus, patients are responsible for reaching out to their family physician and transmitting information themselves. Given this gap in communication, the Herzl sought an intervention to better detect avoidable readmissions and ED visits, especially among frail, elderly frequent health system users, and provide proactive follow-up home care to reduce readmission rates.

The family medicine-based VW was initiated by the director of the Herzl after learning that the VW model demonstrated promise in the United Kingdom. The FMG director asked a family physician and nurse manager if they would champion the adaptation of this program to the JGH/Herzl context. In the development of their program, the Herzl team identified a hospital-based VW program in Toronto (9) and consulted its team to better understand how the program was managed and deployed. Unlike the VW implemented in Toronto (9), however, the director sought to anchor it in family medicine, to achieve greater involvement of primary care practitioners. He conceived the family medicine-based VW as a way of reducing avoidable readmissions by establishing a communications network linking the hospital, patient/caregiver, PHC team, and CLSC home care services, and by providing timely home-based follow-up.

Implementation began in 2015 with an examination of existing interventions, with the support of researchers from McGill's Department of Family Medicine; the research team conducted a systematic review of transitional care models with the aim of identifying and understanding key features that render such programs more effective (6). The systematic review found that transitional care interventions tended to be more successful, in terms of health outcomes and satisfaction, when there was greater continuity of care and communication with patients/caregivers, involvement of multidisciplinary teams, and closer follow-up.

The Herzl team then examined and documented existing discharge practices at the JGH. In particular, they noted that discharge summaries were sent to home care services at the CLSC, often via fax machine. Rarely was there a bi-directional exchange between the discharging ward and home care services; these also included no indication that discharge instructions were followed. Furthermore, CLSC home care services did not systematically provide the hospital ward nor the family medicine group written documentation indicating any changes in the patient's status, results of examinations, or changes to their medications.

Following this examination of existing practices, the Herzl adapted their existing home care program, which involved home visits by family physicians and residents, to provide home care for a small sample of patients recently discharged from the hospital. The program was developed in stages: the Herzl team developed initial clinical protocols, applied them at a small scale, met regularly to discuss, and refined them with input from the McGill University Family Medicine department researchers. The program was first tested using patients from the VW family physician's roster, then expanded to include all Herzl patients. Throughout the first year since its initial implementation (2015 to 2016), over one hundred patients were received for care in the VW. Once processes were sufficiently refined, the ward could handle a concurrent load of around 20 patients.

3.3 | Facilitating Factors

The following were identified, in group and individual interviews, as key conditions that contributed to the VW's successful implementation at the Herzl: 1) funding, 2) home care, 3) communication, 4) standardization of protocols, 5) continuous quality improvement, and 6) positive reception.

| Funding

The FMG director granted initial funding for a full-time nurse case manager for two years and allocated resources and personnel to pilot the program, given its potential to reduce ED visits. After two years, the regional health network, recognizing the program's potential to reduce healthcare costs, agreed to take over the funding of the nurse case manager.

| Established home care

The family medicine-based VW was built around an existing home care program at the Herzl. Prior to the implementation of the program, the VW physician, the nurse manager, and VW coordinator conducted a pilot study examining the discharge process at the JGH to analyze how patients were being admitted and discharged, as well as to identify gaps that could be addressed. They began initially by integrating patients who had been recently discharged from the hospital into their home care program.

As a home care program was already established, the VW procedures were built on pre-existing home visit procedures. The team was already familiar with the CLSCs of the region. The team members had experience working together, their roles were well-established, and they had human, material, and financial resources at their disposal. The establishment of home care protocols for patients transitioning from hospital to home care, however, involved significant initial information gathering as well as gradual development of communication channels with family physicians and CLSCs; these served to establish and define the network structure. As the program evolved, the team members' roles were negotiated and refined.

| Communication

Communication was considered critical to the program's success. The nurse manager's experience in communication and program management was considered an important asset. Implementation of the VW at the Herzl first involved ensuring that the family medicine unit administrators allocate the necessary resources. Communication channels and procedures for coordination with the hospital (e.g. flagging VW patients at the ED) and CLSCs also needed to be established, as well as procedures for including CLSCs and family physicians in rounds. In addition, successful implementation depends on the quality of communication with patients/caregivers, regarding recruitment and follow-up.

| Standardization of protocols

Throughout the initial examination of the discharge process, and throughout the VW program, the team met regularly, discussed emergent issues, and devised plans to address them. Over time, increasingly standardized protocols were developed for identifying and notifying

the patient's family doctor upon ED visit or hospital admission, identifying eligible patients, ensuring post-discharge follow-up. Protocols were also developed and standardized for communicating with family physicians, home care services, and patients/caregivers.

Protocols first developed on a smaller scale were subsequently expanded, refined, and standardized. For instance, only patients covered by CLSCs nearest to the hospital were initially targeted. Eventually, after protocols were established with these CLSCs, the program expanded to include patients covered under other CLSCs.

| Continuous quality improvement

The family medicine-based VW team devoted time during weekly multidisciplinary meetings to discuss not only the patients admitted to the VW but also the processes relating to the program itself. The VW team also took part in evaluating the research examining the program's processes and impact on readmission rates and length of stay (24). This involvement in research provided additional impetus to reflect on practices, standardize protocols, and collect indicators. Whenever issues or gaps in care were identified (e.g. establishing a fixed meeting time with CLSC staff, including family physicians in rounds), they discussed how these should be overcome and who should be responsible. These measures led to the standardization of protocols specifically adapted to the JGH and the network of CLSCs and family physicians.

| Positive reception

The program was well-received at the outset by health care providers and patients/caregivers alike, and this reception was considered to have greatly facilitated its support from stakeholders (administrators, clinicians and patients/caregivers) and uptake at the JGH. The VW explained that patients and providers at the JGH value the provision of home care for elderly patients. Patients and their families relayed to the VW team that they appreciated receiving close follow-up; they also reported feeling better supported and oriented throughout the transition period, which patients often consider complex and confusing otherwise (25). Health care providers at the JGH reported being pleased that their more complex patients received closer follow-up by multidisciplinary teams during this transition. They also reported that the risk of complications may have been subsequently reduced, since these patients occupy a significant portion of their time and workload. Additionally, since the Herzl is a teaching unit, this program was beneficial for residents as they learn about the trajectory of patients from hospital to home and gain a better appreciation of the value of home care and multidisciplinarity.

4 | DISCUSSION

The family medicine-based VW is an innovative transitional care intervention that utilizes the routines, staff, and resources of an FMG, rather than those of the hospital. It combines comprehensive discharge planning, case management, and multidisciplinary follow-up and home care. This program addresses an important gap identified by patients who often report a lack of communication and follow-up following discharge (25). It can also provide improved quality of life for older patients, who tend to prefer recovering at home and avoiding visits to the ED (6). This patient-centered program ensures that patients and caregivers are well informed, and that close follow-up is provided, with the aim of reducing avoidable ED visits and readmissions. Furthermore, it has the potential to reduce health system costs by lightening the ED burden and freeing hospital beds. Six components were deemed essential to the success of the program's implementation at the Herzl: 1) funding, 2) home care, 3) communication, 4) standardization of protocols, 5) continuous quality improvement, and 6) positive reception. The knowledge generated from this research is expected to help administrators and health professions successfully implement a similar transitional care intervention in their own settings.

The family medicine-based VW was designed to address needs expressed by healthcare providers at the JGH, some of which are specific to institutional and

provincial context. It was designed to compensate for gaps in communication and coordination between the hospital, family physician, home care services, and the patient and caregivers. Family physicians in Quebec do not systematically receive formal notification when their patients are hospitalized or present to the ER. While most family physicians in Quebec do not have direct access to hospital documentation systems, family physicians at the Herzl have an advantage in that they can access the JGH clinical information system to view a patient's hospitalization record. However, this information is currently not routinely transmitted to family physicians, and hospital staff are unable to access the Herzl's electronic medical record. Furthermore, in many contexts, faxes are still commonly used as the primary mode of communication for transmitting discharge summaries to CLSC home care services. To overcome these communication barriers through the family medicine-based VW, the nurse case manager coordinated directly with CLSCs to establish a back-and-forth communication channel, serving as the link between the hospital, FMG, and CLSCs. Therefore, the VW team needed to develop clinical and administrative protocols to ensure communication and continuity of care for patients at greater risk of ED visits or readmission who were discharged to their homes or to long-term care.

These protocols may not need to be as elaborate in settings with existing channels of bi-directional communication or interoperable EMRs. Other settings may not have the same needs, priorities, resources, and processes. The transferability of this intervention to other health care settings, therefore, implies adaptation of its constituent elements. This program was conceived in a modular fashion, with flexible components that can be adopted and adapted as needed in other contexts. While discharge planning, case management and multidisciplinary follow-up are considered key components of the family medicine-based VW; the ways in which these might be addressed may differ from context to context.

4.1 | Trustworthiness

One important consideration regarding the trustworthiness of qualitative research is the credibility of the results (26, 27). The description of the family medicine-based VW, its implementation process, and the interpretation of the contextual factors that facilitated this process were synthesized from conversations involving members of the VW team. We consider that the VW descriptions and their interpretation reflect the VW team's understanding, since team members participated in all phases of the research process. In addition, the interview guide was collaboratively developed by researchers and the VW team members. The triangulation of data further contributed to the credibility of the findings. Group interviews were conducted with care teams from the JGH and two other hospitals (a large urban hospital with an affiliated family medicine unit, similar to the JGH, and one sub-urban hospital serving an Indigenous community). In addition, members of the JGH VW participated in the interviews with these other hospitals. This provided points of contrast that enabled a deeper understanding of the relationship between the JGH VW and its institutional and provincial contexts.

Another key consideration is the transferability of the findings to other settings (27). We therefore employed several measures to support this aim. First, contextual detail at the provincial and institutional levels was provided to support readers' adaptation of the VW to their own contexts. Second, the program was conceived and presented in a modular fashion, to support practitioners of different contexts devising a tailored approach according to their priorities, needs, and resources. Finally, the triangulation of data from interviews with the VW team and staff from two other hospitals helped ensure that our understanding of the program and implementation process was framed in contrast to different settings. The findings of this research may not be exhaustive, since interviews were conducted with members of three healthcare institutions. Interviews with healthcare providers from other sites may shed more light on potential challenges or facilitating factors that were not explored here. However, we expect that the

present account of the JGH VW team's experiences in implementing this program are pertinent to a variety of health settings and that sufficient detail was provided to inform future VW implementation initiatives, in Quebec and internationally.

4.2 | Future directions

The family medicine-based VW represents an extension of the home care program at the Herzl clinic and provides protocols for improved communication between health care providers at different points of care. At the JGH, the VW served to lay important ground work for the development of a virtual hospital-at-home, which uses telemedicine to connect providers with patients, facilitating home-based access to specific treatments (e.g. intra-venous infusions).

An evaluation of the impact of the family medicine-based VW on readmission rates suggests that this intervention is associated with a significantly shorter length of stay for patients readmitted to the hospital, compared to a control group (24) This program could result in significant cost savings for frequent health system users, with the reduction in readmissions and ED visits that this program is expected to achieve (28). Comprehensive cost analysis is required to determine the extent of cost saving by reallocating resources from acute care to post-discharge home care. While the cost-effectiveness of VWs are currently unknown (12), the program has the potential for significant savings, given the costs associated with even one ED visit (28, 29).

5 | CONCLUSION

This innovative, family medicine-based transitional care program followed patients in their transition from hospital to home and provided coordinated home care with the aim of reducing avoidable readmissions and ED visits. It addressed the care of complex patients who are among the most frequent health system users and compensates for gaps in communication and coordination between hospitals, family physicians, home care services, and patients and caregivers. This intervention seemed to appeal to patients, health care providers, and health system administrators alike. This research provides insight into how the family medicine-based VW may be adapted to other health care settings.

REFERENCES

1. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The Incidence and Severity of Adverse Events Affecting Patients after Discharge from the Hospital. Annals of Internal Medicine. 2003;138(3):161-7.

2. Kahn JM, Angus DC. Going home on the right medications: prescription errors and transitions of care. JAMA. 2011;306(8):878-9.

3. Bogaisky M, Dezieck L. Early hospital readmission of nursing home residents and community-dwelling elderly adults discharged from the geriatrics service of an urban teaching hospital: patterns and risk factors. J Am Geriatr Soc. 2015;63(3):548-52.

4. Epstein AM, Jha AK, Orav EJ. The relationship between hospital admission rates and rehospitalizations. N Engl J Med. 2011;365(24):2287-95.

5. Aminzadeh F, Dalziel WB. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. Annals of emergency medicine. 2002;39(3):238-47.

6. Mistiaen P, Francke AL, Poot E. Interventions aimed at reducing problems in adult patients discharged from hospital to home: a systematic meta-review. BMC Health Serv Res. 2007;7:47.

7. Le Berre M, Maimon G, Sourial N, Gueriton M, Vedel I. Impact of Transitional Care Services for Chronically Ill Older Patients: A Systematic Evidence Review. J Am Geriatr Soc. 2017;65(7):1597-608.

8. Lewis G. Predictive Modeling in Action: How 'Virtual Wards' Help High-Risk Patients Receive Hospital Care at Home. Issues in International Health Policy, Commonwealth Fund pub 2010;1430(94):1-16.

9. Dhalla IA, O'Brien T, Morra D, Thorpe KE, Wong BM, Mehta R, et al. Effect of a postdischarge virtual ward on readmission or death for high-risk patients: a randomized clinical trial. JAMA. 2014;312(13):1305-12.

10. Lewis C, Moore Z, Doyle F, Martin A, Patton D, Nugent LE. A community virtual ward model to support older persons with complex health care and social care needs. Clin Interv Aging. 2017;12:985-93.

11. Lewis G, Georghiou T, Steventon A, Viathianathan R, Chitnis X, Billings J, et al. Impact of 'Virtual Wards' on hospital use: a research study using propensity matched controls and a cost analysis. Final report. National Institute for Health Research Service Delivery and Organisation programme. Southampton: National Institute for Health Research; 2013. Available from:

http://www.nets.nihr.ac.uk/_data/assets/pdf_file/0011/87923/FR-09-1816-1021.pdf.
12. Lewis G, Wright L, Vaithianathan R. Multidisciplinary case management for patients at high risk of hospitalization: comparison of virtual ward models in the United kingdom, United States, and Canada. Popul Health Manag. 2012;15(5):315-21.
13. van Walraven C, Dhalla IA, Bell C, Etchells E, Stiell IG, Zarnke K, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. CMAJ. 2010;182(6):551-7.
14. Detsky AS, Krumholz HM. Reducing the trauma of hospitalization. Journal of the American Medical Association. 2014;311(21):2169-70.
15. Canadian Agency for Drugs and Technologies in Health (CADTH). The Use of Virtual Wards to Reduce Hospital Readmissions in Canada: Evironmental Scan. 2011.
16. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000(23):334-40.
17. Green LW, George MA, Daniel M, Frankish CJ, Herbert CJ, Bowie WR, et al. Study of participatory research in health promotion. Review and recommendations for development of participatory research in health promotion in Canada Ottowa, Ontario: The Royal Society of Canada. 1995.
18. Jary D, Jary J. Collins dictionary of sociology. Glasgow: Collins; 2005.
19. Cargo M, Mercer SL. The Value and Challenges of Participatory Research: Strengthening Its Practice. Annu Rev Public Health Annual Review of Public Health. 2008;29(1):325-50.
20. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. The Milbank quarterly. 2004;82(4):581-629.
21. Polkinghorne DE. Narrative Configuration in Qualitative Analysis. International Journal of Qualitative Studies in Education. 1995;8(1):5-23.
22. Gagnon J. Using Narrative Construction to Prepare the Ground for Hermeneutic Dialogue. Journal of Applied Hermeneutics. 2019.
23. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
24. Arsenault-Lapierre G, Kremer B, Sourial N, Gagnon J, Ladores M, I. V. Impact of a family medicine-based transitional care intervention on readmission and length of stay: a pilot study. McGill Journal of Medicine. 2020;18(1).
25. Schoen C, Osborn R, How SK, Doty MM, Peugh J. In chronic condition: experiences of patients with complex health care needs, in eight countries, 2008. Health Aff (Millwood). 2009;28(1):w1-16.
26. Lincoln YS, Guba EG. Establishing Trustworthiness. Naturalistic Inquiry. Newbury Park, CA: SAGE Publications; 1985.
27. Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. Education for information. 2004;22(2):63-75.
28. Billings J, Mijanovich T. Improving The Management Of Care For High-Cost Medicaid Patients. Health Affairs. 2007;26(6):1643-54.
29. Lewis G, Bardsley M, Vaithianathan R, Steventon A, Georghiou T, Billings J, et al. Do'virtual wards' reduce rates of unplanned hospital admissions, and at what cost? A research protocol using propensity matched controls. International journal of integrated care. 2011;11:e079-e.

ORIGINAL RESEARCH
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Training Global Surgery Advocates: Strengthening the Global Surgery Voice

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ABSTRACT

Objective: To strengthen knowledge of international medical trainees on global surgery and advocacy and help develop future generations of global surgeons, anaesthesiologists, and obstetricians.

Design: Training Global Surgery Advocates (TGSA), a standardized three-day advocacy workshop developed by the International Student Surgical Network (InciSioN), was built on traditional didactic lectures, role-play exercises, small working group activities, and advocacy and diplomacy training. Assessment was completed using a 5-point Likert scale for 18 components regarding the perceived familiarity, knowledge, and motivation for global surgery.

Setting: Training was provided in the context of the Pre-General Assembly of the International Federation of Medical Students Associations (IFMSA) at Université Laval, in Québec City, Canada.

Participants: Fourteen medical students from seven high-income countries and seven low- and middle-income countries participated in the workshop, from a group of twenty-five chosen applicants selected from a pool of 52 applicants.

Results: An average increase of 1.73 points across all 18 workshop components was observed among participants. After the workshop, all participants agreed or strongly agreed (4.64 average) that they were motivated to train other medical students in their respective countries to become global surgery advocates.

Conclusion: TGSA improved participants' knowledge and advocacy skills underlying global surgery. A mixed didactic and hands-on workshop appears to be feasible, enjoyable for participants, and effective in improving medical students' involvement in the emerging field of global surgery.

KEYWORDS

Global Health; Education; Global Surgery

1 | INTRODUCTION

In 2015, the Lancet Commission on Global Surgery reported that five billion people, or two-thirds of the world's population, lack timely access to safe and affordable surgical, obstetric, and anesthesia care when needed, causing over 17 million preventable deaths every year and responsible for one-third of the global burden of disease (1). Despite the proven cost-effectiveness of surgical services in low-resource settings, the perceived luxury and difficulties of scaling up surgical care remain widespread (2).

Interest in global surgery—improving access to safe, timely, and affordable surgical care in low- and middle-income countries–has grown exponentially since the publication of the Lancet Commission on Global Surgery, especially amongst medical trainees. Nevertheless, availability or access to structured global surgery education in undergraduate or medical curricula is limited (3). Involvement of medical students and residents, however, has been successful in advancing the field of global surgery. InciSioN, the International Student Surgical Network, is an international non-profit organization run by, and for, medical and public health students, residents, and young physicians passionate to work in and advocate for global surgery (4). Formally established in 2016, the network has grown to over 5,000 members in over 80 countries and 39 fully established National Working Groups in countries across all world regions. These provide members with opportunities to become involved with research through peer-support mechanisms, virtual internships to learn from and work with global surgery experts, distance expert and peer mentorships, capacity building and soft skill development, as well as societal partnerships. Accordingly, InciSioN provides a platform to contribute to the development of future generations of global surgeons, anaesthesiologists, and obstetricians around the world.

As future physicians in the 21st century, medical trainees are called to develop not only clinical knowledge and expertise, but also interpersonal skills in order to meet the needs of a diverse population of patients. In 1990, the Royal College of Physicians and Surgeons of Canada developed the CanMEDS concept, which highlights the importance of the medical professional to develop various "soft skills" including communication, leadership, and most notably, health advocacy (5). The need for these skills is more pronounced in the global health and global surgery field, where social, economic, and cultural differences represent challenges on both the receiver and the provider's end of the care continuum.

To strengthen, unify, and escalate InciSioN's impact around the world, we have created Training Global Surgery Advocates (TGSA), a standardized three-day advocacy workshop. TGSA aims to equip participants with the essential knowledge of global surgery, universal health coverage, and health systems, as well as the advocacy and diplomacy skills to integrate this into meaningful communications and campaigns. We report results of the pilot program of this workshop, partaken by an international group of medical students convened in Quebec City, Canada.

2 | METHODS

2.1 | Course Design

A three-day workshop was designed by InciSioN using feedback from InciSioN's core International Team and Board of Trustees on the proposed structure and content. The 27-hour workshop was built on traditional didactic lectures, role-play exercises, and small working group activities, as well as advocacy and diplomacy training in order to provide participants with the necessary knowledge and skills to effectively advocate for global surgery. One-third of the workshop curriculum was conducted through lectures serving as an introduction to global surgery, universal health coverage, health systems, and their constituents. The knowledge that participants gained was consequently integrated in active learning through advocacy training and peer-to-peer small working group activities. Participants were asked to complete both a baseline global surgery "elevator pitch" on the first day of the workshop, as well as a prepared "elevator pitch" at the end of the third day to personally assess progress and receive feedback from

workshop facilitators and peers. The elevator pitches served as advocacy and persuasion practice to enable participants to more succinctly and efficiently deliver their messages to their intended audience.

2.2 | Participants

A description and in-depth outline of the workshop was made available to medical students from the International Federation of Medical Student Associations (IFMSA) member organizations, who applied through a common form. Potential participants were asked to detail their motivation for participating in the TGSA, and to answer questions pertaining to global surgery. The quality of their answers, as well as their regional, country income group, and gender, were taken into account when selecting participants in order to ensure diversity and representation. From a pool of 52 applicants, 25 participants were selected in the initial round of evaluation, of which 14 medical students were able to attend from 14 different countries (7 high-income and 7 low- and middle-income countries, including Haiti, the Netherlands, Qatar, Ecuador, Turkey, Taiwan, Jordan, Denmark, Norway, Japan, Romania, Australia, India, and China). The remaining students were unable to attend due to visa issues (9 students) or personal reasons (2 students).

2.3 | Participant Assessment

A questionnaire assessing familiarity with workshop topics and objectives was filled by participants before the beginning of the workshop and immediately afterwards **(Appendix 1)**. Participants were asked to evaluate their personal motivation for future involvement within the field of global surgery. Questionnaires were scored using a 5-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree) for the 18 questions. The results from the pre- and post-workshop surveys were compared to determine changes for each component.

2.4 | Course Evaluation

The workshop was evaluated by participants with comments at the end of each day. Each participant was required to give a minimum of one positive and one constructive comment on their satisfaction on the day's events. All comments were compiled and summarized according to which aspect of the workshop they addressed.

3 | RESULTS AND DISCUSSION

3.1 | Course Selection

During the three days, participants were exposed to a variety of topics designed to build a comprehensive foundation of global surgery and related topics, and given the opportunity to integrate these into practical interventions through public speaking, pitching, and campaigning **(Table 1)**.

3.2 | Participant's Assessment

Participants' Assessment Participants' self-assessment of their level of understanding of global surgery revealed various levels of experience in the field **(Table 2)**. Statements pertaining to knowledge of global surgery and advocacy (statements 1 to 15) before the workshop range from virtually no experience (1 point, or strongly disagree) to extensive understanding of global surgery (5 points, or strongly agree), though the latter was limited to one participant. After the workshop, self-assessment on the same topics showed a notable increase in scores. In terms of evaluating knowledge (questions 1-15), overall, our cohort reported values of 2.28 points before the workshop and 4.28 points after the workshop, an increase of 2 points. Statements pertaining to motivation for becoming involved in global surgery (statements 16 to 18) showed high levels of motivation before the workshop (4.14 to 4.43 points), which were slightly increased after the workshop (0.14 to 0.5 point increase).

Day 1	Day 2	Day 3
Ice Breaker	Financial Barriers and Health Financing	Rural Health and Rural Surgery
Introduction to Universal Health Coverage	Social Determinants of Health and Social Barriers	Academic Global Surgery
Introduction to Health Systems	Soft Skills: Public Speaking, Communication, and Negotiation	Global Surgery in Medical Education
Introduction to Global Surgery	Advocacy	Health Systems Sustainability
Baseline Elevator Pitch		Global Surgery Campaign Creation
The Three Delays Framework		Final Elevator Pitch
The Three Delays Framework		Final Elevator Pitch
Human Resources for Surgery, Anaesthesia, and Obstetrics		Debrief and Closing

TABLE 1 Outline of the TGSA Workshop

3.3 | Course Evaluation

Feedback received through anonymous submissions from participants are summarized in Table 3. Overall, positive comments were more numerous than negative ones, as some participants gave no negative comments on some days. Many participants re-emphasized their satisfaction with the content and structure of TGSA, which allowed them to translate acquired theory into practical applications, where they were able to receive feedback and improve over the course of the workshop.

3.4 | Discussion

The Training Global Surgery Advocates workshop was a first of its kind, with the aim of introducing medical students to the basics of global surgery and equipping them with advocacy and diplomacy skills for future involvement in the field. This pilot study shows that a global surgery advocacy workshop, built on integration of theory into practice facilitated through discussion, reflections, and advocacy exercises, has a positive effect on participants' confidence regarding the topics of global surgery and universal health coverage.

Participant assessment shows that, on average, participants have increased their understanding across all topics that were presented within the TGSA and assessed via questionnaires. Our results on the assessment of knowledge of global surgery and advocacy, scored during pre- and post- workshop assessments, suggest that participants were generally not introduced to these topics within their respective medical curriculum, although many originated from countries where issues presented throughout the workshop were most prevalent. Participants informally commented on realizing the applicability of global surgery in their respective countries through discussion of challenges present in their medical systems regarding surgical care. Only modest improvements in self assessment responses for motivation in future involvement (questions 16-18) can be further explained by the high pre-workshop motivation of the majority of participants (average of 4.43, 4.29, and 4.14 pre-workshop scores for local involvement in global surgery, international involvement in global surgery, and becoming a trainer for TGSA, respectively). Furthermore, an average score increase for all three of the motivation-related questions implies that overall, this workshop had a positive impact and encouraged future involvement in global surgery. Although the pilot study involved medical students, there is value to expanding and adapting future events to other audiences, including but not limited to residents, faculty, and other health professionals whose clinical duties pertain to surgery, anaesthesia, and obstetrics.

Short courses in medical education commonly report the use of numerical scales in questionnaires as a means to obtain feedback and evaluate participants learning (6-7). Notably, self-assessment is widely accepted as a simple but effective measure to assess participants' understanding of a topic. Our assessment was based on the use of the Likert scale as a simple quantitative tool to evaluate improvement in participants' perception of

their understanding of global surgery before and after the workshop. The Likert scale is a simple instrument that detects self-reported changes and has been widely used and validated in clinical settings (9-11). Additionally, in our study, open-ended qualitative feedback was incorporated to optimize future workshops.

3.5 | Limitations

Within this study, one limitation was the number of participants who were unable to attend the workshop due to visa issues. Fourteen medical students participated in the TGSA, although the initial number of accepted participants was 25, which creates a sampling bias. This problem is concerning as creates limitations in representation from some regions of the world, particularly for participants from sub-Saharan Africa and is regrettably a widespread phenomenon for international conferences and workshops (12). A potential solution to this problem would be to establish an e-TGSA, or online version of the training, which could be conducted as a series of webinars. This method would retain the interactive and participative aspect of the TGSA, whilst making the content accessible to anyone. An online workshop is also attractive due to its modest cost for both facilitators and participants, as it removes the need to physically be present at a specific location. However, online workshops lack a face-to-face component, which would thereby limit the ability of participants to foster relationships with future colleagues during and between sessions, an aspect which was repeatedly highlighted as an important strength of the workshop. Additionally, the quality of the training may vary depending on the quality of the internet connection, and it would be more challenging to determine whether participants are actively engaged.

Another challenge faced by the TGSA workshop is the physical and human resources needed to hold it. This pilot run was designed to allow in-person interactions and feedback, which have limitations as to who and when it can be delivered. A possible future direction for TGSA would be to re-purpose it as a template workshop, which would allow the creation of similar workshops that are catered to the needs of the attendees. Alternatively, an online module could be developed based on the workshops, which would increase accessibility but limit the in-person interactions of TGSA.

Finally, the self-assessment nature of our evaluation method is prone to cognitive bias and the Dunning-Kruger effect, whereas participants could be overestimating their knowledge and skills when answering the survey questions (13). This could explain why, on an individual level, some participants have not indicated an improvement for some topics, as their experience with the training may have clarified how their knowledge and competencies compare to other participants.

4 | CONCLUSIONS

Global surgery is a young and rapidly developing field, hence naturally prone to gaps in understanding feasibility, cost-effectiveness, and the urgent need of scaling up surgical systems. InciSioN's standardized three-day advocacy workshop, Training Global Surgery Advocates, aimed to equip participants with the needed knowledge, as well as advocacy and diplomacy skills to advocate for global surgery, adaptable in any situation and to any target audience. This pilot study of TGSA suggests that this type of workshop is feasible, enjoyable for participants, and efficient in improving medical students' knowledge and involvement in the emerging field of global surgery.

Statement	Pre-assessment average (Standard deviation)	Post-assessment average (Standard deviation)	Average change (Standard deviation)
1. I have a good understanding of global surgery.	2.71 (0.91)	4.79 (0.43)	+2.14 (0.95)
2. I have a good understanding on how non-governmental organizations (NGOs) work for global surgery.	2.36 (0.93)	4.21 (0.70)	+1.86 (1.03)
3. I have a good understanding on how academic centres and universities work for global surgery.	2.57 (0.94)	4.43 (0.51)	+1.86 (0.86)
4. I have a good understanding on how governments work for global surgery.	2.43 (0.94)	4.07 (0.62)	+1.64 (0.84)
5. I have a good understanding on the different ways a student can get involved in global surgery.	2.69 (0.63)	4.92 (0.28)	+2.21 (0.70)
6. On a scale of 1-5, how well is your understanding of... [The Lancet Commission on Global Surgery]	1.92 (0.95)	3.69 (0.63)	+1.71 (0.82)
7. On a scale of 1-5, how well is your understanding of... [UHC2030]	2.54 (1.05)	4.08 (0.76)	+1.64 (1.01)
8. On a scale of 1-5, how well is your understanding of... [Financial Risk Protection]	1.85 (0.69)	3.85 (0.80)	+2 (0.78)
9. On a scale of 1-5, how well is your understanding of... [The Bellwether Procedures]	1.46 (0.78)	4.54 (0.66)	+3 (1.11)
10. On a scale of 1-5, how well is your understanding of... [InciSioN - International Student Surgical Network]	2.08 (0.95)	4.46 (0.66)	+2.43 (1.16)
11. On a scale of 1-5, how well is your understanding of... [National Surgical Plans (NSOAPs)]	2.08 (1.04)	4.31 (0.63)	+2.29 (1.20)
12. On a scale of 1-5, how well is your understanding of... [Catastrophic Expenditure]	1.62 (0.65)	4.31 (0.75)	+2.64 (0.84)
13. On a scale of 1-5, how well is your understanding of... [Health Systems Financing]	2.31 (0.75)	3.69 (0.95)	+1.5 (1.29)
14. On a scale of 1-5, how well is your understanding of... [Social Determinants of Health]	2.5 (1.02)	4.29 (0.91)	+1.79 (1.42)
15. On a scale of 1-5, how well is your understanding of... [Advocacy]	3.07 (1.14)	4.5 (0.94)	+1.43 (1.40)
16. I am motivated to get involved in global surgery locally in my country.	4.43 (0.76)	4.86 (0.36)	+0.43 (0.65)
17.I am motivated to get involved in global surgery on the international level.	4.43 (0.65)	4.57 (0.65)	+0.14 (0.77)
18. I want to train other students to become global surgery advocates.	4.14 (0.53)	4.64 (0.50)	+0.5 (0.52)

TABLE 2 Participant's self-assessment before and after attending the workshop

Aspect Evaluated	Positive Feedback	Construtive Feedback
Content of the Workshop	1. Variety of topics 2. Pertinent and enjoyable exercises, especially for advocacy and soft skills (e.g., elevator pitch)	1. Depth of some topics to re-assess depending on participants' level of knowledge
Structure of the Workshop	1. Opportunities to put theory into practice 2. Balance between theoretical presentations and practical workshops	1. Room set-up to be improved 2. Time management (longer duration of activities, order of the workshops, punctuality of participants)
Social Interaction	1. Ice breaker activity 2. Diversity of participants' background	1. Lack of group activities beyond the workshop hours

TABLE 3 Course Evaluation by Participants

Appendix A: Pre- and Post-Workshop Survey

Pre- and post-workshop survey statements (rated on a scale of 1 to 5, 1 being "strongly disagree" to 5 being "strongly agree")

1. I have a good understanding of global surgery.

2. I have a good understanding on how non-governmental organizations (NGOs) work for global surgery.

3. I have a good understanding on how academic centres and universities work for global surgery.

4. I have a good understanding on how governments work for global surgery.

5. I have a good understanding on the different ways a student can get involved in global surgery.

6. On a scale of 1-5, how well is your understanding of...
   a. The Lancet Commission on Global Surgery
   b. UHC2030
   c. Financial Risk Protection
   d. The Bellwether Procedures
   e. InciSioN - International Student Surgical Network
   f. National Surgical, Obstetric, and Anaesthesia Plans (NSOAPs)
   g. Catastrophic Expenditure
   h. Health Systems Financing
   i. Social Determinants of Health
   j. Advocacy

7. I am motivated to get involved in global surgery locally in my country.

8. I am motivated to get involved in global surgery on the international level.

9. I want to train other students to become global surgery advocates.

REFERENCES

1. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386(9993):569–624. doi: 10.1016/j.ijoa.2015.09.006.

2. Grimes CE, Henry JA, Maraka J, Mkandawire NC, Cotton M. Cost-effectiveness of surgery in low- and middle-income countries: A systematic review. World J Surg. 2014;38(1):252–63. doi: 10.1007/s00268-013-2243-y.

3. Scott EM, Fallah PN, Blitzer DN, NeMoyer RE, Sifri Z, Hanna JS, et al. Next Generation of Global Surgeons: Aligning Interest with Early Access to Global Surgery Education. J Surg Res. 2019 Apr;240:219–26. doi: 10.1016/j.jss.2019.03.009.

4. Vervoort D, Bentounsi Z. InciSioN: Developing the Future Generation of Global Surgeons. J Surg Educ. 2019 Jul-Aug;76(4):1030-1033. doi: 10.1016/j.jsurg.2019.02.008.

5. Doiron RC. Health advocacy in a competency-based curriculum: The emerging role of global surgery. Can Urol Assoc J. 2016 Mar-Apr;10(3-4):82. doi: 10.5489/cuaj.3771.

6. Schoeb DS, Brennecke E, Andert A, Grommes J, von Trotha KT, Prescher A, Neumann UP, Binnebösel M. Assessment of a course of

realistic surgical training during medical education as a tool for pre-residential surgical training. BMC Med Educ. 2016 Feb 3;16:45.

7. Rempell JS, Saldana F, DiSalvo D, Kumar N, Stone MB, Chan W, Luz J, Noble VE, Liteplo A, Kimberly H, Kohler MJ. Pilot Point-of-Care Ultrasound Curriculum at Harvard Medical School: Early Experience. West J Emerg Med. 2016 Nov;17(6):734-740. Epub 2016 Sep 12.

8. Ross JA. The Reliability, Validity, and Utility of Self-Assessment. Practical Assessment, Research Evaluation 2006, 11(10). Available online: http://pareonline.net/getvn.asp?v=11n=10.

9. Krzych ŁJ, Lach M, Joniec M, Cisowski M, Bochenek A. The Likert scale is a powerful tool for quality of life assessment among patients after minimally invasive coronary surgery. Kardiochir Torakochirurgia Pol. 2018 Jun;15(2):130-134. doi: 10.5114/kitp.2018.76480.

10. Koksel Y, Gencturk M, Spano A, Reynolds M, Roshan S, Caycı Z. Utility of Likert scale (Deauville criteria) in assessment of Chemoradiotherapy response of primary oropharyngeal squamous cell Cancer site. Clin Imaging. 2019 May - Jun;55:89-94. doi: 10.1016/j.clinimag.2019.01.007.

11. van Laerhoven H, van der Zaag-Loonen HJ, Derkx BH. A comparison of Likert scale and visual analogue scales as response options in children's questionnaires. Acta Paediatr. 2004 Jun;93(6):830-5.

12. Nshemereirwe C. Tear down visa barriers that block scholarship. Nature. 2018 Nov;563(7729):7. doi: 10.1038/d41586-018-07179-2.

13. Kruger J, Dunning D. Unskilled and unaware of it: how difficulties in recognizing one's own incompetence lead to inflated self-assessments. J Pers Soc Psychol. 1999 Dec;77(6):1121-34.

ORIGINAL RESEARCH
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The Role of Probiotics in Inhibition Mechanism of Methicillin-Resistant Staphylococcus Aureus

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ABSTRACT

Down-regulation of the mecA gene is considered as a promising approach to control over antibiotic resistance in methicillin resistant Staphylococcus aureus (MRSA). This in vitro study evaluated the ability of synbiotics to inhibit the growth of MRSA and modify the expression of mecA. Moreover, susceptibility testing was performed to investigate synbiotic-induced changes in MRSA resistance. MRSA isolates were collected from different clinical specimens and explored for antibiotic susceptibility using both disk-agar diffusion method as well as polymerase chain reaction (PCR) for detection of mecA gene. Synbiotics in the form of Kidilact®, Vitalact®, and Protexin® sachets were applied to prepare cell-free culture supernatants. Their antibacterial activity was determined by disk and well diffusion methods. The impact of synbiotics on the expression of mecA that denotes penicillin susceptibility was tested by real time PCR. It was shown that the synbiotics produced components with antimicrobial activities against MRSA. The supernatant produced by synbiotics can afford to confer penicillin susceptibility in the MRSA isolates in a time-dependent fashion. Two third of susceptible MRSA isolates carried decreased levels of mecA expression. In conclusion, synbiotics are effective for reducing MRSA growth and antibiotic resistance through suppression of mecA.

KEYWORDS

Methicillin-resistant Staphylococcus aureus (MRSA), probiotics, mecA gene, synbiotics, antibacterial activity, penicillin susceptibility

1 | INTRODUCTION

Staphylococcus aureus is considered as a commensal micro-organism that can cause hospital and community-acquired infections, namely, skin wound, sepsis, endocarditis, and pneumonia (1). Antibiotic therapy appear frequently ineffective because of emerging antibiotic-resistant strains, including methicillin-resistant S. aureus (MRSA), which becomes prevalent in hospitals across the globe (2-5), imposes medical and socio-economic burden for both patients and health care providers, and contributes to morbidity and mortality (6). It has been reported that S. aureus respectively affects 12 million and 292,000 patients attending outpatient clinics and hospitals. As many as 126,000 present with MRSA infection each year in the United States (7). More importantly, an approximate of 90,000 Americans is estimated to die owing to hospital-acquired bacterial infections (8). As documented, the antimicrobial resistance appears to be a natural biological phenomenon that can be augmented by various factors, such as human practices. Indeed, the administration of antimicrobial agents against any pathogens leads them to either adapt or die (selective pressure). In so doing, those surviving carry genes for resistance, which can be transferred upon bacterial replication (9). The resistance in MRSA arises from the expression of Penicillin binding protein (PBP2a) encoded by mecA genes (10, 11).

There have been two main microbial approaches to manage antimicrobial resistance, including bacteriophage-based therapies as well as microbiome restoration. The former strategy deals with the application of phage or its component proteins however some have concerns over immunogenicity and bacterial resistance to bacteriophages (12, 13). The latter focuses on different mechanisms to decolonize antibiotic-resistant bacteria. Recent efforts have been directed towards the positive effects of probiotics on fecal microbiota (14, 15). Probiotics are beneficial micro-organisms that its consumption in adequate amounts promotes human health and affords protection against a variety of diseases (16). The use of these bacteria has been observed to ameliorate symptoms of gastrointestinal infections, prevent the growth of pathogenic strains, regulate the mucosal physiology or strengthen the intestinal immunity in hosts (17-20). Of note, supernatants released by multiple probiotics display inhibitory activity against different pathogens (21, 22). Chen et al. found that supernatants secreted by L. fermentum, B. longum subsp. longum, and B. animalis subsp. lactis could successfully deactivate MRSA (23). Of bacterial genera widely utilized in probiotic preparations, Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, Bacillus, and Streptococcus have attracted more attention (24-26). The first group includes those strains producing lactate and lactic acid as the main end-product. Lacto-bacillus rhamnosus GG is a well-known probiotic that has been extensively investigated hitherto (27, 28). In general, lactobacilli, bifidobacteria, and lactococci are shown as safe considering their long history of use in food processing and dairy production (29). Though a rare case, no extant evidence has been recorded to date concerning any high risk of developing bacteremia or endocarditis following intake of probiotics (30, 31). The mechanisms whereby probiotics carry out their physiological role are chiefly contingent on the features, manufacturing, and formulation of the used strains (32) however the following processes have been observed to be involved as a result of probiotic treatment (33): competition for the ability of pathogens to colonization in the gastrointestinal tract through limiting their adhesion sites and/or nutrients (34, 35); biosynthesis of inhibitory metabolites, including organic acids and bacteriocins that improve peristalsis, inhibit the growth of pathogens or indirectly exclude them (36-39); immunomodulatory effects on the host (35, 37, 40-42); and counteraction of bacterial toxins (43).

A body of literature has been conducted on the antagonistic interactions between probiotics and S. aureus/MRSA (44-49); for example, Karska-Wysocki et al. used a commercial probiotic (Bio-K+^{ő}) containing Lactobacillus acidophilus CL1285^{ő} and Lactobacillus casei LBC80R^{ő} in an in vitro setting to examine its inhibitory activities of against the growth of standard ATCC MRSA strain 43300 and human clinical isolates of MRSA by

means of solid agar diffusion and liquid medium methods (50). It was indicated that L. acidophilus CL1285® or L. casei LBC80® caused an inhibition of MRSA growth, but to a different extent, with the former showing a zone diameter of 1.7-2.9 cm and the latter 1.4-2.9 cm depending on the MRSA clinical isolate. Direct interaction between Bio-K+® and MRSA in liquid medium resulted in the elimination of almost all MRSA cells (99%). The effects of acidic supernatants of L. acidophilus isolated from a vinegar were explored against clinical MRSA samples related to acne pimple with lipolytic activity (45). It was exhibited that cell-free supernatant notably impacted MRSA isolates versus control. Subinhibitory concentrations of acid supernatants appeared very effective in preventing the lipase release from biofilm and planktonic cells of MRSA isolates (51). More to the point, prebiotics are nondigestive food constituents with selective actions on the growth and/or activity of one or more bacterial strains in the colon that culminate in health promoting effects (52, 53). The synergistic administration of probiotics and prebiotics is known as synbiotics (52). Given several possible combinations, the use of synbiotics for the regulation of intestinal microbiota in humans is expected to have promising outcomes (54). This study was an attempt to investigate the effect of synbiotics in the form of Kidilact®, Vitalact®, and Protexin® sachets on the growth of clinical MRSA isolates and expression of mecA gene.

2 | MATERIALS AND METHODS

2.1 | Samples Collection

MRSA isolates from clinical specimens, including, blood, urine, sputum, wound, and lung tissue, were gathered from July to September 2015 from two main general hospitals affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. All MRSA isolates were identified by routine laboratory procedures, such as, Gram stain, catalase test, oxidase test, coagulase activity, and mannitol salt fermentation (55). The antibiotic susceptibility of isolated strains was explored using the disk-agar diffusion method (56).

2.2 | Detection of mecA Gene in Clinical MRSA Isolates

DNA extraction was conducted by Sinaclone DNA extraction kit (Sinaclon, Iran). Bacterial pellet was resuspended in 100 µl of G+ pre lysis buffer as well as 20 µl of lyzosyme, and subsequently mixed and incubated at 37 °C for 35 min. After adding 20 µl of ributinase, the solution underwent another incubation (at 55 °C for 35 min) for complete cell lysis. Thereafter, lysis buffer as well as precipitation solution were added and the final mixed solution was loaded into a spin column. Following three wash steps, DNA was eluted by elution buffer in 65 °C (57, 58). To amplify mecA gene, the following forward and backward primers were respectively

Kidilact®	Vitalact®	Protexin®
Lactobacillus Casei	*Lactobacillus gasseri*	*Lactobacillus Casei*
Lactobacillus acidophilus	*Bifidobacterium bifidum*	*Lactobacillus acidophilus*
Lactobacillus rhamnosus	*Bifidobacterium longum*	*Lactobacillus rhamnosus*
Lactobacillus bulgaricus		*Lactobacillus bulgaricus*
Bifidobacterium infantis		*Bifidobacterium infantis*
Bifidobacterium breve		*Bifidobacterium breve*
Streptococcus thermophilus		*Streptococcus thermophilus*

TABLE 1 The bacterial strains in each synbiotic supplement.

selected: 5'-AAAATCGATGGTAAAGGTTGGC and 5'-AGTTCTGCAGTACCGGATTTGC). Genomic DNA was analyzed for the presence of the mecA gene employing the PCR system (Astec, Japan). The PCR products were visualized (UV duct, USA) under the UV transillumination after electrophoresis on 1.5% agarose gel containing Green viewer.

2.3 | Probiotic Strains and Growth Conditions

Synbiotics in the form of Kidilact®, Vitalact® (Zisttakhmir Company, Iran), and Protexin® (Science and Nature in Balance Company, UK) sachets were purchased. Each sachet contained 109 CFU probiotic strains. The bacteria used for the synbiotic supplements are shown in Table 1.

The pre-culture preparation is of utmost importance for providing optimal conditions for the bacteria to show their ability of releasing anti-MRSA components. Prior to analyses of anti-MRSA activity, these sachets were dissolved in normal saline (2 mL), added to brain-heart infusion broth (BHI; 5 mL), and then incubated at 37 °C for 24 h. Afterwards, a 9 mL of each synbiotic supplement was subcultured on Man-Rogosa-Sharpe (MRS) broth to adapt them to the growth conditions during incubation for 24 h at 37 °C. Routine laboratory procedures (i.e., Gram stain, catalase test, coagulase activity, and motility) were carried out for these strains, as well. Cell-free culture supernatant was obtained by centrifugation at 5000 rpm for 15 min at 4 °C, as well as filtration using a 0.2 μm syringe filter.

2.4 | Assessment of Bacteria Antagonistic Activities as Probiotics

Disk diffusion. Initially, the supernatants at pH 4.0 were neutralized to pH 7.0 by NaOH (0.1 N). Then, four test pathogens cultured in BHI agar were used. Spread culture of the bacterial suspensions were subsequently prepared on an agar plate using a turbidity equivalent to 0.5 McFarland standards. The plates were allowed to incubate for 30 min at 37 °C. A 20 μl of each supernatant was loaded onto a 6 mm sterile disk. Three disks were separately put on the plate and maintained at 4 °C for 30 min to facilitate the diffusion of the loaded compounds. Another disk loaded by water was considered as the negative control. They were transferred into an incubation at 37 °C for 24 h, afterwards. Finally, the inhibition zone diameters were evaluated in triplicate.

Well diffusion. After neutralizing the supernatants as described in disk diffusion method, MRSA cultures were diluted to a suitable turbidity. The bacterial inoculum suspension was spread by swabbing on a BHI agar plate, which was subsequently allowed to dry at 37 °C for 30 min. A sterile Pasture pipette was applied to punch three wells, 9 mm in diameter, on the surface of agar. 130 μl of each supernatant was poured inside the wells before incubation at 37 °C for 24 h. A vancomycin disk served as the positive control. The antimicrobial effect of each supernatant was expressed as the inhibition zone diameter in millimeter around the wells.

2.5 | Penicillin-Susceptibility Testing

Disk diffusion test was carried out on Mueller–Hinton agar plates with a penicillin disk (Padtan Teb, Iran). MRSA strains were incubated for 24 h at 37 °C. This test was iterated for 48, 72, 96, 120 h. The zone diameter was measured in triplicate. Strains with the most sus-

Length	5'→ 3'	Gene
199 bp	*ACTCCTACGGGAGGCAGCAGTGTATTACCGCGGCTGCTGGCA*	*16s rRNA*
273 bp	*GATAAAAAAGAACCTCTGCTACTGCCTAATTCGAGTG*	*mecA*

TABLE 2 mecA and 16s rRNA primers

ceptibility to penicillin were used for further analyses by real time PCR.

2.6 | Real Time PCR

The bacterial RNA was extracted by the RNX-plus kit (Sinagene, Iran) as described by Morin et al (59). Purity and quality of the extracted RNA were assessed by NanoDrop spectrophotometer (Ipoch, China). Then, RNA underwent electrophoresis in a 2% agarose gel. Following purification steps, RNA was examined for the absence of protein, phenol, and genomic DNA through electrophoresis in a 1.5% agarose gel. Thereafter, complementary DNA (cDNA) was synthesized from RNA employing Easy cDNA Synthesis Kit (Parstoos, Iran) according to the manufacturer's instructions. The quality of cDNA was confirmed by PCR using mecA and 16s rRNA primers (Table 2). Quantitative analyses were carried out by means of SYBR Green Real Time PCR Master Mix (Parstoos, Iran) and Real-Time PCR System (ABIverity, USA). Each reaction mixture included 5 µl of master mix (2X), 1 µl of cDNA, 6 µl of dH2O, 0.2 µl of ROX Reference Dye (50X), and 1 µl of primer (0.02 µM). The condition of PCR amplification contained an initial denaturation at 95 °C for 7 minutes, followed by 40 cycles of denaturation for 30 seconds at 94 °C, annealing for 35 seconds at 45 °C, and extension for 40 seconds at 72 °C. The 2-Ct method was applied to calculate the relative expression of mecA gene with 16s rRNA as a housekeeping gene.

3 | RESULTS

3.1 | Collection of MRSA isolates

The presence of S. aureus in all the clinical specimens was verified using a number of routine laboratory tests (Figures 1). A total of eight MRSA strains was isolated from various clinical specimens. As can be seen in Table 3, these strains were shown to be resistant against most common antibiotics, including, ampicillin, oxacillin, erythromycin, cefoxitin, tetracycline, penicillin, gentamicin, and clindamycin. All strains developed sensitivity to vancomycin and ofloxacin, but resistance to ciprofloxacin. Only two samples (B and C) were sensitive to almost all antibiotics, thus they were excluded from the next experiments.

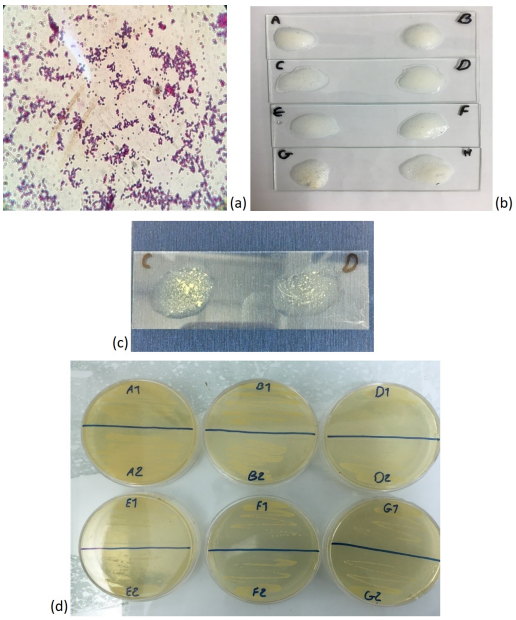

FIGURE 1 Identification of S. aureus by Gram stain (a), catalase test (b), coagulase activity (c), and monitol salt agar (d).

The genomic identity of the clinical MRSA isolates was substantiated through amplifying a 533 bp fragment of the mecA gene by the PCR analysis. Figure 2 demonstrated that six clinical isolates (A, D, E, F, G, and H) were PCR positive for mecA.

3.2 | Probiotic strains and their anti-MRSA properties

The identification of probiotic strains in the commercial synbiotics was performed applying Gram stain (Figure 3a), coagulase test (Figure 3b), oxidase test (Figure 3c), and motility (Figure 3d). It appeared that these strains were Gram-positive, catalase-negative, oxidase-negative, and non-motile.

The antimicrobial activity of the supernatants produced by the commercial synbiotics is shown in Figure 4. Two different methods were used to test the anti-MRSA potential of probiotics at pH 7.0, wherein the lac-

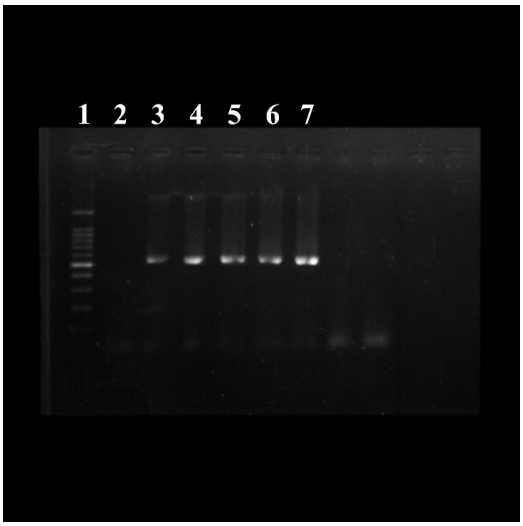

FIGURE 2 Agarose gel electrophoresis showing ladder (1), negative control (2), and samples D (3), E (4), F (5), G (6) and H (7).

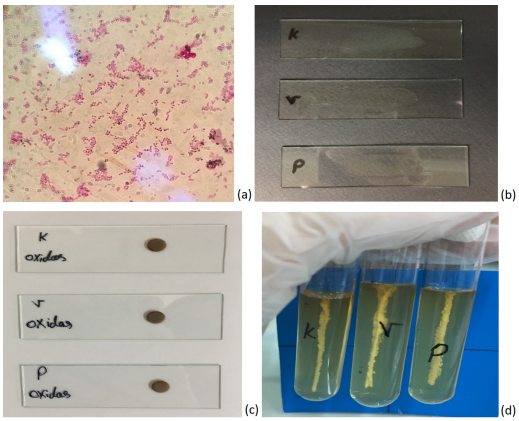

FIGURE 3 Identification of probiotics by Gram stain (a), coagulase test (b), oxidase test (c), and motility (d).

tic acid effects of components that may exist in the supernatants were removed. It was found that the disk diffusion method failed to indicate the inhibitory impacts of free-cell supernatants on MRSA isolates. There was no obvious inhibitory zone and slight decreases occurred in the pathogen growth only on the surface of the plate (Figure 4a). On the contrary, the well diffusion method could obviously exhibit the anti-bacterial properties of the supernatants; the growth of MRSA in all sex isolates was inhibited as exposed to the supernatants (Figure 4b). Of note, the inhibition zone diameters of Protexin supernatant were greater than those of vancomycin. Table 4 summarizes the zone diameters of growth inhibition by the supernatants.

The inhibitory effects of the supernatants were also quantified using the following equation:

$$x = \frac{\left(r_2{}^2 - r_1{}^2\right) \times 100}{r_1{}^2}$$

This denotes the comparative inhibition caused by the supernatants versus vancomycin. The positive values are indicative of the additional inhibition. Accordingly, Protexin supernatant induced an additional inhibition as opposed to vancomycin (Table 5).

*	AM	OX	V	OFX	E	FOX	TE	P	GM	CC	CP
A	R	R	S	S	R	R	R	R	R	R	R
B	S	S	S	S	S	S	S	S	S	S	R
C	S	S	S	S	S	S	S	S	S	S	R
D	R	R	S	S	R	R	R	R	S	R	R
E	R	R	S	S	R	R	R	R	S	R	R
F	R	R	S	S	R	R	R	R	S	R	R
G	R	R	S	S	R	R	R	R	S	R	R
H	R	R	S	S	R	R	R	R	S	R	R

TABLE 3 The inhibition zone of growth for MRSA strains by antibiotics. R: Resistance, S: Sensitive, AM: Ampicilin, OX: Oxacillin, V: Vancomycin, OFX: Ofloxacin, E: Erythromycin, FOX: Cefoxitin, TE: Tetracycline, P: Penicillin, GM: Gentamicin, CC: Clindamycin, CP:Ciprofloxacin.

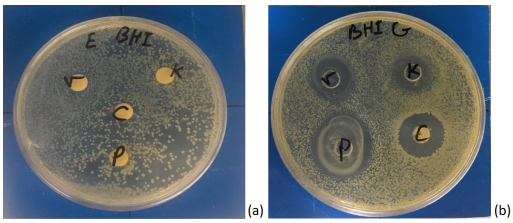

FIGURE 4 Different responses to antibiotics using the disk (a) and well (b) diffusion methods.

	Kidilact^{ő}	Vitalact^{ő}	Protexin^{ő}	Vancomycin (C+)
A	22	21	24	23
B	15	13	18	18
D	21	24	24	23
E	12	22	28	22
F	16	20	28	20
G	16	19	29	19
H	15	22	26	20

TABLE 4 Different responses to antibiotics using the disk (a) and well (b) diffusion methods

3.3 | Penicillin susceptibility testing

The results of penicillin-susceptibility testing presented that the supernatant produced by synbiotics can afford to confer penicillin susceptibility in MRSA isolates at 72, 96, and 120 h (Figure 5). Therefore, the supernatants were observed to possess either bactericidal or bacteriostatic activities in a time-dependent fashion.

The penicillin zone diameters in MRSA isolates following 96 and 120 h co-culture with the supernatants

	Kidilact^{ő}	Vitalact^{ő}	Protexin^{ő}
A	-8.5066	-16.6351	+8.8846
D	-16.6351	+8.8846	+8.8846
E	-70.2479	0	+61.9833
F	-36.00	0	+96.00
G	-29.0858	0	+132.9639
H	-0.4375	+21.00	+69.00

TABLE 5 The comparative inhibition caused by the supernatants versus vancomycin

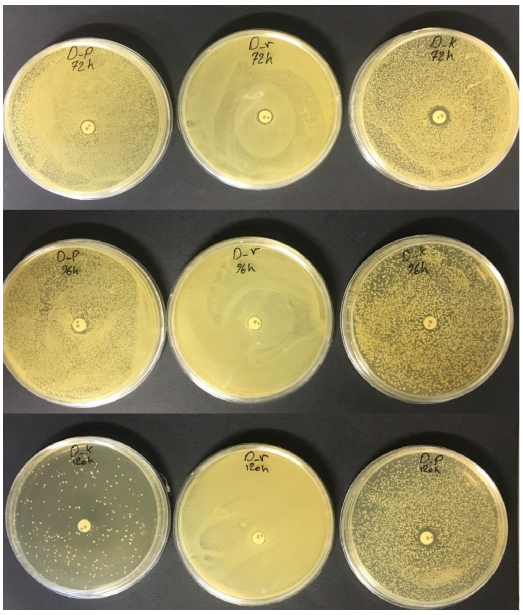

FIGURE 5 Penicillin susceptibility of MRSA isolates at different time points (72hrs,96hrs and 120hrs).

are presented in Table 6. It was revealed that isolates A, D, and E were the most susceptible samples at 120 h, while differently the other three isolates (F, G, and H) had the highest susceptibility at 96 h. Moreover, the levels of susceptibility to penicillin caused by the supernatants are shown in Table 7. The neutralized supernatant of all three symbiotic supplements showed no activity against MRSA in isolates G and H after 120 h. Unexpectedly, the neutralized supernatant of Kidilact^{ő} was active against MRSA in isolate F after 120 h, whereas no activity was observed for that of Protexin^{ő}.

4 | DISCUSSION

Commercial probiotics packed in one tablet or capsule are largely consumed across the globe. Considering the growing effects of antibiotic resistance, these dietary supplements have garnered more attention due to their potential against the spread of resistant determinants (60). This study aimed at elucidating whether cell-free supernatant from such dietary supplements can inhibit the growth of MRSA and affect their susceptibility to penicillin. The findings of this study indicated that

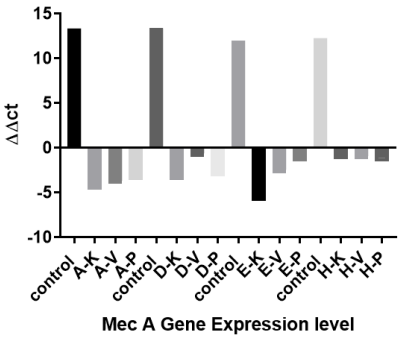

FIGURE 6 The expression level of mecA in different MRSA isolates following treatment with the supernatants of probiotics. A,D,E,H : MRSA isolates, K,V,P : Kidilact, Vitalact, Protexin.

the commercial synbiotics, including Kidilact®, Vitalact®, and Protexin®, produced components with antimicrobial properties that can impede the growth of multi-antibiotic resistance MRSA. This event was only manifest in the results of the well diffusion test. Moreover, the supernatant produced by synbiotics can afford to confer penicillin susceptibility in the MRSA isolates in a time-dependent fashion, which might be partly ascribed to the decreased expression of mecA gene. Indeed, two third of susceptible MRSA isolates carried declined levels of mecA gene expression. This is the first research study providing the in vitro evidence that supported the ability of the supernatant produced by commercial synbiotics not only to counteract against the MRSA isolates collected from clinical specimens, but also to induce penicillin susceptibility in these samples. The supernatant-reduced susceptibility mechanism of multi-antibiotic resistance MRSA can be regulated through the expression of mecA gene. These findings were corroborated by Karska-Wysocki et al., whose study showed

*	96 h	120 h	*	96 h	120 h
A-K	9	6	**F-K**	7	6
A-V	8	8	**F-V**	8	7
A-P	7	6	**F-P**	10	0
D-K	5	8	**G-K**	9	0
D-V	8	6	**G-V**	0	0
D-P	7	12	**G-P**	6	0
E-K	13	13	**H-K**	7	0
E-V	7	14	**H-V**	10	0
E-P	8	9	**H-P**	7	0

TABLE 6 The inhibition zone of growth for MRSA strains at different time points after co-culture with the supernatants.

*	The levels of susceptibility to penicillin	*	The levels of susceptibility to penicillin
A-K	244.89	**F-K**	300
A-V	359.18	**F-V**	359.18
A-P	244.89	**F-P**	489.79
D-K	359.18	**G-K**	422.44
D-V	244.89	**G-V**	0
D-P	636.73	**G-P**	244.89
E-K	716.32	**H-K**	300
E-V	800	**H-V**	489.79
E-P	422.44	**H-P**	300

TABLE 7 The levels of susceptibility to penicillin caused by the supernatants.

the bactericidal impact of mixed lactic acid bacteria (LAB) against MRSA. They concluded that the mixed culture of LAB strains contains several antibacterial components, which are not found in pure monoculture (50). Also, Matto et al. observed that a probiotic mixture containing several strains with distinct characteristics possessed the ability to effectively prevent infections caused by pathogenic bacteria (61). In addition to the production of organic acids (e.g., lactic acid), which has a lowering effect on pH, certain strains can synthesize and secrete bioactive molecules, including ethanol, formic acid, fatty acids, hydrogen peroxide, and bacteriocins with marked antimicrobial actions (62). The genera Lactobacillus and Bifidobacterium along with their by-products have appeared to be effective for multiple conditions. Their antimicrobial activities arise from the inhibition of cellular functions through undesirable changes in the intracellular pH (63). The lack of activity against MRSA in isolates G and H could be justified by the effect of neutralized pH on the antagonistic activity of these probiotic bacteria in vitro. Therefore, the inhibition zones found despite the removal of lactic acid effects suggest the possible influences of other inhibitory by-products, namely hydrogen peroxide, bacteriocin and bacteriocin-like components (64). Given the findings of the present study, it was concluded that synbiotics are effective for reducing MRSA growth and antibiotic resistance through suppression of mecA.

REFERENCES

1. Malani PN, Rana MM, Banerjee M, Bradley SF. Staphylococcus aureus bloodstream infections: the association between age and mortality and functional status. Journal of the American Geriatrics Society. 2008;56(8):1485-9.

2. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant Staphylococcus aureus. The Lancet. 2010;375(9725):1557-68.

3. Otto M. Basis of virulence in community-associated methicillin-resistant Staphylococcus aureus. Annual review of microbiology. 2010;64:143-62.

4. Chambers HF, DeLeo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. Nature Reviews Microbiology. 2009;7(9):629-41.

5. DeLeo FR, Chambers HF. Reemergence of antibiotic-resistant Staphylococcus aureus in the genomics era. The Journal of clinical investigation. 2009;119(9):2464-74.

6. Sachdev D, Amladi S, Natraj G, Baveja S, Kharkar V, Mahajan S, et al. An outbreak of methicillin-resistant Staphylococcus aureus (MRSA) infection in dermatology indoor patients. Indian Journal of Dermatology, Venereology, and Leprology. 2003;69(6):377.

7. Goetghebeur M, Landry P-A, Han D, Vicente C. Methicillin-resistant Staphylococcus aureus: a public health issue with economic consequences. Canadian Journal of Infectious Diseases and Medical Microbiology. 2007;18(1):27-34.

8. Gilbert M, MacDonald J, Gregson D, Siushansian J, Zhang K, Elsayed S, et al. Outbreak in Alberta of community-acquired (USA300) methicillin-resistant Staphylococcus aureus in people with a history of drug use, homelessness or incarceration. Canadian Medical Association Journal. 2006;175(2):149-54.

9. Berger-Bächi B. Resistance mechanisms of gram-positive bacteria. International Journal of Medical Microbiology. 2002;292(1):27-35.

10. Zapun A, Contreras-Martel C, Vernet T. Penicillin-binding proteins and -lactam resistance. FEMS microbiology reviews. 2008;32(2):361-85.

11. Matsuhashi M, Song MD, Ishino F, Wachi M, Doi M, Inoue M, et al. Molecular cloning of the gene of a penicillin-binding protein supposed to cause high resistance to beta-lactam antibiotics in Staphylococcus aureus. Journal of Bacteriology. 1986;167(3):975-80.

12. Lu TK, Koeris MS. The next generation of bacteriophage therapy. Current opinion in microbiology. 2011;14(5):524-31.

13. Pires DP, Cleto S, Sillankorva S, Azeredo J, Lu TK. Genetically engineered phages: a review of advances over the last decade. Microbiology and Molecular Biology Reviews. 2016;80(3):523-43.

14. Donskey CJ. The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens. Clinical infectious diseases. 2004;39(2):219-26.

15. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. nature. 2010;464(7285):59-65.

16. Reid G. The importance of guidelines in the development and application of probiotics. Current pharmaceutical design. 2005;11(1):11-6.

17. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics—approaching a definition–. The American journal of clinical nutrition. 2001;73(2):361s-4s.

18. Teitelbaum JE, Walker WA. Nutritional impact of pre-and probiotics as protective gastrointestinal organisms. Annual Review of Nutrition. 2002;22(1):107-38.

19. Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis JW, et al. Prebiotic oligosaccharides in dietetic products for infants: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2004;39:465-73.

20. Gaggìa F, Mattarelli P, Biavati B. Probiotics and prebiotics in animal feeding for safe food production. International journal of

food microbiology. 2010;141:S15-S28.

21. Talarico T, Casas I, Chung TC, Dobrogosz W. Production and isolation of reuterin, a growth inhibitor produced by Lactobacillus reuteri. Antimicrobial agents and chemotherapy. 1988;32(12):1854-8.

22. Arqués JL, Fernández J, Gaya P, Nuñez M, Rodrıguez E, Medina M. Antimicrobial activity of reuterin in combination with nisin against food-borne pathogens. International journal of food microbiology. 2004;95(2):225-9.

23. Chen P-W, Jheng TT, Shyu C-L, Mao FC. Synergistic antibacterial efficacies of the combination of bovine lactoferrin or its hydrolysate with probiotic secretion in curbing the growth of meticillin-resistant Staphylococcus aureus. Journal of medical microbiology. 2013;62(12):1845-51.

24. Alvarez-Olmos MI, Oberhelman RA. Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. Clinical infectious diseases. 2001;32(11):1567-76.

25. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. The Journal of nutrition. 1995;125(6):1401-12.

26. Gupta V, Garg R. Probiotics. Indian journal of medical microbiology. 2009;27(3):202-9.

27. Goldin B, Gorbach S. Clinical indications for probiotics: an overview. Clinical Infectious Diseases. 2008;46(Supplement_2):S96-S100.

28. Gorbach SL. Probiotics and gastrointestinal health. The American Journal of Gastroenterology. 2000;95(1, Supplement 1):S2-S4.

29. Salminen S, von Wright A, Morelli L, Marteau P, Brassart D, de Vos WM, et al. Demonstration of safety of probiotics — a review. International journal of food microbiology. 1998;44(1):93-106.

30. Snydman DR. The safety of probiotics. Clinical infectious diseases. 2008;46(Supplement_2):S104-S11.

31. Sorokulova I. Preclinical testing in the development of probiotics: a regulatory perspective with Bacillus strains as an example. Clinical infectious diseases. 2008;46(Supplement_2):S92-S5.

32. Grześkowiak Ł, Isolauri E, Salminen S, Gueimonde M. Manufacturing process influences properties of probiotic bacteria. British Journal of Nutrition. 2011;105(6):887-94.

33. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A. Probiotic mechanisms of action. Annals of Nutrition and Metabolism. 2012;61(2):160-74.

34. Lu L, Walker WA. Pathologic and physiologic interactions of bacteria with the gastrointestinal epithelium–. The American journal of clinical nutrition. 2001;73(6):1124S-30S.

35. Zhang L, Xu Y-Q, Liu H-Y, Lai T, Ma J-L, Wang J-F, et al. Evaluation of Lactobacillus rhamnosus GG using an Escherichia coli K88 model of piglet diarrhoea: Effects on diarrhoea incidence, faecal microflora and immune responses. Veterinary Microbiology. 2010;141(1):142-8.

36. Barefoot SF, Klaenhammer TR. Detection and activity of lactacin B, a bacteriocin produced by Lactobacillus acidophilus. Applied and Environmental microbiology. 1983;45(6):1808-15.

37. Kailasapathy K, Chin J. Survival and therapeutic potential of probiotic organisms with reference to Lactobacillus acidophilus and Bifidobacterium spp. Immunology and Cell Biology. 2000;78(1):80-8.

38. Kopp-Hoolihan L. Prophylactic and therapeutic uses of probiotics: a review. Journal of the Academy of Nutrition and Dietetics. 2001;101(2):229-41.

39. Yamano T, Iino H, Takada M, Blum S, Rochat F, Fukushima Y. Improvement of the human intestinal flora by ingestion of the probiotic strain Lactobacillus johnsoniiLa1. British Journal of Nutrition. 2006;95(2):303-12.

40. Ibnou-Zekri N, Blum S, Schiffrin EJ, von der Weid T. Divergent patterns of colonization and immune response elicited from two intestinal Lactobacillus strains that display similar properties in vitro. Infection and immunity. 2003;71(1):428-36.

41. Salminen S, Bouley C, Boutron M-C, Cummings J, Franck A, Gibson G, et al. Functional food science and gastrointestinal physiology and function. British Journal of Nutrition. 1998;80(S1):S147-S71.

42. Schiffrin E, Rochat F, Link-Amster H, Aeschlimann J, Donnet-Hughes A. Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. Journal of Dairy Science. 1995;78(3):491-7.

43. Corthier G, Dubos F, Raibaud P. Modulation of cytotoxin production by Clostridium difficile in the intestinal tracts of gnotobiotic mice inoculated with various human intestinal bacteria. Applied and environmental microbiology. 1985;49(1):250-2.

44. Bendjeddou K, Fons M, Strocker P, Sadoun D. Characterization and purification of a bacteriocin from Lactobacillus paracasei subsp. paracasei BMK2005, an intestinal isolate active against multidrug-resistant pathogens. World Journal of Microbiology and Biotechnology. 2012;28(4):1543-52.

45. Fahad HJ, Radeef HM. Capability of Lactobacillus acidophilus supernatant to inhibit production of lipase from methicillin-resistant Staphylococcus aureus. J Univ Anbar Pure Sci. 2011;5:1-5.

46. Sadowska B, Walencka E, Wieckowska-Szakiel M, Różalska B. Bacteria competing with the adhesion and biofilm formation by Staphylococcus aureus. Folia microbiologica. 2010;55(5):497-501.

47. Charlier C, Cretenet M, Even S, Le Loir Y. Interactions between Staphylococcus aureus and lactic acid bacteria: an old story with new perspectives. International journal of food microbiology. 2009;131(1):30-9.

48. Prince T, McBain AJ, O'Neill CA. Lactobacillus reuteri protects epidermal keratinocytes from Staphylococcus aureus-induced cell death by competitive exclusion. Applied and environmental microbiology. 2012;78(15):5119-26.

49. Jones ML, Ganopolsky JG, Labbé A, Prakash S. A novel nitric oxide producing probiotic patch and its antimicrobial efficacy: preparation and in vitro analysis. Applied microbiology and biotechnology. 2010;87(2):509-16.

50. Karska-Wysocki B, Bazo M, Smoragiewicz W. Antibacterial activity of Lactobacillus acidophilus and Lactobacillus casei against methicillin-resistant Staphylococcus aureus (MRSA). Microbiological research. 2010;165(8):674-86.
51. Sikorska H, Smoragiewicz W. Role of probiotics in the prevention and treatment of meticillin-resistant Staphylococcus aureus infections. International journal of antimicrobial agents. 2013;42(6):475-81.
52. Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. The American journal of clinical nutrition. 1999;69(5):1052s-7s.
53. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. Gastroenterology. 1995;108(4):975-82.
54. Scavuzzi B, Henrique F, Miglioranza L, Simão A, Dichi I. Impact of prebiotics, probiotics and synbiotics on components of the metabolic syndrome. Ann Nutr Disord Ther. 2014;1:1009.
55. Merlino J, Watson J, Rose B, Beard-Pegler M, Gottlieb T, Bradbury R, et al. Detection and expression of methicillin/oxacillin resistance in multidrug-resistant and non-multidrug-resistant Staphylococcus aureus in Central Sydney, Australia. Journal of Antimicrobial chemotherapy. 2002;49(5):793-801.
56. McDougal LK, Thornsberry C. New recommendations for disk diffusion antimicrobial susceptibility tests for methicillin-resistant (heteroresistant) staphylococci. Journal of clinical microbiology. 1984;19(4):482-8.
57. Asgharzadeh M, Kafil HS, Roudsary AA, Hanifi GR. Tuberculosis transmission in Northwest of Iran: using MIRU-VNTR, ETR-VNTR and IS6110-RFLP methods. Infection, Genetics and Evolution. 2011;11(1):124-31.
58. Toledo-Arana A, Valle J, Solano C, Arrizubieta MaJ, Cucarella C, Lamata M, et al. The enterococcal surface protein, Esp, is involved in Enterococcus faecalis biofilm formation. Applied and environmental microbiology. 2001;67(10):4538-45.
59. Morin NJ, Gong Z, Li X-F. Reverse Transcription-Multiplex PCR Assay for Simultaneous Detection of Escherichia coli O157:H7, Vibrio cholerae O1, and Salmonella Typhi. Clinical Chemistry. 2004;50(11):2037-44.
60. Broaders E, Gahan CG, Marchesi JR. Mobile genetic elements of the human gastrointestinal tract: potential for spread of antibiotic resistance genes. Gut microbes. 2013;4(4):271-80.
61. Mättö J, Fondén R, Tolvanen T, von Wright A, Vilpponen-Salmela T, Satokari R, et al. Intestinal survival and persistence of probiotic Lactobacillus and Bifidobacterium strains administered in triple-strain yoghurt. International dairy journal. 2006;16(10):1174-80.
62. De Vuyst L, Leroy F. Bacteriocins from lactic acid bacteria: production, purification, and food applications. Journal of molecular microbiology and biotechnology. 2007;13(4):194-9.
63. Kivanc M, Yilmaz M, Cakir E. Isolation and identification of lactic acid bacteria from boza, and their microbial activity against several reporter strains. Turkish Journal of Biology. 2011;35(3):313-24.
64. Georgieva R, Yocheva L, Tserovska L, Zhelezova G, Stefanova N, Atanasova A, et al. Antimicrobial activity and antibiotic susceptibility of Lactobacillus and Bifidobacterium spp. intended for use as starter and probiotic cultures. Biotechnology Biotechnological Equipment. 2015;29(1):84-91.

COMMENTARY

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Sanitation, Sanity, and (Moral) Suitability: The History of the Medical Inadmissibility of Immigrants into Canada

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ABSTRACT

Study of the history of medical inadmissibility and deportation of Canadian immigrants uncovers three important themes as criteria for immigration selection and control: sanitation, sanity, and moral suitability. As the understanding of human health changed with history, so too did the basis for exclusion and deportation of Canadian immigrants for medical purposes. Immigration policy mirrored then current notions of health and disease, growing in complexity as immigration policy increased its selectivity contemporaneous to increasing immigration rates. Immigration control developed from simple quarantine measures to prevent the transmission of infectious diseases from other continents, to physical and mental health inspections to prevent the propagation of hereditary dysfunction, to selection of morally fit immigrants resembling Canadian values for easy assimilation into society. Physical, mental, and moral health were key criteria in the first century of Canadian immigration policy, highlighting Canada's history of antiimmigrant sentiment through the medicalization of specific ethnic groups.

KEYWORDS
history of medicine, immigration, policy

1 | INTRODUCTION

Canadian history of the medical inadmissibility of immigrants introduces the fluid concepts of health and medicine to the study of immigration policy. Among many new scientific innovations, rapid development in the field of medicine aligned with the increasing acceptance of the germ theory of disease in the nineteenth century, the emerging notions of heredity and eugenics at the turn of the twentieth century, and the legitimization of psychiatry in the early-to-mid-twentieth century. As understanding of human health transformed with his-

tory, so too did the basis for exclusion and deportation of Canadian immigrants for medical purposes. Indeed, immigration policy mirrored then current concepts of health and disease, growing in complexity as Canadian immigration policy increased its selectivity contemporaneous to increasing immigration rates. Immigration control developed from simple quarantine measures to prevent the transmission of infectious diseases from other continents, to physical and mental health inspections to prevent the propagation of hereditary dysfunction and disease, to selection of morally fit immigrants resembling Canadian values for easy assimilation into society (1,2,3). Over the course of the first century of Canadian immigration policy, notions of physical, mental, and moral health were inextricably intertwined (4).

This paper aims to provide a comprehensive study of the history of medical inadmissibility and deportation of Canadian immigrants from the 1840s to the 1950s, addressing three important themes as criteria for immigration selection and control: sanitation, sanity, and (moral) suitability. While scholarship in this field generally focuses on quarantine to prevent the entry of infectious disease, the mission of Canadian immigration policy stretched beyond the control of cholera and typhus as medical inspectors surveyed for physical disability, mental illness, and moral depravity (5). Indeed, the health inspection of immigrants was used as a principal tool for selecting members of an ideal Canadian society. As a result, the medicalization of the newly arrived immigrant contributed greatly to discrimination against specific races and ethnicities, ultimately manifesting as an anti-immigrant social environment throughout much of Canadian history.

2 | SANITATION: QUARANTINE AND EARLY IMMIGRATION CONTROL

The years 1846 to 1854 marked the peak of Canadian immigration prior to the twentieth century, as the massive influx of 400,000 British—primarily, Irish—immigrants set sail to North America. Many immigrants were starving and impoverished, bringing with them a multitude of infectious diseases including typhus and dysentery (6). Furthermore, sporadic cholera outbreaks that swept through British North America from 1832 onward seriously affected Canadian mortality rates (1). To meet the threat of spreading infectious diseases, all cargo and passengers of incoming ships underwent extensive quarantine and inspection before allowed to dock at the mainland ports, a practice first established in the 1830s (7).

The Act to Consolidate the Laws Relative to Emigrants and Quarantine of 1853 standardized quarantine regulations for all ships arriving in the Province of Canada and set the foundation for systematic medical inspection in immigration policy (8). Immigrant ships were processed at the quarantine station at Grosse Île in the St. Lawrence River before continuing to Québec City and eventually moving on to Montreal, Kingston, and Toronto. The passengers, cargo, and vessels stationed at quarantine underwent inspection by one or several medical officers searching for signs of infectious disease, including “Asiatic Cholera, Fever, Small Pox, Scarlatina, Measles, or any other infectious and dangerous disease”. The medical superintendent was charged with inspecting the vessel by asking a list of eleven specific questions, such as, “Was such place or places, or any and which of them, infection with the cholera, plague, or any pestilential fever or disease?” (8). If the answers to these questions were satisfactory, the person in charge of the vessel was given a “Clean Bill of Health”, while unsatisfactory answers merited placement under “Quarantine of Observation” as the passengers and crew were subjected to a “strict purification” (8). The medical superintendent sent any passengers who required treatment for “pestilential or infectious diseases” to the hospital located on the island, and passengers showing less severe illness were treated on board of the vessel. Similarly, upon arrival at the Port of Quebec after passing Grosse Île, a secondary screening was performed by an inspecting physician. If no sickness was found on board, the master of the vessel was granted a Certificate verifying the healthy state of all passengers. If sickness was found, the inspecting physician sent the vessel back to

be detained in quarantine for further inspection (8).

By April 1866, the threat of an incoming cholera outbreak brought the Minister of Agriculture, Thomas D'Arcy McGee, to propose new quarantine regulations in an attempt to close loopholes in past practice (1). Ships to undergo quarantine now included all vessels from outside the colony, and inspection was further systematized through a more thorough questionnaire and record-keeping process. Personnel at the quarantine stations were also awarded more power; the superintendent or his deputy was to be a justice of the peace with a jurisdiction extending for a mile in all directions around the island (1). The Quarantine Health Act of 1868, incorporated into Canada's first Immigration Act in 1869, expanded "regular quarantine ports" to Halifax and St. John in addition to Grosse Île, as the creation of the Intercolonial Railway rendered New Brunswick and Nova Scotia increasingly important for the disembarkation of immigrants (7,9,10). As the Canadian population grew towards the end of the nineteenth century, immigration law became increasingly more scrupulous, no longer simply excluding the diseased but also selecting for the "desirables" (11). Indeed, pressure to control the influx of immigrants increased with fear of infectious diseases, and specific immigrant groups were blamed for outbreaks. Reports that smallpox arrived on an immigrant train in Winnipeg in 1876, and measles, scarlet fever, diphtheria and leprosy outbreaks throughout Canadian cities brought in by immigrants in the 1890s, all increased antagonism towards immigration, despite no statistical evidence directly relating these groups to the outbreaks. These "loathsome" diseases were often linked to already unpopular groups, confirming suspicions they were not "suitable" for Canada (11).

Infectious diseases were not seen as the only threat to Canadian society during this period, as concern that Europe was sending its unwanted residents to Canada influenced immigration policy as well (11). Quarantine stations were also designed to identify all passengers deemed "Lunatic, Idiotic, Deaf and Dumb, Blind or Infirm, not belonging to any Immigrant family, and such person in, in the opinion of the medical superintendent, likely to become permanently a public charge" (9). Pauperism and disability were viewed as an increasing threat to Canadian society, and fears that immigrants were becoming a public burden shaped the Immigration Act of 1869 (10). The Governor General was charged to "prohibit the landing of pauper or destitute immigrants", while in 1880, an Order in Council barred paupers from entry. Unhealthy children were also viewed as a threat to the public, as many poor immigrant children were described as the "offal of the most depraved characters of the cities of the old country". The House of Commons Select Standing Committee for Agriculture and Colonization thus resolved "to prevent the importation of immigrants, either children or adults, who would be likely to become a burden on our charitable institutions" (11). The Committee recommended a strict medical inspection and certificate of healthiness for all immigrant children, ensuring none suffered from problems related to cardiac disease, vision, hearing, and smallpox, and even went as far as to assess whether children seemed "intellectual" (11). By 1902, the Department of the Interior began to examine all immigrants after passing through quarantine in order to deport those with "loathsome, dangerous, or contagious diseases". By 1904, immigrants were also being examined before they left Britain (11). Indeed, the increasing Canadian population rendered policy more selective of its immigrants' overall health, a trend that was to compound with the growing discourse on eugenic theory (12).

3 | SANITY: EUGENICS, RACE AND THE MENTAL HYGIENE MOVEMENT

Eugenics emerged across the Western world at the turn of the twentieth century, embedded in ideas of nationalism and fear of "social suicide" (5). Nineteenth-century industrialization led to the urbanization of societies, creating chaotic, densely populated city environments. Large waves of immigrants entering Canada in the early twentieth century inspired fear that "inferior" families were overtaking the Canadian population as conditions of the First World War allowed Europe to

"dump" its diseased and degenerate classes onto Canadian soil (13). With high urban mortality rates and overcrowded asylums increasing public expenditure, as well as the loss of Canada's young and healthy in the First World War, immigration policy began to mirror the fears of the social and intellectual elite regarding the massive influx of immigrants (12). The solution appeared to be stricter immigration laws barring entry or deporting immigrants from specific countries, assisting migration from Britain to preserve Canada's British character, performing more thorough medical inspections, and preventing entry of the "feeble-minded" in order to ensure the propagation of a physically, intellectually, and mentally fit society (13).

Supported by eugenic theory, the concept of "racial origin" was a major consideration in the selection of immigrants during the early twentieth century. Prior to the 1890s, nearly all immigrants were of British and Irish decent; by the 1920s, these countries accounted for only 54.5 per cent of immigrants (12). Origin statistics in the nineteenth century were primarily used to assess the population numbers of the two founding races—French and English. During the inter-war period, however, racial origin statistics were used as a means to evaluate efforts to attract immigrants from "preferred" countries. Preferred immigrants were considered those better fit to adapt to Canadian society: the British, Dutch, and Nordic over those from Southeast Europe and Asia (12). In addition to being more easily subject to "Canadianization", those of Germanic and Scandinavian ancestry were believed to be of superior physical and mental health (3). As issues of race and degeneracy became increasingly connected, the immigration system was designed to both select immigrants of desirable nationalities and races and deselect those of undesirable ones (14).

The Immigration Act of 1906 contributed to the medicalization of social "fitness", barring entry of the feebleminded, idiot, epileptic, insane, or pauper immigrant "likely to become a public charge" (4). Individuals of certain nationalities and races were understood to be disproportionately prone to these deficiencies. Italians, for example, were considered more prone to emotional instability and violent outbursts, while Slavs were more susceptible to feeblemindedness (14). Similarly, it was believed that Jews were physically inferior and even harmful to society (5). Canadian psychiatrist Charles Kirk Clarke—a central member of the "mental hygiene" movement in the early twentieth century—was largely influenced by the eugenics movement, and thus sought to reduce the hereditary transmission of mental, physical, and behavioural defects (5). As immigrants were believed to contribute disproportionately to the insane and feebleminded populations, Clarke described the barring of "defect immigrants" as a "preventative medicine" for Canadian society (4). Supported by the theory of degeneracy, immigration restriction of certain nationalities and races thus seemed the solution to this problem.

Proponents of the degeneracy theory and the mental hygiene movement argued that present immigration restrictions were failing, as increasingly larger proportions of asylum and hospital patients were immigrants (4). Asylums consumed almost 20 per cent of Ontario's provincial budget by the turn of the twentieth century, rendering economic efficiency an increasing concern in public policy debate (5). However, those occupying beds in these public institutions were not only from non-preferred countries; the majority of hospital and asylum inmates were British paupers, thus supporting the Act's exclusion of the poor and destitute. British newcomers were recognized as representing the greatest percentage of mentally defective immigrants. Fearing that their "hereditary taint" would increase asylum admission rates and negatively impact the Canadian race, Clarke and colleagues pushed for limitations on the influx of "diseased" newcomers (5).

Thus, the Immigration Act of 1906 provided for the deportation of immigrants proven to be a "charge upon public funds" within two years of Canadian residency. Medical inspectors "skilled in assessing mental health problems" were assigned to inspect asylums and hospitals for resident immigrants, as the systematization and formalization of deportation procedures improved during the first and second decades of the twentieth century (5). From 1906 onwards, the medical deportation of new residents within the first two years in

Canada required evidence that the medical problem was also present upon arrival. To avoid this clause, deportations were often explained as due to "public charge"—representing more than one-third of all deportations from 1907 until 1926—thus allowing for the deportation of hospital and asylum inmates without the difficulty of proving medical reasons (15).

4 | MORAL SUITABILITY: MORAL REGULATION AND THE FOREIGN THREAT

As immigrant populations rose in Canadian cities and notions of eugenics arose in public discourse, social issues such as crime and moral degeneracy gained prominence in the immigration debate. The Immigration Act of 1910 included provisions allowing deportation for moral and political unsuitability; the 1910s and 1920s therefore saw a period of deportation and immigration restriction of individuals considered undesirable on the basis of their political beliefs. Furthermore, the "Red scare" anti-Communist hysteria during this period promoted the inspection of incoming immigrants to detect possible enemy intelligence as well as exclude socialists, leftists, and union activists (15). These illegal activities were sufficient to convict individuals of crime, which was seen as a form of degeneracy due to genealogy (5). In order to deport the "undesirables and communists", political radicals were often charged as vagrants—cases built by officials' personal impressions of the accused would-be immigrant (15). Political radicals were therefore often barred from entering as immigrants to Canada out of fear that their ideas threatened not only the safety of Canadian society, but also the moral stability of the generations to come (5).

In addition to exclusion for political beliefs or perceived criminal tendencies, a vast number of Canadian immigrants were targeted for "sexual immorality", the majority of which were women (4). Prostitutes, for example, were believed to pose a great threat to Canadian society, both as perpetrators of degenerating immorality as well as reservoirs of sexually transmitted infections (14). Immigrants charged with prostitution were considered undesirable and thus candidates for deportation, forced to undergo medical inspection for a doctor's certificate to support the case. Despite being often found "healthy enough", prostitutes were considered "likely to spread sexual disorder" and were thus charged as vagrants for deportation (4). Prostitutes were blamed for bringing venereal disease into the homes of Canadian families; in contrast, men seemed immune to charges of sexual immorality, but were instead measured as desirable citizens based on their bread-winning capacity (4). Furthermore, women found unable to align with their female roles were rejected from entry for sexually immoral tendencies, including "hermaphrodites" and "homosexuals". "Feminism" was viewed as a hormonal deficiency resulting in underdeveloped sexual organs—an explanation for rejection of gender norms and domesticity (14). These conditions were believed to threaten the well-being of Canadian society and were thus used as criteria for immigrant exclusion.

The admission of war brides and displaced persons into Canada after the Second World War exposed a new cohort of women to prejudices in immigration law, as female immigrants were far more likely to be charged with "deviance", committed to an asylum, or deported on moral grounds (3). By the 1950s, 82 per cent of asylum inmates in British Columbia were deviant women who rejected norms of femininity, heterosexuality, and domesticity. Deviance threatened women's ability to conform to Canadian standards of domestic life, and women were instead labelled with psychiatric pathologies treatable by electroshock therapy, insulin-induced comas, cold baths, pills, and lobotomies (3). Pressure from the Immigration Branch to deport inmates and free beds for Canadian citizens promoted more thorough inspection; approximately 600 immigrant inmates were estimated to have been deported between 1946 and 1956, the majority of which were women. Women's commitment to asylums, treatment as mentally ill, and deportation for moral deviance served as methods of "gender regulation" and "moral quarantine" for the betterment of Canadian society (3).

The exclusion and deportation of Canadian immi-

grants for moral indigence was largely intertwined with eugenic notions of heredity and racial inferiority, fear of political radicals, and the threat of sexual deviance. Political turmoil during and between the First and Second World Wars promoted hostility towards immigrants with diverging political views, while convicted immigrants were believed to menace Canadian society through the permeating power of their immorality. Similarly, sexually deviant immigrants threatened the natural order of domesticity and health of Canadian families and were pathologized through commitment to asylums and regulated through deportation. By the 1950s, immigration law had developed into a highly restrictive process through selecting immigrants not only deemed physically and mentally fit for Canadian society, but also whose morals appeared to align with Canadian ideals.

5 | CONCLUSION

The history of immigration policy is evidently susceptible to changes in the Canadian social milieu, with laws often driven by racist sentiments, fear of political radicals, and the perceived threat of the "outsider". Furthermore, the transforming understanding of human health has also greatly influenced immigration policy. Early fears of the introduction of deadly infectious diseases from other continents drove the establishment of quarantine sites and medical inspections, while developing ideas of the heredity of physical, mental, and moral deficiencies influenced criteria for immigrant exclusion and deportation. It would be difficult to attempt the study of Canadian immigration policy without reference to the complex and intertwined concepts of sanitation, sanity, and (moral) suitability as standards for immigrant acceptance. As immigration rates continued to rise with the development of Canadian society, so did the use of medical inspection as a central tool for selecting ideal immigrants worthy of "Canadianization", resulting in the overall medicalization of and discrimination against specific ethnic groups. It thus remains important to recognize Canada's history of anti-immigrant sentiment in future policy making. While Canadian policies have indeed improved in recent decades, social discrepancies between Canadian-born citizens and new immigrants and refugees continue to plague modern society, emphasizing the importance of extending justice and equality for new citizens beyond fair admission standards into Canada.

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REFERENCES

1. Curtis B. Social investment in medical forms: The 1866 cholera scare and beyond. Canadian historical review. 2000 Sep 1;81(3):347-79. Available from: https://www.utpjournals.press/doi/abs/10.3138/CHR.81.3.347

2. Dowbiggin IR. Keeping America sane: Psychiatry and eugenics in the United States and Canada, 1880-1940. Cornell University Press; 1997. Available from: https://www.jstor.org/stable/10.7591/j.ctv75d20d

3. Scheinberg E. Canada's Deportation of 'Mentally and Morally Defective' Female Immigrants After the Second World War. In: Migration and Mental Health. London: Palgrave Macmillan; 2016. p. 171-198. Available from: https://link.springer.com/chapter/10.1057/978-1-137-52968-8$_9$

4. Miller FA. Making citizens, banishing immigrants: the discipline of deportation investigations, 1908-1913. Left History: An Interdisciplinary Journal of Historical Inquiry and Debate. 2000 Mar 1. Available from: https://lh.journals.yorku.ca/index.php/lh/article/download/5411/4606

5. Dowbiggin I. 'Keeping this Young Country Sane': CK Clarke, Immigration Restriction, and Canadian Psychiatry, 1890–1925. Canadian Historical Review. 1995 Dec 1;76(4):598-627. Available from: https://www.utpjournals.press/doi/abs/10.3138/CHR-076-04-03?journalCode=chr

6. Knowles V. Strangers at our gates: Canadian immigration and immigration policy, 1540–2015. Dundurn; 2016 Mar 5. Available from: https://www.questia.com/library/journal/1P3-2004718481/strangers-at-our-gates-canadian-immigration-and-immigration

7. Chilton L. Receiving Canada's immigrants. Canadian

Historical Association; 2016. Available from: https://cha-shc.ca/_uploads/5c37fa1a3341.pdf
8. Early Canadiana Online. An Act to Consolidate the Laws Relative to Emigrants and Quarantine. Québec; 1853.
9. Library and Archives Canada. An Act Relating to Quarantine and Public Health, 1868. Ottawa: Malcolm Cameron; 1868.
10. Library and Archives Canada. Statutes of Canada. An Act Respecting Immigration and Immigrants, 1869. Ottawa: SC 32-33 Victoria; 1869. ch 10.
11. Bilson G. "Muscles and health": health and the Canadian immigrant (1867-1906). Essays in the history of Canadian medicine. Toronto: McClelland and Stewart. 1988:398-411.
12. Beaud JP, Prevost JG. Immigration, eugenics and statistics: Measuring racial origins in Canada (1921-1941). Canadian Ethnic Studies. 1996;28(2):1-24.
13. Cavell J. The imperial race and the immigration sieve: The Canadian debate on assisted British migration and empire settlement, 1900–30. The Journal of Imperial and Commonwealth History. 2006 Sep 1;34(3):345-67. Available from: https://www.tandfonline.com/doi/abs/10.1080/03086530600825977
14. Baynton DC, Hirschmann NJ, Linker B. Defect: A selective reinterpretation of American immigration history. NJ Hirschmann B. Linker (red.), Civil Disabilities: Citizenship, Membership and Belonging. 2015:44-64.
15. Roberts B. Whence they came: Deportation from Canada 1900-1935. University of Ottawa Press/Les Presses de l'Université d'Ottawa; 1998. Available from: http://library.oapen.org/handle/20.500.12657/33019

COMMENTARY
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Artificial Intelligence – the EHR savior?

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SUMMARY

Electronic health records have limited humanistic aspects of medicine while further increasing redundancy and are often perceived as counterproductive. Artificial intelligence has the potential to address the gaps by creating a practice of evidence-based, personalized, and cost-effective medicine. It will augment efforts to make electronic health records more streamlined, accessible, and, ironically, less computerized.

KEYWORDS
electronic health record; artificial intelligence; humanities

1 | THE PROBLEM

Since its origins, medicine has always been regarded as a patient-centered enterprise. The ethical basis of the Hippocratic Oath values humanism such that the patient's interest has always been put first. (1) But, do these principles hold in the digital age of medicine? The humanistic practice of medicine requires the physician to have two things: adequate time and prime focus afforded to the patient. (2) Unfortunately, the fashion in which medicine is delivered today, in a "distraction-filled environment", makes it difficult to provide either of these. (2) Meaningful interactions with patients have become limited, and as a result, the humanistic element of medicine has diminished.

The Electronic Health record (EHR), a "lauded innovation", arrived with both opportunity and limitations. Looking at its implications from a humanism-focused lens, the EHR does more harm than good. Although widely thought to be transformative of the paper record, the EHR is a greater distraction than note taking because it diverts the attention away from the patient inevitably reducing quality of care. (3) As many physicians argue, the framework compels one to give the "computer complete attention, the kind of attention (physicians) reserved for a patient." (4) Numerous patients have also complained that doctors "seems more interested in looking at the computer screen than (them)". (5) Research has shown that one-third of the time used during a patient visit is spent navigating and inputting data into the EHR. (6) More alarming, the distraction of

the EHR presents a barrier to the indispensable personal connection that dictates a functional patient-physician relationship. (2) The rapid changes in digitizing medicine have led to a focus on refining methods for billing, administration, and regulatory issues yet have excluded the core value of capturing the patient's narrative. (3) The healthcare field as a whole has unknowingly shifted the focus towards "clinical productivity." (7)

The design and implementation of EHRs nationwide has been inconsistent and ineffective resulting in many technical and usability flaws. Because of the increased system complexity, the user interface has been compromised and made even more confusing. (8) A staggering 92% of nurses in the US are dissatisfied with the use of technology, a concern mainly stemming from the convoluted interface of the EHR. (9) Another study showed the increased probability of system failures and maintenance harms patients in events of technical difficulties, such as muddling patients' allergies or medications between numerous medical records. (10) Additional errors arise from the redundancy of data, prompting clinicians to cut and paste data from previous, potentially outdated, encounters contributing to malpractice and hurting the necessary integrity of the EHR. (11) As a result of irrelevant information, some clinicians assert that "EHRs are cluttered making it difficult to locate and comprehend important details" of the patient. (8)

Not only does the structure of the EHR make finding information difficult, but also has a grave impact on clinical reasoning skills and decision-making abilities of both current and future physicians. Certain characteristics of the record eliminate the need to interact directly with the patient which encourages "superficial clinical thinking" in a virtual environment where medical reasoning is limited. (3) Research has shown that medical students now use a flawed method of information acquisition where questions are asked as they appear on the computer screen. (12) Making matters worse, the physician cannot effectively demonstrate their thought process as they are inclined to pick the "best option in a drop-down list" instead of typing, and are distracted by many irrelevant fields or prompts. (12) Altogether, the development of vital reasoning and communication skills are disrupted as medical students become accustomed to the inflexible and redundant data entry methods. (3) In addition to impeding the doctor's development of good judgement, EHRs themselves have poor usability and employ linear decision making - linear in the sense that it is difficult for EHRs to produce helpful recommendations in novel situations and emulate the "flexible and fluid ways in which healthcare is provided in real life." (13) The non-intuitive clinical decision support systems, unable to handle all possibilities, present uniform recommendations or redundant alerts which remind the physician of a recommended treatment or warn of a possible medical risk associated with a treatment. (14) Clinical decision practice, in its current state, is founded on preliminary decision support rules, major design flaws and misuse of systems conflicting with developer expectations. (14) Additionally, the physician may not understand which clinical factors or relevant premises have been taken into consideration by the computer and these systems are perceived to be interruptive.(8)

Last but not least, EHRs add increased responsibility and redundancy to a physician's already busy schedule, making the use of the EHR counterproductive. The EHR has been held responsible for physician burnout because of the increased documentation of nonclinical data. (19) Furthermore, the unsystematic purposes aggravate physician mental health and increases frustration. (15) Similarly, the rising pressure of capturing accurate and structured data adds to the negative impact of EHRs on the physician's wellbeing. For example, workflow incompatibility is an added concern to a poorly designed EHR infrastructure. (8) EHR data varies widely across entities such that "building an insightful, granular database is next to impossible." (43) Many physicians are dissatisfied by the fact that exchanging records is a demanding process, and are thereby forced to fall back on the conventional method of faxing medical documents. (16) When a simple task such as generating a referral or prescription becomes tedious, addressing the issue is of essence as the "care of patients also requires attention to the care of clinicians." (17) The irony of electronic records in improving the practice of medicine now

becomes evident as they "break care" for both patient and physician. (18) Overall, the present-day dilapidated EHR system is "enough to make old Hippocrates roll over in his grave!" for the many reasons discussed above. (2) Having discussed the complications of the EHR, in the next section we will present what is believed to be the needs of the clinical community and detail essential considerations in restricting the use of technology in medicine.

2 | WHAT IS NEEDED?

Although the EHR systems have streamlined the ways healthcare is delivered, they have given rise to unanticipated usability issues. Research from Stanford Medical School reports 9 out of 10 physicians want the EHR to be more responsive, intuitive and have an improved interface. (19) Furthermore, 38% of physicians hoped for highly accurate voice recording technology that acts as a scribe during patient visits, while six out of ten physicians (59%) think EHRs need a complete overhaul. The scribe profession may help lower the burden for the need of data entry, but they prove to be expensive in the long run. (20) David Blumenthal, M.D., M.P.P., president of The Commonwealth Fund, envisions natural language processing and artificial intelligence as a long-term solution to the tribulation. It may not be enough to redesign the EHR with an improved interface. Indeed, novel functionalities to minimize EHR-associated errors and a "fundamental redesign" is needed. (8,15) As a result of this change, clinicians will have greater control of the system's customization aligning well with their needs, flexibility and realistic prospect.

The improvement of the one-dimensional decision-making capabilities endemic to the EHR must also be addressed. There is a need for using clinical data to build more predictive models and a more efficient Clinical Decision Support System (CDSS). (21) The utilization of big data and large databases are therefore encouraged. Improved support and ease of use of such systems make clinicians' lives better and allow them to focus on patient-centered communication and participate in confident decision making. (22) With the advent of artificial intelligence, machine learning and "big data", the EHR can be wisely used for increased adaptability in improving diagnostics, personalizing care and discovering disease associations. (23) Only when we step outside of "paper-chart thinking"¬–EHRs as simply a replacement for paper charts–can these systems allow the natural recording of a physician's thinking focused on a patient's unique story and experience. (4) Several studies have hinted that EHRs should support data analysis/mining with "intelligent stimulus" and "goal-oriented functionality" to allow a holistic view of patient data. (15) Consequently, these systems should also employ the idea of machine learning where the computer learns from its mistakes and tailors itself to the physician it assists.

3 | THE SOLUTION – ARTIFICIAL INTELLIGENCE

Artificial Intelligence (AI) has the potential to create a way of practicing evidence-based, personalized and cost-effective medicine. Since humanism is becoming increasingly important in a changing healthcare landscape, artificial intelligence (AI) is a possible solution to the various shortfalls of the EHR we have so far discussed. But what is AI? AI is the term used to describe the use of computers and technology to simulate intelligent behavior and critical thinking comparable to a human being. (24) The broad benefits of AI such as efficiency, monitoring and reasoning may help tame the growing disconnect between the physician and patient by providing increased patient-physician face time. As Dr. Eric Topol, cardiologist and director of the Scripps Research Translational Institute in California, said "The greatest gift that AI can give us is to go back to the future, to get us to the humanity in medicine, which is presence." (25) Professors at the University of Stanford have argued that AI is an overlooked opportunity that can "help clinicians deliver better and more humanistic care." (26) But how exactly can AI be used to refocus our attention on the patient-doctor relationship? Here we present four ways which can make this possible.

First is increasing physician-patient engagement by assisting the doctor in capturing patient data more efficiently. As an alternate to dictation, most hospitals now have scribes to help physicians document the visit while the physician interacts with the patient. Indeed, medical dictation has been the standard method to take the verbal notes of a physician and convert them into written notes. However, as we mentioned above, there are several problems with scribing and dictation, namely being expensive and inaccurate. Compared to these traditional methods, AI has its advantages in easing the healthcare documentation burden. For example, AI will help with automatic charting through speech recognition during a patient visit. This would be valuable and could free clinicians to return to facing the patient rather than spending almost twice as much time on computer. (27) Capturing clinical notes with natural language processing allows clinicians to focus on their patients rather than keyboards and screens. While AI is being applied in EHR systems principally to improve data discovery and extraction and personalize treatment recommendations, it has great potential to make EHRs more user friendly and easy to understand. This is a basic objective, as EHRs are confounded and difficult to utilize and are frequently referred to as adding to clinician burnout. (28)

Because of this, several companies are working on digital scribes, machine-learning algorithms that can take a conversation between a doctor and a patient, parse the content and use it to fill in the applicable data in the patient's EHR. (29) This may seem far-fetched but Kara, a 2017 iOS application, uses machine learning, voice recognition and language processing to capture conversations between patients and physicians and turn them into notes, diagnoses and orders in the EHR. Past renditions of the application required prompts from the doctor—much like Apple's Siri—however the present form can be placed in "ambient mode," in which it essentially tunes in to the whole conservation and afterward chooses the important data filling in as a smart, proficient colleague. Since AI would have access to health data sets similar to current technologies, it would need to adhere to the same regulations.

Second is the use of machine learning to facilitate the physician's task in a more personalized and flexible manner. Machine learning is a subset of AI where the computer systems can learn from data, identify patterns and make decisions with minimal human intervention. Machine learning can be supervised or unsupervised. Supervised learning starts with the goal of predicting a known output or target while unsupervised learning tries to find naturally occurring patterns or groupings within the data. (42) The key distinction between traditional approaches and machine learning is that in machine learning, a model learns from examples rather than being programmed with rules. (30) In applications where predictive accuracy is critically important, the ability of a model to find patterns across millions of features and examples is what enables superhuman performance. This is particularly helpful in making clinical decisions since the algorithms can help expose relevant information in a patient's chart for a clinician without multiple clicks or arduous searching. Data entry of forms and text fields can be improved with the use of machine-learning techniques such as predictive typing, voice dictation, and automatic summarization. Automation of chart documentation also makes it easier to prevent improper payments by authorizing payments based on information already recorded in the patient's chart. (40) An AI could search through the large amount of EHR data to find the most important information for the situation. Furthermore, AI systems learn to recognize key terms and pull out data from clinical notes and other patient data. (31) For example, Amazon Web Services recently launched a service where AI pulls out and indexes data from clinical notes. (32) The capability of AIs can also produce material beyond the rote medical and family or environmental history, "digested in a vivid useable form with graphics and animation equivalent to what is readily available in other spheres of the digital world." (26) This can help clinicians get a more accurate picture of their patient's health, help diagnose and, treat more accurately, and better set up appointments.

Third, AI can help drive down the expanding costs of healthcare by having financial implications in multiple areas. For example, AI will enable clinicians to make better, more sophisticated decisions since a more com-

plex and robust system might list the likelihood of a side effect with drug option A versus drug option B and provide a cost comparison. (29) AI applications can be utilized to reduce unnecessary testing, decrease the disparities, discrepancies and reduce hospital admissions and length of stay. (33) With the integration of AI, clinicians could use a virtual assistant to make phone calls, place prescription orders, take notes, and better navigate the EHR system allowing staff to perform their tasks faster and more efficiently. (31) AI applications in medical workflow management are estimated to save $18 billion per year for the healthcare industry by 2026. (41) Further, costly errors in clinical documentation are reduced since AI streamlines the tedious clinical documentation process and can automatically generate accurate and complete reports.

Lastly, AI can increase insights from unstructured data by providing more precise, pertinent data and highly intuitive systems. Currently, customizing EHRs to make them easier for clinicians is largely a manual process, and the systems' rigidity is a real obstacle to improvement. AI, and machine learning specifically, could help EHRs continuously adapt to users' preferences, improving both clinical outcomes and clinicians' quality of life. (28) Machine learning and predictive analytics models also furnish healthcare providers with analytics on patient satisfaction or help foresee patient risk. (34) The potential to create a graphical synthesis of patient data using a combination of natural language processing and AI technology is exciting because AI systems perform a rapid and thorough search of single or multiple patient electronic medical records, the Internet, textbooks, and journals for data. (33) It is worth mentioning that AI would help differentiate between the importance "to know what sort of patient has a disease than what sort of a disease a patient has" –the former attainable by the power of AI. (26) Further, this technology could also be utilized to cross correlate data from a patient's family history, find patients similar to that patient, and evaluate ultimate diagnoses and treatment responses. Overall, the benefits of AI are numerous and by streamlining the healthcare field, humanism might be restored.

4 | CONSIDERATIONS AND THE FUTURE OF AI IN MEDICINE

The wide applicability of machine learning will require a sophisticated structure of regulatory oversight, legal frameworks, and local practices to ensure the safe development, use, and monitoring of systems. (35) Critically, clinicians who use machine-learning systems need to understand their limitations, including instances in which a model is not designed to be generalized to a different particular scenario. (36) Another major challenge involves concerns about patient data privacy breaches. This is especially true for AI, as hospitals will most likely rely on third-party providers of AI software to provide highly integrated EMR solutions. (33) Crucially, since AI's predictive prowess comes from sifting large data sets, we must be careful to use representative data sets of society which are not biased by sex, race, ethnicity, socioeconomic status, age, ability, and geography. (37) Not only will an unrepresentative sample build a bad model, it will raise a moral question in the absence of equal representation whose disastrous effects are already evident in inequitable criminal justice sentencing, unfair hiring practices, and many other injustices. (38)

Lastly, the use of AI raises specific medicolegal concerns–who should be blamed if the system provides an incorrect diagnosis. Is it the "authors of the software, the technology provider, the hospital who provided the technology, the doctor or all of the above"? For widespread adoption to take place, AI frameworks must be endorsed by regulators, integrated with EHR systems, standardized to a sufficient degree that similar products work in a similar fashion, taught to clinicians and updated over time. (39) It is becoming progressively evident that AI frameworks won't fully replace clinicians, but rather will augment their efforts to care for patients and enlarge their endeavors to focus on patients. (39) As a result, clinicians will be able draw on remarkable human aptitudes like empathy, social intelligence and patient-level connections that machines cannot replicate. Patients not only must be placed at the focal point of care, but also at the center of health technology. All in all, we must empower clinicians to help us nav-

igate through the technological jungle and re-establish humanism in the age of digital health.

REFERENCES

1. Thibault GE. Humanism in Medicine. Academic Medicine 2019; 94:1074–7. https://doi.org/10.1097/ACM.0000000000002796.

2. Bertman S. Pursuing Humanistic Medicine in a Technological Age 2017. https://doi.org/10.1177/2374373517699269.

3. Sulmasy LS, María López A, Horwitch CA. Ethical Implications of the Electronic Health Record: In the Service of the Patient 2017. https://doi.org/10.1007/s11606-017-4030-1.

4. Toll E. The Cost of Technology. JAMA 2012;307:2497–8. https://doi.org/10.1001/jama.2012.4946.

5. Bernat JL. Ethical and quality pitfalls in electronic health records. Neurology 2013;80:1057–61. https://doi.org/10.1212/WNL.0b013e318287288c.

6. Kumah-Crystal YA, Pirtle CJ, Whyte HM, Goode ES, Anders SH, Lehmann CU. Electronic Health Record Interactions through Voice: A Review. Applied Clinical Informatics 2018;9:541–52. https://doi.org/10.1055/s-0038-1666844.

7. Rider EA, Gilligan MC, Osterberg LG, Litzelman DK, Plews-Ogan M, Weil AB, et al. Healthcare at the Crossroads: The Need to Shape an Organizational Culture of Humanistic Teaching and Practice. J Gen Intern Med 2018;33:1092–101. https://doi.org/10.1007/s11606-018-4470-2.

8. Bowman S. Impact of electronic health record systems on information integrity: quality and safety implications. Perspectives in Health Information Management / AHIMA, American Health Information Management Association 2013;10.

9. Heath S. 92% of Nurses Dissatisfied with EHR Technology, Health IT 2016. https://ehrintelligence.com/news/92-of-nurses-dissatisfied-with-ehr-technology-health-it (accessed March 14, 2020).

10. Hoffman S, Podgurski A. Finding a Cure: The Case for Regulation and Oversight of Electric Health Record Systems. Harvard Journal of Law Technology 2008;22.

11. Balestra ML. Electronic Health Records: Patient Care and Ethical and Legal Implications for Nurse Practitioners. Journal for Nurse Practitioners 2017;13:105–11. https://doi.org/10.1016/j.nurpra.2016.09.010.

12. Lown BA, Rodriguez D. Commentary: Lost in translation? How electronic health records structure communication, relationships, and meaning. Academic Medicine 2012;87:392–4. https://doi.org/10.1097/ACM.0b013e318248e5ae.

13. Fox J, Thomson R. Clinical decision support systems: a discussion of quality, safety and legal liability issues. Proceedings / AMIA . Annual Symposium AMIA Symposium 2002:265–9.

14. Coiera E, Westbrook J, Wyatt J. The safety and quality of decision support systems. Yearbook of Medical Informatics 2006:20–5.

15. Colicchio TK, Cimino JJ, Guilherme ;, Fiol D. Unintended Consequences of Nationwide Electronic Health Record Adoption: Challenges and Opportunities in the Post-Meaningful Use Era. J Med Internet Res 2019;21:13313. https://doi.org/10.2196/13313.

16. Friedberg M, Crosson FJ, Tutty M. Physicians' Concerns About Electronic Health Records: Implications And Steps Towards Solutions | Health Affairs 2014. https://www.healthaffairs.org/do/10.1377/hblog20140311.037786/full/ (accessed March 14, 2020).

17. Bodenheimer T, Sinsky C. From triple to Quadruple Aim: Care of the patient requires care of the provider. Annals of Family Medicine 2014;12:573–6. https://doi.org/10.1370/afm.1713.

18. Pipes S. Electronic Health Records Are Broken 2019. https://www.forbes.com/sites/sallypipes/2019/05/28/electronic-health-records-are-broken/103ea2b6546a (accessed March 14, 2020).

19. Stanford Medicine. How Doctors Feel About Electronic Health Records National Physician Poll by The Harris Poll 2 Background, Objectives, and Methodology. 2018.

20. Blumenthal DMD. The Electronic Health Record Problem | Commonwealth Fund 2014. https://www.commonwealthfund.org/blog/2018/electronic-health-record-problem (accessed March 15, 2020).

21. Nibbelink CW, Young JR, Carrington JM, Brewer BB. Informatics Solutions for Application of Decision-Making Skills. Critical Care Nursing Clinics of North America 2018;30:237–46. https://doi.org/10.1016/j.cnc.2018.02.006.

22. Levit L, Balogh E, Nass S, Ganz PA. Committee on Improving the Quality of Cancer Care: Addressing the Challenges of an Aging Population; Board on Health Care Services. 2013.

23. Hema Mariya Re. A CONTEMPLATION ON BIG DATA ANALYTICS IN HEALTH CARE USING MACHINE LEARNING TECHNIQUES. 2018.

24. Amisha, Malik P, Pathania M, Rathaur V. Overview of artificial intelligence in medicine. Journal of Family Medicine and Primary Care 2019;8:2328. https://doi.org/10.4103/jfmpc.jfmpc$_{4}$40$_{1}$9.

25. Ramirez VB. We Should Use AI to Rescue Modern Medicine From Itself 2019. https://singularityhub.com/2019/11/11/can-ai-rescue-modern-medicine-from-itself/ (accessed April 24, 2020).

26. Israni ST, Verghese A. Humanizing Artificial Intelligence. JAMA - Journal of the American Medical Association 2019;321:29–30. https://doi.org/10.1001/jama.2018.19398.

27. Verghese A. Culture Shock — Patient as Icon, Icon as Patient. New England Journal of Medicine 2008;359:2748–51. https://doi.org/10.1056/NEJMp0807461.

28. Davenport TH, Hongsermeier TM, Mc Cord KA. Using AI to Improve Electronic Health Records 2018. https://hbr.org/2018/12/using-ai-to-improve-electronic-health-records (accessed April 26, 2020).

29. Willyard C. Can AI Fix Medical Records?Nature 2019;576: S59–62. https://doi.org/10.1038/d41586-019-03848-y.

30. Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. New England Journal of Medicine 2019;380:1347–58. https://doi.org/10.1056/NEJMra1814259.

31. Hovey N. Could Artificial Intelligence Supplement EHR Systems? | BestNotes 2019. https://www.bestnotes.com/could-artificial-intelligence-supplement-ehr-systems/ (accessed April 25, 2020).

32. Knowles M. 4 ways AI can make EHR systems more physician-friendly 2018. https://www.beckershospitalreview.com/ehrs/4-ways-ai-can-make-ehr-systems-more-physician-friendly.html (accessed April 26, 2020).

33. Dilsizian SE, Siegel EL. Artificial intelligence in medicine and cardiac imaging: Harnessing big data and advanced computing to provide personalized medical diagnosis and treatment. Current Cardiology Reports 2014;16:1–8. https://doi.org/10.1007/s11886-013-0441-8.

34. Qualetics Data Machines Inc. AI in EHRs: Using AI To Improve Electronic Health Records - 2019. https://qualetics.com/ai-in-ehrs-using-ai-to-improve-electronic-health-records/ (accessed April 26, 2020).

35. Auerbach AD, Neinstein A, Khanna R. Balancing innovation and safety when integrating digital tools into health care. Annals of Internal Medicine 2018;168:733–4. https://doi.org/10.7326/M17-3108.

36. Amarasingham R, Patzer RE, Huesch M, Nguyen NQ, Xie B. Implementing electronic health care predictive analytics: Considerations and challenges. Health Affairs 2014;33:1148–54. https://doi.org/10.1377/hlthaff.2014.0352.

37. Caplan A, Friesen P. Health disparities and clinical trial recruitment: Is there a duty to tweet? PLOS Biology 2017;15:e2002040. https://doi.org/10.1371/journal.pbio.2002040.

38. O'Neil C. Weapons of math destruction: how big data increases inequality and threatens democracy. 2017.

39. Davenport T, Kalakota R. The potential for artificial intelligence in healthcare. Future Healthcare Journal 2019;6:94–8. https://doi.org/10.7861/futurehosp.6-2-94.

40. Brady M. CMS thinks artificial intelligence could help cut Medicare fraud 2019. https://www.modernhealthcare.com/information-technology/cms-thinks-artificial-intelligence-could-help-cut-medicare-fraud (accessed July 31, 2020).

41. Saince C. The Cost of Care: How AI is Revolutionizing Healthcare and Driving Down Prices | | 2017. https://www.saince.com/cost-care-ai-revolutionizing-healthcare-driving-prices/ (accessed July 31, 2020).

42. Deo RC. Machine learning in medicine. Circulation 2015;132:1920–30. https://doi.org/10.1161/CIRCULATIONAHA.115.001593.

43. Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. Health Information Science and Systems 2014;2. https://doi.org/10.1186/2047-2501-2-3.

REFLECTION

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Stories of Institutional and Local Policy Change from Harvard's Cambridge Health Alliance

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ABSTRACT

In May of 2017, myself and five other first and second year McGill Medical students embarked on a cultural exchange with Harvard medical students. This is an annual program run by Dr. Semaan, professor at Harvard Medical School, and McGill Medicine graduate. During the exchange, we had the opportunity to attend some pointed lectures which had the goal of illustrating some of the realities of the health care system in the Cambridge-Boston area. This article is a reflection on the talk given by Dr. David Bor of the Cambridge Health Alliance titled "Cambridge Health Alliance: A Public, Academic Community-Responsive Health Care System", wherein he provided inspiring personal stories of institutional and policy change pursuits he was involved in in response to needs of the local population.

KEYWORDS
advocacy, policy change, institutional change, public engagement

Social Accountability has been defined by the World Health Organization as "the obligation [of health professionals and institutions] to direct their education, research and service activities towards addressing the priority health concerns of the community, region, and/or nation they have a mandate to serve." (World Health Organization's World Health Report, 1995). I was privileged to attend an inspiring lecture on social accountability in the context of community health delivered by Dr. David Bor, Associate Dean for Undergraduate Medical Education, Head of the Department of Medicine, and Charles S. Davidson Professor of Medicine at the Cambridge Health Alliance (CHA) in May of 2017 during a medical-student exchange between McGill and Harvard Universities. His lecture was titled, "Cambridge Health Alliance: A Public, Academic Community-Responsive Health Care System." I found Dr. Bor's recounting of his years with the Cambridge Health Alliance fascinating, highly educational, and above all, inspiring. In this piece I will be reflecting on concepts such as possible approaches to responding to the needs of a changing population, holding institutions and governing bodies responsible, and building support for social projects, all through examples given by Dr. Bor from his personal experiences.

The first example of social accountability presented

was the history of the development of the Cambridge City Hospital as it grew and evolved to become a part of the multicentered Cambridge Health Alliance. The CHA is a multicentered integrated health care system with a focus on primary care. The rise of the institution occurred as a response to the needs of the vulnerable population in Cambridge city, and later its surrounding areas. Originally, Cambridge was inhabited by an immigrant population who were labourers within the community. The hospital was founded with a charitable mandate: to keep these workers healthy. Over time, Cambridge grew in population, and soon the City Hospital became over capacitated with patients. This overburden leading to limited resources left the poor, uninsured population behind, both in terms of hospital services and their place in the growing, thriving community. As a result, this vulnerable population became marginalized, and were pushed out of Cambridge to the surrounding areas. The Cambridge City Hospital saw the opportunity to fulfill their mandate to serve the population by expanding their reach beyond Cambridge. They accomplished this by collaborating with other hospitals in the surrounding areas, creating the CHA.

These individual centres were originally culturally oriented to serve the population who lived in their respective local areas. This focus evolved in response to the social need for cultural understanding with regards to how health care is approached. For example, a large Portuguese population was in the area served and thus one of the Hospitals was largely staffed by individuals from within the Portuguese community. This meant patients could be served in their mother tongue and receive care from individuals who were more likely to understood their cultural values. The cultural specificity served the community in some ways, however soon anonymity became an issue as the patients would be recognized by their neighbors and peers when seeking care.

The story of the evolution of the Cambridge Health Alliance and the challenges faced along the way provide an excellent illustration of similar challenges Montrealers, and more broadly, Canadians, are facing still today in our own communities. The combined priorities of cultural understanding, a sense of community, and the need for anonymity create a complex issue not easily managed. This is especially true in small communities. There is also the issue of alienating individuals from other cultures when institutions are geared toward one specific cultural group. To deal with these challenge of providing both inclusive and culturally sensitive care to all and to better serve the multicultural populations in our communities today, I think that what is needed are multicultural centres (i.e. centres open to all cultures with clearly identified and accessible resources for those desiring more cultural or linguistic specificity in their care) with healthcare professionals and support staff who excel in their cultural competency. This should go hand in hand with in-place institutional policies that promote access to cultural and language interpreters in order to ensure that patients feel heard. Though training in cultural awareness and sensitivity is already integrated in the undergraduate medical curriculum, as we see in our first-year courses in at McGill, institutional changes, including access to interpreters, is still lacking. Specialized community centres exist, such as the CLSC Parc-Extension in Montreal, which is catered toward specific populations, such as asylum seekers, for primary care delivery. An example of analogous programs offered at the CHA include culturally specific mental health programs for the Asian, Haitian, Latino and Portuguese communities respectively. At the CLSC, some of the specialized services offered include health assessments for asylum seekers newly arrived to Canada, Punjabi interpreters available on site, as well as interpretation services readily available at any time for any language via telephone. Despite the availability of such specialized resources on a primary care level, for higher levels of care in hospitals, these efforts need to be improved upon - especially as the populations of Montreal and Quebec grow more multicultural and diverse. For example, interpretation services are not standard in Quebec Hospitals.

The Cambridge Health Alliance's history is an excellent example of how a public institution recognized the needs of the population and took action on their own to achieve a healthier, better served population, as well as a working toward improving the effective running of an institution/set of institutions. Other examples of so-

cial accountability Dr. Bor discussed involved instances when the public sector was not taking the actions required to best serve the public, and physician-led advocacy projects were undertaken in order to make the desired changes happen. These examples will be discussed next.

How does one make change in a community? According to Dr. Bor, change in a community is accomplished by forming a constituency that will demand the services they want. For example, during the AIDS epidemic in the 1980's, physicians struggled to help their AIDS inflicted patients given the lack of an effective treatment, and as a result they sought opportunity to help by other means. In order to have the greatest impact, the physicians made effort to find out the needs of this population of patients, and what community services would most contribute to their health and wellbeing. To discover the priorities of the population, Dr. Bor turned to the constituency and asked them. This particular constituency group decided that availability of housing during times of illness was the biggest issue they faced. With the collective voice of this group, Dr. Bor and his colleagues were able to change policy , which gave those affected by AIDS top priority for publicly available housing.

Amongst those presented by Dr. Bor, I found this story particularly inspiring. Not only was an important change effected to improve the wellbeing of a vulnerable group, but this group was able to prioritize and voice the changes they wanted to see. This story demonstrates that one voice can grow louder through the building of a community of like-minded individuals, and that once the collective voice is loud enough, change can and will be made. That being said, I would like to acknowledge that my recounting of the story may misleadingly suggest that making such impact is simply a matter of asking. In many cases, I'm certain that enacting such change is not so simple. In this case, Dr. Bor was well placed with the right connections to bring his project in front of those in a position of power more readily than the average person. Physicians, as highly respected members of the community, are privileged to have a powerful voice with respect to influencing health policy. It is my hope that as a medical student, while I progress in my career, that I may expand my own network of allies and be well placed to enact change on behalf of the groups I serve.

A final story from Dr. Bor I would like to share is a beautiful illustration of how one can successfully overcome obstacles to make change in a community. In this story, Dr. Bor struggled to get the patient population in need to become engaged in demanding social accountability from the governing institutions to provide the care they needed. The population in question were the African-American men in the area around Cambridge - a group which had been under-reached through the medical strategies in place. Not only were these men seeking care less frequently, they were also among those who were less healthy. Dr. Bor sought to create a task force of African-American men to once again understand their priorities and advocate with them their needs to the city for change of policy and program implementation. Unfortunately, this population was not drawn to being engaged in this discussion, which was incidentally at the root of the problem being addressed. In order to inspire participation in the community, the task force reached out to the grandmothers of the African-American community - a group who were thought to have the time for and interest in protecting and improving the health of their families. This strategy indeed proved effective, as in the African-American community the grandmothers were valued and respected by their sons and grandsons. Thus, through this creative seeding, the men's health was prioritized in the community.

It is my hope that these three stories might illustrate how social accountability is an important concept to bear in mind – not only from the point of view of public institutions, but also from the point of view of members of the general public. Institutions should be seeking ways to better serve and reach the communities that utilize their services in order to continue growing and evolving along-side the changing needs of the diversifying population. When the institutions are unable to identify the needs of the population on their own, it is important for the public to become involved in voicing their needs and priorities to those who can enact

change. Finally, obstacles are plentiful in the course of striving for social accountability, whether in the form of addressing challenging issues or in garnering support to present the importance of an issue. In the face of these obstacles, one must be creative, and seek collaboration. The louder the voice behind a project, the broader the potential reach.

A quote from Dr. Bor in response to this article: *"Social accountability is not just an ideal. It's a necessary component of successful democracy. The beauty of democracy's potential is that resulting policies and initiatives should be unique to a particular place and moment, and should mature with time. Sadly, our national democratic institutions are too susceptible to corruption and influence by moneyed interests. However, at the local level, the ideal can work well. Health professionals have surprising influence, partly by our status in society, but mainly through our ability to listen and explain. You've got those skills. Use them well."*

REFERENCES

1.Bor D. Cambridge Health Alliance: A Public, Academic Community-Responsive Health Care System. Oral Presentation presented at McGill->Harvard Medical Student Exchange; 2017; Harvard University, Cambridge USA.

REFLECTION
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Smize: A Mid-Pandemic Guide to Non-Verbal Communication

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ABSTRACT

Communication, whether it be verbal or non-verbal, is a key element in establishing trust and comfort in a physician-patient relationship. In the time of COVID-19, we have seen that non-verbal communication, which is conveyed through facial expression, gestures, and other signs that a person is engaged in the conversation, is lost, largely due to the use of Personal Protective Equipment (PPE). It has become important during these times to find ways to surmount this obstacle to keep providing professional and meaningful care to our patients. This article will discuss the definition and the importance of non-verbal communication in physician-patient care, as well as why effective communication is crucial to good patient outcomes. Finally, this article will present several strategies to overcome the communication obstacles we are currently facing, in order to continue offering elevated levels of care in this time when communication is most needed.

KEYWORDS
COVID-19, Communication, PPE, Physician-patient relationship

1 | OVERVIEW OF THE PROBLEM

It is undeniable that communication is of vital importance to complete and excellent patient care. Communication is a complex science, with many of the important cues being non-verbal. With our return to patient care, the limitations imposed by (Personal Protective Equipment) PPEs are evident in that many of our non-verbal cues will be more difficult, if not impossible, to convey. It has been shown that patients perceive physicians wearing masks as less caring and less empathetic than those without, (1) and in a time where uncertainty and worry is so high among the general public, "concealing social smiles behind masks may contribute to… danger, isolation, or paranoia." (2) We must now figure out how to overcome our lack of nonverbal cues, while contin-

uing to show warmth and compassion. This will be a time in history where we will need to be at our most compassionate, and at the same time, we may have the most difficulty conveying it. In the time of COVID-19, aside from the fact that patients are struggling physically, there has also been a negative impact to patients' mental well-being, as well as lifestyle and financial well-being. This article will first define non-verbal communication and explain why it is of vital importance in healthcare. Next, it will address the importance of effective communication in doctor-patient relations and will be exemplified through two fields of scientific studies. Finally, it will discuss potential strategies that we can employ in the healthcare field, to encourage empathic patient relations during these times.

2 | THE IMPORTANCE OF NON-VERBAL COMMUNICATION

On March 13th, 2020, upon the designation of the Quebec government, all non-essential medical services were halted, and medical students were relegated to learning from home. Upon my return to the hospital after a COVID-enforced 2 month-hiatus, I quickly realized that my traditional reflex to smile would be ineffectual as my face was hidden by a mask and visor. I was struck by the fact that patients were unable see the gesture, a reflex that comes so naturally to us to help patients feel at ease. Equally importantly, I could not easily ascertain whether they were at ease, uncomfortable, or terrified, because the lower half of their faces, which were now covered by masks, usually convey a large proportion of important emotions. Non-verbal communication is described by the American Psychological Association (APA) as "the act of conveying information without the use of words," and lists examples of the concept such as facial expressions, body language, hand gestures, and any other movements we make to convey our emotions or opinions. (3) Nonverbal communication has several key uses. It has been proven that clinicians who show more engagement and caring characteristics through nonverbal cues are ones that can expect a quicker and more complete recovery in their patients, (4) as well as various improvements in physiological values such as blood glucose and cholesterol control, leading to an overall improvement in patient health. (5) In a study done in 2017, it was found that having a warmer interpersonal style, one involving eye contact and use of facial expressions, resulted in increased expectations of patient outcomes as well as patient perception of improvement. (6) In addition, different cultures and different languages largely share the same facial expressions, so being able to see and understand nonverbal communication also allows for inter-cultural and inter-lingual communication.

3 | HOW COMMUNICATION HELPS IN PATIENT CARE

In general, when physicians communicate effectively, patients respond in kind and thereby contribute more effectively towards their own care, and the overall satisfaction of the doctor's care improves. Physicians who display true empathy have consistently been shown to have better medical outcomes for their patients; by allowing patients to feel more comfortable, they are better able to express their concerns, which allows doctors to treat them more effectively. (7) Establishing this empathy requires many elements: one, the doctor must be able to show through verbal communication as well as facial expressions that they are there to listen; two, the patient has to understand that message; and three, the patient has to respond to it, and this mutual connection often leads to greater exchange of information. Unfortunately, roadblocks to efficient communication can occur at any one of these steps. Carter Hardy writes in *Empathizing with patients: the role of interaction and narratives in providing better patient care*, "Much of the information given by a patient is hinted at nonverbally," (7) and for us to be able to receive these nonverbal clues, understand them, and then implement this new knowledge to reach the correct diagnosis, we have to be able to see them, which is in part impossible due to the mask every doctor and patient must now wear. Further, as

Malcolm Gladwell recounted in his book *Blink* after analyzing articles by Ambady et al. (8) and Levinson et al., (9) doctors are more likely to be sued due to bad communication skills over doctors who administered/performed the wrong treatment. (10) What this means is that if a patient does not feel the doctor is listening to them, or does not form the proper connection with the patient, he/she is more likely to complain than if they had a doctor who did have the communication skills, but did not treat their problem correctly. These two examples show that communication is of vital importance in the healthcare field, and that a lack of communication can lead to significant problems in the relationship between patient and physician, as well as poorer treatment outcomes.

4 | WHAT ARE OUR OPTIONS?

Fortunately, there are ways to overcome the obstacle of the mask and PPE when it comes to connecting with patients. Firstly, it can be helpful to use more gestures when communicating, such as becoming more expressive with your eyes and your eyebrows and adding more eye contact. As well, hand movements such as thumbs up as well as more head movements, such as nodding to encourage patients, can also be effective in establishing a meaningful connection. (2) As the famous American model Tyra Banks so famously described, when you can't smile with your mouth, you should instead smile with your eyes, otherwise known as "smizing." Next, the facemasks you wear can help ease tension, rather than elicit fear. Physicians can wear interesting masks to express their individuality, or even draw a smiley face on their mask to show patients that even though they can't physically smile at them, they are still expressing the feeling. Inspiring messages, quotes, or sayings, such as the oft-used "Ça va bien aller," can also be written or integrated into the face masks, to help put a smile and distract potentially stressed patients. Another potential idea could be to create and utilize clear masks with the same protective level as the ones used in hospitals, so that patients will still be able to see the facial expressions of their physicians, and will then be able to see the smiles that can be so comforting to a suffering or worried patient. This strategy also offers the benefit of helping hearing-impaired patients that rely on lip-reading for communication. Finally, an interesting option that healthcare workers in San Diego started was to wear photos of themselves smiling on their scrubs or PPE to help put patients more at ease and make them feel comfortable, even when they can't see the full face of their doctor. (11) These suggestions are an excellent starting point, but we must keep working on finding new solutions to better enable effective and compassionate communication.

5 | CONCLUSIONS

In conclusion, communication, and more specifically nonverbal communication, is key to successful physician-patient relationships, to establish empathy, trust, and to work towards better patient outcomes. Unfortunately, the masks that are worn in pandemic situations, such as COVID-19, inhibit these types of connections from forming, which can cause fear, distrust, and worry in the patient population. Fortunately, solutions exist, such as compensating by using other non-verbal cues such as gestures, "smizing," individualizing and creating reassuring masks, and even using images to diminish the relationship gap that masks and other PPE can cause. In the future, we will have to rely on each other's creativity in order to establish more and more nonverbal cues towards a goal of maintaining positive doctor-patient relations.

REFERENCES

1. Wong CKM, Yip BHK, Mercer S, Griffiths S, Kung K, Wong MC, et al. Effect of facemasks on empathy and relational continuity: a randomised controlled trial in primary care. BMC Fam Pract. 2013 Dec;14(1):200.

2. Heid M. I See You but I Don't: How Masks Alter Human Connection [Internet]. Elemental Medium. 2020 [cited 2020 Jun 25]. Available from: https://elemental.medium.com/i-see-you-but-i-dont-how-masks-alter-human-connection-fbf2e21dd748

3. Nonverbal Communication. In: American Psychological Association [Internet]. [cited 2020 Jun 25]. Available from:

https://dictionary.apa.org/nonverbal-communication
4. Ambady N, Koo J, Rosenthal R, Winograd CH. Physical therapists' nonverbal communication predicts geriatric patients' health outcomes. Psychol Aging. 2002 Sep;17(3):443–52.
5. Hojat M, Louis DZ, Markham FW, Wender R, Rabinowitz C, Gonnella JS. Physicians Empathy and Clinical Outcomes for Diabetic Patients: Acad Med. 2011 Mar;86(3):359–64.
6. He X, Sun Q, Stetler C. Warm Communication Style Strengthens Expectations and Increases Perceived Improvement. Health Commun. 2018 Aug 3;33(8):939–45.
7. Hardy C. Empathizing with patients: the role of interaction and narratives in providing better patient care. Med Health Care Philos. 2017 Jun;20(2):237–48.
8. Ambady N, LaPlante D, Nguyen T, Rosenthal R, Chaumeton N, Levinson W. Surgeons' tone of voice: A clue to malpractice history. Surgery. 2002 Jul;132(1):5–9.
9. Levinson W. Physician-patient communication. The relationship with malpractice claims among primary care physicians and surgeons. JAMA J Am Med Assoc. 1997 Feb 19;277(7):553–9.
10. Gladwell M. Blink. New York: Back Bay Books; 2019.
11. Asmelash L, Ebrahimji A. Health care workers are wearing smiling photos of themselves to put coronavirus patients at ease. CNN [Internet]. 2020 Apr 10 [cited 2020 Jun 26]; Available from: https://www.cnn.com/2020/04/10/us/healthcare-workers-photos-smile-coronavirus-trnd/index.html

REFLECTIONS

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Forget Two-Faced, We're Infinitely Faced: On Facial Plastic and Reconstructive Surgery

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ABSTRACT

Facial anatomy and function are wildly impressive examples of the intricate nature of the human body. Here, the author reflects on two clinical scenarios involving facial reconstruction and facial transplantation in the field of plastic surgery. A commentary on societal interpretations of facial plastic surgery is included, highlighting the importance of reconstructive surgery in advancing patient functioning, self-confidence, and overall psychological well-being

KEYWORDS

facial plastic surgery, facial transplantation, reconstruction, anatomy, ethics, society

"The face is a picture of the mind with eyes as its interpreter.

- Marcus Tullius Cicero

"Gussie, a glutton for punishment, stared at himself in the mirror."

- P.G. Wodehouse, Right Ho, Jeeves

"First principles, Clarice. Simplcity. Read Marcus Aurelius. Of each particular thing, ask: What is it, in itself, what is its nature...? What does he do, this man you seek?"

- Hannibal Lecter, The Silence of the Lambs

The marvels of medicine are numerous and often awe-inspiring when properly appreciated. Facial anatomy and function are wildly impressive examples of the human body's intricate nature. The facial skeleton consists of fourteen bones in total, with their size and shape determining the structure on which the subsequent soft tissue rests. The elaborate nature of this soft tissue is remarkable, including more than twenty different muscles, as well as a handful of vitally important blood vessels and functionally paramount nerves. Injury to these structures can be devastating to facial function and all that relies on it.

Cicero's quote above bundles up the importance of the face eloquently and at the same time, incompletely. Beyond a picture of the mind in any one moment, the face defines us in innumerable ways. Regardless of any state of mind, the face, for better or worse, always takes center stage. When we see the world, we do so from a space behind our face. When we view the faces of others, the tendency to react is hard-wired. Whether it be a first impression during a job interview, or the way a smile or smirk is carefully released on a first date, perceptions of facial anatomy, contour, and expression can be consequential.

As medical practitioners, we often find ourselves in the position of seeing patients at their most vulnerable. When patients suffer facial disfigurement, this vulnerability tends to invade realms far beyond the clinic or operating room. Whether at the hands of trauma or disease, the prospects of facial disfigurement can fuel feelings of uncertainty, anxiety, and anger. In these scenarios, given that the literal means by which one interfaces with the world is being jeopardized, this range of experience is both unsurprising and understandable. In these cases, the role of the surgeon to counsel patients, by providing options and advice, as well as managing expectations, is critical and must be achieved with care and precision.

In 2018, a Montréal-based team fulfilled this responsibility in a unique way after completing the first facial transplant in Canada. The case was one that I was not especially familiar with, despite the media attention it garnered at the time. As a medical student, one tends to vacillate between states of appreciable fatigue and unrelenting exhilaration, and during this maze of experience, unplanned opportunities can present themselves. During my core surgery rotation, I had the opportunity to observe a facial transplant skills session, which was organized for otolaryngology and plastic surgery residents and directed by Dr. Daniel Borsuk, the lead surgeon who orchestrated the Montréal facial transplant. Following his Grand Rounds lecture at my home university, residents made their way to the university's skills lab. The entrance to the lab was memorable. After gowning and gloving, residents entered the room and approached Dr. Borsuk, who asked their specialty and rank before dispatching them to competing tables. My turn came, and I stated, "Third year medical student, here to observe". Dr. Borsuk, almost amused, replied "No observation today, you can join team six!" As Dr. Borsuk circulated the room, observing and teaching learners about key aspects of the transplant procedure, I was able to speak with him personally. I inquired whether there had been any deviation from the stepwise plan outlined during his talk, which had been posted on the operating room wall in Montréal during the surgery. He commented that facial transplant surgery was a domain in which improvisation was not heavily relied upon, remarking that they had treated the surgery like a spacewalk. Second thoughts, it turned out, were truly a last resort during the 30-hour operation. This interaction certainly had the effect of focusing my mind when it came time to select a specialty to pursue. The intense attraction that I had been developing to surgery, and to the theatre of the theatre over the past 18 months, were only strengthened by this brief but meaningful interaction. The stakes were high, and the consequences associated with error were as appreciable as the meticulous planning and work required to make the procedure a success. For some reason, I felt very much drawn in by this combination of circumstances and the idea that one could build a career around the concept of surgery of this kind.

The transplant skills session was certainly interesting enough, however, a second experience also proved to be formative for a medical student with a keen eye

for the face and its wonders. The setting was a plastic surgery clinic and I was the third-year clerk. I was assigned to interview and examine a post-operative recheck and then report back to the staff physician. The patient spent the previous four weeks recovering from a right-sided alar-facial basal cell carcinoma excision and reconstruction. After reading the patient's chart, I was able to gain an appreciation for the lead up to the discovery of the lesion and the details of the procedure. As I walked into the room and began talking to and examining the patient, I suddenly found myself unable to discern where the lesion had in fact been located. The healing process was indeed underway, but I had expected a more obvious presentation. As I quietly observed, my eyes wandering over his face, he soon became aware of what was happening, and he smirked almost uncontrollably. We had agreed that the outcome of the procedure was successful and left little in the way of desire. This simple and seemingly unremarkable moment had in turn left its mark on me. It was not that the affected area was difficult for my untrained eyes to see, but rather his reaction to this outcome and the satisfaction that came with it. This patient was fortunate to have a relatively small lesion and the luxury of negative margins. Cancers of this kind virtually never undergo metastatic spread but are known to be quite locally destructive as they eat away surrounding soft tissue. He had been lucky in several ways from a medical perspective, and I had also been lucky when it came to his smirk and the interaction we shared, through the meaning it held for me. It was a moment I will not forget as it drove home just how consequential facial plastic surgery was for the undergoing patients. As doctors, all of us enter the field of medicine with the goal of improving the lives of our patients. While this specific case did not involve life and death per se, and the extent of the insult was relatively limited, the power of reassurance and improvement was both shared, powerful, tangible, and perhaps, habit-forming.

These experiences represent part of the fundamental privilege associated with choosing medicine as a career. This memorable interaction, along with many others I have experienced thus far, have greatly stimulated both personal reflection and clinical development by cementing my interests, establishing patient connections, and allowing me to better understand their point of view. Importantly, these interactions have also nurtured an awareness of the related philosophical and ethical facets involved at times. In considering the growing field of facial transplantation, we are beginning to place more importance on the psychological implications associated with the procedure. There are many areas of intrigue within this type of transplant ethics. Psychological screening for potential recipients is robust and for good reason. Conceptualizing what being a facial transplant recipient would be like post-operatively must be complicated, self-altering and at the same time immensely intimate and intimidating. In the case of a patient who has suffered facial trauma through a self-inflicted gunshot wound, for example, and who now wishes to become a transplant recipient, questions gauging psychological well-being and fitness as a recipient must be answered. Moreover, beyond screening for suitability, dilemmas still exist. In cases where facial organs are scarce, should victims of accidental or disease-related trauma take precedence over those who have self-inflicted wounds? Over time, other concerns have been raised regarding the intensive immunosuppressive therapy required following transplant. In some jurisdictions, the patient's ability to pay for what amounts to a lifelong and life-sustaining therapy may unfortunately become important.

Such questions meaningfully challenge physicians, ethicists, and societies who are responsible for deciding eligibility criteria and the level of investment in these procedures and their downstream management, given the staggering costs. As our transplant science and techniques advance, the ethical difficulties in these more delicate cases will be no less apparent, but as medical professionals, we must keep our eye on the ball that is bettering the lives of our patients. The advent of several facial transplants in the mid 2000's led to an increased acceptance of the procedure, its utility in appropriate cases, and a heightened interest in advancing the science and technology of transplant itself. Assuming that issues related to cost can be mitigated, and they can

be by enhancing understanding of the procedure's importance to societies and governments, it seems that the consenting patient, with their understanding of risks and benefits firmly in hand, should be able to pursue the surgery in a more unhindered manner as time goes on. This can only be expected given the advances thus far, as well as the paradigm shift witnessed over the past two decades in respect to acceptance of the procedure in medicine and society.

More generally, these experiences have granted me a refined lens through which to view perceptions related to plastic surgery in society. The power of aesthetics in medicine can be underappreciated and, in some cases, mischaracterized outright. There does exist a certain stigma associated with reconstructive surgery in popular culture and society. This is a notion that aims to characterize plastic surgery as unnecessary or, in its worst forms, existing only as a pursuit in vanity and image rather than the more conventional and accepted medical themes of health and wellness. A fixation on physical image or aesthetic outcome can have deleterious effects in some circumstances and, of course, can be realized as pathological. However, our collective fascinations or infatuations with aesthetics, outcomes, and image are simply part of the social web in which we are tangled. Once that state of play is accepted and acknowledged, the obvious benefits associated with bettering perceived image should be as well. The importance of self-image to the individual and to their self-confidence, no matter how critical our stance is on an increasingly image-driven society, is hard to discount outright.

In cases of facial disfigurement, a spectrum of the degree of insult certainly exists, with the need for complete facial transplantation on one end, and less involved or necessary procedures on the other. Nonetheless, the successful restoration to some semblance of the desired tissue structure is a meaningful and worthwhile goal in most cases. Here, success can give much to our patients in terms of their identity, confidence, interpersonal interactions, and in the best cases, overall psychological well-being. These kinds of successes, the unique relationships they engender between surgeon and patient, and the impacts they have on both are readily appreciable, and to me, worth chasing.

REFLECTION

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On Psychiatry in Cinema

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SYNOPSIS

Hannibal Lecter, Malcolm Crowe, and Arthur Fleck are three cinematic characters that relentlessly captivate viewers for different but powerful reasons. A common thread between these characters is their explicit connection to psychiatric illness or its treatment. The author explains how these characters obtain the audience's attention through the lens of mental illness and how the viewer's reservoir for compassion stands to deepen during this process. The author concludes with a social commentary on Todd Phillips' *Joker* (2019) and the controversy surrounding its depiction of mental illness on the silver screen. (1)

KEYWORDS

Psychiatry, cinema, society, responsibility, joker

"We live in a primitive time—don't we, Will? —neither savage nor wise. Half measures are the curse of it. Any rational society would either kill me or put me to some use."

- Hannibal Lecter, Red Dragon

"How about another joke, Murray? What do you get when you cross a mentally ill loner with a society that abandons him and treats him like trash? I'll tell you what you get!"

- Arthur Fleck, Joker

"When people ask me if I went to film school, I tell them, 'no, I went to films.'"

- Quentin Tarantino

Artistic expression at its very best, *moves*. In cinema, medical themes are often used to effectively paint characters, build atmospheres, and emotionally provoke audiences. The very nature of the human experience that these themes are derived from allows for a special and highly variable kind of creativity to find its way to the screen. Few areas in medicine provide as much depth to both on screen character and plot development as psychiatric illness. The struggles, successes, and setbacks inherent to mental illness urge the viewer to invest emotionally in the film, often via connecting empathetically to the involved characters. Given that it is quite likely virtually every viewer has had either exposure to or experience with mental illness, either directly or indirectly, this investment doubles as an inherent artistry-driven phenomenon and experience.

1 | BOTH SIDES OF THE SO-CALLED "GURNEY"

Astute audiences of modern-day cinema are likely familiar with the powerful amalgam formed when medicine and theatre collide. The cannibalistic serial killer and psychiatrist, Dr. Hannibal Lecter[1] in The *Silence of the Lambs* (1991), serves as an intriguing example of this. (2) Prior to even appearing on screen, Lecter is introduced in a terrifying and quasi-mythical way by his physician handler, Dr. Frederick Chilton, in the basement-level depths of the *Baltimore State Hospital for the Criminally Insane*. While escorting FBI agent Clarice Starling to interview the menacing psychiatrist, Chilton enthusiastically describes in vivid detail how Lecter savagely and gruesomely attacked a nurse after faking chest pains and finding a gap in prison security[2]: "the doctors managed to reset her jaw more or less. Saved one of her eyes. His pulse never got above 85, even when he ate her tongue[3]". The scene is juxtaposed immediately with the introduction of Lecter in the flesh. He poses as a thoughtful and extremely well-mannered inmate during his initial interactions with Starling. As has been pointed out elsewhere more generally, this timid and unassuming outward demeanor when combined with the character's ruthless tendency to physically harm, torment, and eat others, proves extremely unsettling. However, this dynamic also serves as a major point of intrigue from the perspective of the audience. As viewers, we do not necessarily find ourselves rooting for Lecter at any one point in time, but we do find ourselves yearning to witness his hypnotic interactions and crisp intellect increasingly as the story unfolds. This encapsulates the power of great character development and, importantly, the utility of intrigue in cinema. This is especially true in portrayals of mental illness – at times, one can find themself at ease and unguarded when faced with a character or situation normally regarded as the personification of capricious evil. It is true that we often fear what we do not understand and the kind of cinema presented in *The Silence of the Lambs* offers us the ability to let that fear slowly slip away given the invitation to be empathetic towards Lecter. This is true despite its meaning we will become more comfortable in the presence of something that does tend to terrify us in real life.

There is some irony to be found in this fact, given the potential risks of such portrayals supporting the familiar stigmas associated with mental illness. Because the filmmakers and actors had the fortitude to tell the story in light of these risks, we are more likely to become intimately familiar with the person behind the pathology, their life-story, and all the ins and outs that led to them to where they stand today. In Lecter, we do not become familiar with his origin story *per se* in *The Silence of the Lambs*, but we are able to see things from his point of view in a way that shifts our perception of his capacity to in fact, *be* vulnerable. His mistreatment and abuse at the hands of the hospital administrator is likely the best example of this in the film. A line that perhaps summarizes the injustice and cruelty of solitary confinement

[1] Lecter is played by the renowned actor Anthony Hopkins in the film and despite being on screen for just over 16 minutes, captured the academy award for best actor.

[2] Lecter pounced after healthcare workers removed his restraints to complete an electrocardiogram (ECG).

[3] To the best of the author's knowledge, this serves as the most prominent description of hemiglossectomy in the history of cinema.

best is delivered by Lecter, quoting from William Blake's *Auguries of Innocence* (1863) in *Red Dragon* (2002): "A robin red breast in a cage puts all heaven in a rage". (3, 4) Despite the robust depiction of his psycho- or sociopathic tendencies throughout the film, we are given the opportunity to realize and understand a character as a patient and as a person first and foremost, and that is a meaningful thought experience audiences would do well to lean into more. That is to say that part of the value of the cinematic experience in these cases comes from viewing the character beyond the superficial impressions we are initially offered and returning to reflect on a more fundamental ethic. In the case of Lecter, this would mean viewing him as both a patient with a psychiatric illness as well as a jailed cannibalistic killer, while at the same time not forgetting that he is a human being who can and does suffer in ways we should care about.[4]

Suffering, as we have seen, can become a centerpiece in a character's story. Suffering itself and the role of those tasked with mitigating it in psychiatric contexts provide much in the way for fascinating plot development on screen. Despite the popular appeal of the villainous in film, there are also several powerful examples of characters who treat the mentally ill, giving us the unique perspective of the healthcare professional. M. Night Shyamalan's classic *The Sixth Sense* (1996) offers the viewer an interesting parallel to *The Silence of the Lambs*. (5) We become acquainted with the child psychologist, Malcolm Crowe, who, in contrast to Lecter, still has a medical license, patients under his care, and the will to help rather than to eat them. His character follows and treats a disturbed young boy who harbors the uncanny supernatural ability to see the dead in ghost form. Crowe appears as someone earnest in his work and commitment to the child's well-being. It is entirely likely that child and adolescent mental health professionals stand to create the most change for patients in healthcare systems, given the nature and timing of their illness.[5] Many factors impact the plight of these patients, such as brain plasticity, stress response, time, and luck, as well as the impacts of successful and timely intervention on life trajectory. Moreover, considering trajectory here briefly, the polemicist Christopher Hitchens once used a visceral analogy for life as akin to being "expelled from your mother's uterus as if shot from a cannon toward a barn door studded with old nail files and rusty hooks". He went on to say that "it's a matter of how you use up the intervening time in an intelligent and ironic way". Bleak and cold as this analogy may seem[6], there is an undeniable truth to the fact that life trajectories are consequential, and that we are all headed towards the same end at a rather startlingly steady pace. In this context, psychologists like Crowe work hard to pour a stable foundation to provide support for the rest of their young patients' lives. Crowe's commitment to his patient and the sheer complexity that the boy provides are immensely satisfying. This film is particularly unique as it offers a *realistic* perspective of the experience of caring for sick patients while suffering in one's own personal life, a perspective that few lay viewers will have encountered.

2 | *JOKER*: THE TRANSFORMATION AND THE SETUP

One criticism that *The Sixth Sense* endures is the blurring of the lines between reality and the supernatural in preparation for the breathtaking and truly unbelievable twist ending Shyamalan serves us. In contrast to this, a recent film that blows the doors to realistic depictions of mental illness wide open is Todd Phillip's *Joker* (2019), starring Joaquin Phoenix as the makeup-laden villain. (1)

[4] Interesting, some may argue that Lecter in fact stands to suffer more in solitary confinement than most others given his wide-reaching and appreciable intelligence. We see this preyed upon in the film with punishment involving removal of his books or drawings from his jail cell.

[5] Such comparisons between medical specialties are fraught with complexity. It seems uncontroversial, however, to say that child and adolescent mental healthcare workers are providing interventions at a time and with an illness that will, for better or worse, dictate the terms of the next decades (at least in an appreciable number of cases).

[6] Hitchens was celebrated for his ability to turn a clever phrase and did indeed end the point (during an impromptu street corner interview) by saying that one should also "try not to do anything ghastly to your fellow creatures".

What sets the film apart from previous incarnations of the character is the focus on a more realistic and lengthy transformation into depravity. We are first introduced to the timid and relatively unassuming Arthur Fleck, a mentally ill, impoverished, and unsuccessful stand-up comedian. During the film's first act, we come to realize Fleck is a hard-working and committed caretaker and early on, his intentions provide little cause for concern. Comfort begins to set in, despite the viewer being somewhat aware of the twisting road they are travelling and an inkling of the final destination it portends. This comfort with the player, if not the stage, or this calm feeling before the storm, is a full credit not only to Phoenix and his command of the screen, but to the vision of writer director Todd Phillips.

Joker is set in a turbulent time for the city and society. An ominous garbage collector's strike and the build-up of trash and debris symbolize the decay of normal interpersonal relations. Over the course of the film, the insults to Fleck, his dignity, and his health steadily accumulate. His story, over time, becomes one of suffering, and his prospects continue to steadily worsen. In all tragedies, we can identify a breaking point; in *Joker*, there are perhaps multiple. The loss of Fleck's job, his social supports, and prescription medications in the face of mental illness prove to be devastating. Frustrations in both romantic, social, and familial life plague him almost continuously. Physical and emotional traumas are revealed to be driving forces behind the character's development, both those in the past and in that unfolded on screen.

This storm of events culminates in two defining moments in the character's transformation. The first, on the subway when three corporate employees intimidate and harass a lone female passenger. Fleck is perhaps as tortured by inaction as we are, and this moment unfortunately becomes overtaken by a symptom of one of his illnesses, emotional incontinence, otherwise known as pseudobulbar affect. His unrelenting laughter draws the attention of the men and a physical assault ensues, culminating in his ruthless execution of one of the attackers. In this scene, Fleck transitions from a clown down on his luck into a dark and unforgiving character. As the masterful Hildur Guðnadóttir's *Bathroom Dance* plays ominously, Joker dances hypnotically, accepting the role of someone no longer shackled to the rules of a society that he has carefully obeyed for so long. We begin to appreciate the destruction and caprice he is suddenly capable of, and of which he develops an unquenchable thirst for. The dramatization of the transformation is impressive by any standard, but so too is the story-telling and screenwriting itself. It is perhaps the cumulative nature of the insults and the breaking points we anticipate that allows us to reflect on how easily such a person could be abandoned by society and how such evil may result.

The second seminal moment takes place near the end of the film, when Fleck appears on *The Murray Franklin Show*. The late-night host, with his clearly corrupt intentions, invites Fleck on presumably as a freak show attraction. Again, a calmer and seemingly benign Fleck presents himself initially. Had we watched this scene as a standalone without knowledge of his newfound homicidal tendencies and suicidal ideation, we may not make much of the initially bizarre interactions. Franklin, however, was unaware of just how sick his guest was, and after chastising him for misplaced jokes, the tempo of the scene shifts dramatically. Quickly, after admitting his misdeeds, Fleck questions the worth of the corporate rats in relation to his own and those in similar socio-economic positions. Almost childlike in the way he morally evaluates the society that he believes has in part created him, he admonishes its baseline etiquette and defends his killing spree. After forceful pushback from Murray, that which the viewer is tempted to see as irritating or at least ironic given the host's transgressions, Fleck transforms into *Joker* amid the roar of the score. His eyes liquify, and he seems to tear up as his grin becomes more and more unstoppable; we are owned by Phoenix in this moment. Without any sense of concordance between emotion and expression, he revels in both the chaos he has created and the attention he is about to ensure. A yelling match and lecture on mental health and society occurs before Murray himself is executed on live television.

3 | ON VIOLENCE, STIGMA, AND MEDICAL ADVOCACY IN *JOKER*

Much analysis of the themes and violence put forth by *Joker* has been completed by audiences and critics. Both Phoenix and Phillips have been criticized for attempting to normalize or glorify the actions of the homicidal character. Some have remarked that the movie makers and studio behind its release are acting immorally given the possibility of copycat attacks in an era of gun violence. In response, they have claimed that it is simply not up to artists, writers, or directors to decide levels of morality for the general population or viewers of their work. Of course, they are right. Movies are not real, in the same way that books and television shows are also fiction. Free expression, as with free speech, should be viewed as an absolute if it is going to be called free at all. It is no matter that the film is exceedingly dark, and a viewer may spend most of the two hours sitting somewhat uncomfortably. The arts are supposed to move us, and what a bore it would be if these moves were always in one concerted, predicable, comfortable, and uncontroversial direction.

Others have also taken issue with the film's portrayal of mental illness and the unfounded link it makes to violence. Some have even commented on the elusiveness of an actual diagnosis in the case of Fleck. These criticisms land glancing blows at best. Those suffering from mental illness are no more likely to commit crime compared to members of the general public, but this does not make the population exempt from misbehaving. Implicit in such criticism is the idea that these stories should not be told, given the risks of glorification or stigmatization. There are several issues with this sort of criticism. First, outlawing stories of this kind would be a clear and present affront to the cherished sentiment of free expression in the arts, and for that reason, indefensible. Second, this line of thought willingly ignores the obvious benefits of adapting the story to serve purposes of self-reflection and societal reflection. The main point the film attempts to underscore is that the character is ill and has, over time, succumbed to several devastating insults. *Joker*, in essence, asks us to question whether the society Fleck lives in, or the reservoir holding these insults, shares any of the burden of his transformation. Indeed, some viewers may extrapolate certain stereotypes about mental illness and violence, but this is a very small price to pay for the larger seminar on compassion and introspection that the film provides to audiences intent on listening. Further, whether Fleck portrays an authentic medical presentation related to any of his illnesses seems beside the point if the filmmaker's aim was to force viewers to ponder their own decency and compassion, and the impact of society on the vulnerable. A useful analogy here may be the case of films related to space or time travel. While not always based in the most accurate versions of our physical or scientific understanding of the world, these narratives are still valuable to viewers because they invite audiences to begin thinking about big scientific ideas, the future, or the point of life or existence itself. The science behind the depictions need not be wholly true for the film to meet these objectives.

Joker, at the end of the day, is a rollercoaster of experience. In terms of the violence or potential glorification of evil doers in cinema, the film is not unique; Hannibal Lecter also demonstrates these themes, as well as Michael Corleone in *The Godfather Part I* (1972) and *Part II* (1974) and Jack Torrance in *The Shining* (1980).[7] (6-8) *Joker* sets new heights in both the quality of presentation of the subject matter and the discomfort it creates, by forcing us to turn a critical eye on our own society and medical systems. The realistic and progressive nature of the transformation is surely unsettling, however this is a result of the potential for viewers to see it as a disturbing reality, not because it is immoral, *per se*. Similar to Lecter, we also find ourselves alternating between feeling sympathetic for, and then horrified by, Fleck; this is an artistic accomplishment on the part of the filmmakers. Additionally, the film has promoted dis-

[7] While we may find ourselves rooting for these characters more or less at different times throughout the respective movies, they have all, to some extent, become adored and glorified by film audiences and pop culture. The point here is that this is despite the clear issues they provide from a moralistic standpoint whether derived from illness, the supernatural or their own worldly nature.

cussion via controversy at times, around the topics of the disenfranchised in society, mental illness, and access to healthcare; this is perhaps ironic, but valuable and important. Moreover, this depiction is the role of the arts as perfectly intended, and a powerful example of effective medical advocacy in film.

4 | CONCLUSION

In discussing the appeal of cinema as a medium in a 2009 broadcast interview for *Inglourious Basterds*, the writer-director Quentin Tarantino quipped that as an art form, movie making was singular in its ability to bring stories to life: "and music doesn't quite do that on its own. And novels don't quite do it and a painting doesn't quite do it. It does – they do it their way, but in cinema, especially if you are in a theater and you are sharing the experience with a bunch of other people, so it's this mass thing going on, it is just – it's just truly, truly thrilling".[8] (9) Tarantino here, was in effect articulating the idea that cinema has the unique ability to take the best parts of these mediums and package them in a way that defines storytelling in its purest and most reachable form. When faced with a hard-hitting screenplay, underlying message, and the right players on the stage, the thoughtful audience has no choice but to reflect deeply on the authenticity of the content.

In terms of its ability to convey medical themes and experiences in art, cinema is unmatched. An exhilarating and intense example of this lies in the onscreen adaptions of psychiatric illness and its treatment. Characters who deal with mental illness, whether they are viewed as good or bad, have something special to offer to us. They bequeath an emotional experience, a window into the very depths of a tortured mind, as well as the human experience that comes with that torture and its potential resolution. However sick or disturbing we may find it, perceiving these experiences can unlock doors to compassion, understanding, and self-reflection. Importantly, such experience may also allow us an appreciation for the great art, that maybe, just maybe, we did not know existed within us.

[8] Tarantino went on to say: "And if the movie is more than that, if there is a lot underneath, if there is more there, and you go out and you have a piece of pie and coffee and you talk about it and you find that there is more to talk about – I mean, one of the things that is actually fun is if you go with somebody and they don't like a movie and you do and you start talking about it. And yet they start digging deeper and deeper in the movie, you are not really talking about a movie – this is not like you don't like it – you're realizing there is a lot there. I love – that is one of the things I love about film criticism when it is really good, is just the digging deep."

REFERENCES

1. Joker. 2019. [film] Directed by T. Phillips. Los Angeles: Warner Bros.
2. The Silence of the Lambs. 1991. Directed by J. Demme. Los Angeles: Strong Heart/Demme Production.
3. Blake, W. Auguries of Innocence. 1863.
4. Red Dragon. 2002. Directed by B. Ratner. Los Angeles: Universal Pictures.
5. The Sixth Sense. 1996. Directed by M. Night Shyamalan. Los Angeles: Hollywood Pictures.
6. The Godfather Part I. 1972. Directed by F. F. Coppola. Los Angeles: Paramount Pictures.
7. The Godfather Part II. 1974. Directed by F.F. Coppola. Los Angeles: Paramount Pictures.
8. The Shining. 1980. Directed by S. Kubrick. Los Angeles: Warner Bros.
9. Quentin Tarantino on Charlie Rose. 2009. Charlie Rose LLC. Transcript available: https://charlierose.com/videos/26959.

EDITORIAL

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McGill Journal of Medicine

Healing Starts with Understanding: Addressing Language Barriers in Patient Care Through Medical Student Interpreters

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ABSTRACT

Where communication is a cornerstone of the relationship and therapeutic alliance between the patient and the healthcare provider, language barriers are a serious obstacle in a medical setting. Ji et al. identify the essential barriers to providing medical care to non-English, non-French speaking populations through their experiences with Dr. Juan-Carlos Chirgwin in Montreal's Parc-Extension community, the founding of MedComm to address language barriers within the McGill University Health Network, and the larger importance of trained medical interpreters in the circle of care.

KEYWORDS
Language barriers, medical interpretation, medical students

As the most ethnically diverse metropolitan of the most multicultural country in the world, Montreal's 2016 census profile found its immigrant population to be at a staggering rate of 23.4%, which does not include its second and third generation immigrant population (1). While this diversity undoubtedly gives Montreal its unique charm, it can create social, political, as well as healthcare challenges. Indeed, a majority of our most vulnerable patients include immigrants and refugees.

Dr. Juan-Carlos Chirgwin is a name you can mention in any community centre or school in the Parc-Extension neighbourhood of Montreal and expect people to recognize with a smile. Over the past years, Dr. Chrigwin has done extensive work reaching out to the local residents, comprised mostly of asylum seekers and new immigrants. In fact, a demographics analysis shows that this small neighbourhood of 1.6 km2 hosts 32.9% of Montreal's visible minorities (1). In collaboration with medical student interpreter volunteers from McGill University, Dr. Chirgwin's advocacy includes making effort

to break the language barrier he faced with his patients from the Parc-Extension community

Language barriers in healthcare services are common, but unfortunately, professional medical interpreters are often unavailable. This problem is not just limited to the Parc-Extension community. In a city as diverse as Montreal, this issue impacts all healthcare institutions, including hospitals and medical clinics. In 2018 alone, at just 4 of the McGill University Health Centre (MUHC) sites, over 500 layman interpreter requests were made through overhead intercom announcements. In fact, as medical students completing clerkship rotations, we have the privilege of circulating through various specialties and institutions, which provides us with an overview of the healthcare network. In every rotation, without fail, there would be at least one allophone (non-English and non-French speaking) patient for which the healthcare provider struggles to find an interpreter

It is the elephant in the room: interpreters can be just as essential to patient care as a stethoscope, if not more. These barriers, unaddressed, impede the physician's ability to fulfill the Hippocratic Oath. As Dr. Chirgwin so candidly explains:

> *"History is everything," we are told in medical school, and yet a glaring blind spot in our medical system is the lack of trained interpreters in large cities with inhabitants from different regions of the world. We are asked to be "patient-centered" in our interview style yet are given no tools to address a patient who cannot understand either French or English. Quality control in our hospitals would frown upon any type of practice that represented an avoidable risk for a patient; however, it is customary to hear hospital overhead announcements requesting any person who speaks such and such a language to assist for interpretation in the emergency room. We are asked to depend upon friends or relatives of patients to gather details of medical complaints, which may be embarrassing to describe or simply "taboo" subjects. The assumption is that it is the patient's responsibility to provide an interpreter, although we are not asking them to bring a stethoscope, gauze or an IV bag.*

Where communication is a cornerstone of the relationship and therapeutic alliance between the patient and the healthcare provider, language barriers are a serious obstacle in a medical setting.

Ample evidence in the literature speaks for the importance of linguistic concordance in provider-patient communication and the negative consequence of language barriers in healthcare: increased diagnostic testing, decreased quality of management, increased medical errors, etc. (2-5). Further evidence suggests that medical errors with potential consequences are highest when an untrained, ad hoc interpreter is utilized for medical interpretation—as compared to no interpreter intervention at all (6). Currently, in the context of urgent care, communication between the health professional and the allophone patient relies largely on layperson interpretation through a friend or family member, or a volunteer recruited through the hospital intercom. In these circumstances, the layperson, often untrained in interpretation and inexperienced with medical terminology, does not transmit fully or accurately all the necessary information. In the context of scheduled appointments, interpretation services are occasionally requested from professional agencies, which are often costly (45–150/hour), scarce, and complicated to arrange. As expressed by the hospital administration, major current barriers to accessing professional medical interpreters include cost, time availability, variety of languages requested, coordination with interpretation services, and quality of interpretation

The need for more adequate and more accessible interpretation services is, however, ever so significant. To reiterate, barrier to quality communication increases chances of misunderstanding, negatively impacts the thoroughness of health investigations, and can undoubtedly lead patients to lose control of their health. These issues are mainly due to poor patient education, poor

compliance, lower patient satisfaction, lack of safety, and negative clinical experiences (7, 8). Consequently, there is a stark increase in health disparities, and this already marginalized population is at a heightened level of vulnerability. With this in mind, healthcare workers and administrators must strive to meet the need. We must be reminded that the need to provide adequate interpretation is reinforced by provincial regulations: Quebec's Act Respecting Health Services and Social Services establishes a structure "to foster, to the extent allowed by the resources, access to health services and social services in their own languages for members of the various cultural communities of Québec (9)."

Current alternative "leading practices" to on-site professional medical interpretation services can be found in Manitoba and Toronto, where remote professional interpreter services in over 200 languages are available by phone 24/7. However, many of these companies are US-based and interpret only to English as the reference language. In Quebec, where both French and English are regularly used in our working environment, the necessity to provide an additional service in French translates to a greater budget need. The use of mobile translation applications, such as Google Translate, is another avenue that is already widely used. However, this practice has its own caveats, such as user friendliness and patient familiarity with the technology. Importantly, there are dangers associated with inaccurate application translations, which can be particularly inappropriate during medico-legal discussions, such as obtaining informed consent (10).

Dr. Chrigwin is not alone in his frustration: "This issue is not restricted to one hospital or even to one city. It is a phenomenon being played across the country and across borders." A brief survey of physicians in any MUHC hospital site would reveal a dearth of interpreters to meet their patients' language needs. This is of course also shared by all healthcare professionals, including nurses who are in most contact with patients, as well medical trainees who may have their teaching inhibited by those language barriers. Fortunately, the cultural and linguistic diversity of Montreal is not only reflected in the patient population but also in the cohorts of medical students. In McGill's Class of 2021, for example, 35.36% of the students declared having a mother tongue other than English or French. This begs the question, what role can multilingual medical students play in breaking the language barrier in the healthcare setting? A simple call to action for medical student volunteers showed over 100 students that expressed interest in offering their interpretation services. As such, with appropriate medical training etiquette, there is, in fact, a potentially important role for multilingual medical students to facilitate both clinical encounters as well as community outreach events—introducing MedComm.

MedComm is a student-founded and student-led outreach initiative that aims to 1) train medical student volunteers who speak different languages in medical interpretation, and 2) develop an online platform to connect volunteering interpreters with healthcare professionals requesting interpretation services across the MUHC network. MedComm believes that medical students are in a unique position to bridge this gap for medical interpretation. Students have sufficient medical training to communicate the nuances in history taking with professionalism, and they carry an innate cultural competence to respectfully build patient rapport. To optimally harvest this potential resource (multilingual medical students), it needs to be collectively recognized and training needs to be organized through the curriculum. It is only with faculty support and physician recognition of the potential that this change can be in effect. Medical student interpreters can play an important role and significantly benefit countless families in our ever so diverse community.

It is the responsibility of physicians and students in training to provide the highest quality of care for patients, which means breaking the language barrier. To achieve this, action must be made at an institutional level. With an urban population as diverse as the one in Montreal, interpretation services should always be available and easily accessible, and all healthcare providers, including allied health professionals, should be comfortable in requesting, booking and interacting with interpreters.

To support the initiative and learn more about MedComm, visit our Facebook page: https://www.facebook.com/MedComm-Medical-Interpretation-107488790739458/

REFERENCES

1. Statistics Canada. (2017). Montréal [Census metropolitan area], Quebec and Canada [Country] (table). Census Profile, 2016 - Montréal.

2. Jackson C. Medical Interpretation. In: Loue S, editor. Handbook of Immigrant Health. Boston, MA: Springer US; 1998. p. 61-79.

3. Bowen S. (2015). The Impact of Language Barriers on Patient Safety and Quality of Care. In: Canada H, editor. Société Santé en français.

4. Bowen S. (2001). Language barriers in access to healthcare. In: Canada H, editor. Ottawa.

5. Jacobs E. The Need for More Research on Language Barriers in Health Care: A Proposed Research Agenda. The Milbank Quarterly. 2006;84(1):111-33.

6. Flores, G., Abreu, M., Barone, C. P., Bachur, R., Lin, H. (2012). Errors of medical interpretation and their potential clinical consequences: A comparison of professional versus ad hoc versus no interpreters. Annals of Emergency Medicine. https://doi.org/10.1016/j.annemergmed.2012.01.025

7. Karliner, L. (2019). When Patients and Providers Speak Different Languages. AORN Patient Safety Network. https://doi.org/10.1002/aorn.12757

8. Vargas Pelaez, A. F., Ramirez, S. I., Valdes Sanchez, C., Piedra Abusharar, S., Romeu, J. C., Carmichael, C., … Silveyra, P. (2018). Implementing a medical student interpreter training program as a strategy to developing humanism. BMC Medical Education. https://doi.org/10.1186/s12909-018-1254-7

9. Act Respecting Health Services and Social Services (1991, c.42, s.2; 2002, c.71, s.1). Retrieved from Legis Quebec website: http://legisquebec.gouv.qc.ca/en/showdoc/cs/s-4.2#se:2

10. Chen, X., Acosta, S., Barry, A. E. (2017). Machine or Human? Evaluating the Quality of a Language Translation Mobile App for Diabetes Education Material. JMIR Diabetes, 2(1), e13. https://doi.org/10.2196/diabetes.7446

EDITORIAL
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75 Million Syringes but Nothing to Put in Them: What is Canada's Plan for a COVID-19 Vaccine?

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ABSTRACT

The Canadian government recently announced, to much fanfare, that they have begun procuring the supplies that will be essential for mass vaccination against COVID-19, beginning with an agreement for 75 million syringes, alcohol swabs, and bandages. This is certainly good news, and it is absolutely worthwhile to think about these potentially overlooked items when planning to vaccinate the population. But what will we vaccinate them with? Dankner and Michell-Robinson argue that in the current political climate, the Canadian Government must act now to invest in securing early vaccine doses from promising trials as well as make long term plans to bolster the Canadian biomedical sector in order to avoid future issues with drug development in times of international crisis.

KEYWORDS
Vaccine, Drug Development, Clinical Trials, Corona Virus, Public Health

The Canadian government recently announced, to much fanfare, that they have begun procuring the supplies that will be essential for mass vaccination against COVID-19, beginning with an agreement for 75 million syringes, alcohol swabs, and bandages. (1) This is certainly good news, and it is absolutely worthwhile to think about these potentially overlooked items when planning to vaccinate the population.

But what will we vaccinate them with?

The United States has "Operation Warp Speed,", an initiative to rapidly test and manufacture multiple vaccine candidates in clinical trials that they expect to be ready by the end of 2020 or early 2021. (2) Early data suggests that this timeline may be realistic. (3) Given that manufacturing of any effective vaccine will be initially limited, European nations have lined up contracts with AstraZeneca and Pfizer to distribute their vaccine candidates, which are already approaching final-phase clinical trials, with negotiations with Johnson & Johnson in the works as well. (4, 5) Asian countries also have a number of candidates that are rapidly progressing through clinical trials in China. (6, 7) Even Australia and Russia have vaccine candidates in advanced human clinical trials, (7) and nations such

as Israel, Egypt, and India, among others, have signed agreements for early doses of promising vaccines. (8-10)

Where does this leave Canada?

There are a number of promising Canadian COVID-19 vaccine candidates, but they are all much further behind. Manitoba-based researchers are testing a candidate in animals, University of Laval has a vaccine candidate in the preclinical stages, and the Quebec-based biotech firm Medicago has just recently begun testing humans with its candidate that does not have the financial backing required to move as quickly as international candidates. (7, 11) Together, this means that it is unlikely for a made-in-Canada COVID-19 vaccine to be proven safe and effective before the fall of 2021 at the earliest. If international vaccine candidates are indeed successful and begin mass vaccination in the next 6 months, where will that leave Canadians? There is roundabout talk of sharing of vaccines between nations, but it seems increasingly likely that countries will vaccinate their own first in order to restore their economies and way of life. Canada missing the boat on being an early country to vaccinate could result in thousands of Canadian deaths and more economic turmoil caused by a prolonged pandemic. Enduring a cold Canadian winter indoors while being unable to see friends and family will be particularly difficult for Canadians watching their neighbours to the south getting vaccinated and resuming a new normal way of life.

The Canadian government has reached an agreement with the Chinese company CanSino Biologics to develop and eventually manufacture its vaccine candidate that just published results from its phase 2 clinical trials in China and was approved for emergency use in the Chinese military in the absence of phase 3 trial data. (6, 12) This agreement was announced in the press on May 12th, but according to updated trial information on clinicaltrials.gov, the Canadian phase 1/2 trial has yet to begin enrolling patients. (13, 14) It has been recently reported that the hold-up is due to the Chinese government preventing shipments of vaccines coming to Canada. (15) This emphasizes the issues inherent to partnering with the Chinese government to ensure access to a vaccine and the importance of having multiple "shots on goal"–increasing our odds of success by having multiple vaccine candidates in the pipeline at the same time. This is the recipe being pushed by the United States, Europe, and China, and will likely be successful in one way or another.

Prime Minister Justin Trudeau recently published an op-ed with leaders of several other countries that have also failed to procure early doses of promising vaccine candidates, including Ethiopia, Sweden, and South Korea, wherein they argue that COVID-19 vaccines should be a global good not subject to hoarding. (16, 17) This may be true, but the reality is that the US, the European Union, China, India *et al.* have already accumulated these early doses, so such a strategy is already an impossibility and a moot point.

Certainly, the aggressiveness of the American approach to both the negotiations and clinical development of vaccines has invited criticism from Canadian pundits. Even the name "Operation Warp Speed" seems satirical, given the Trump administration's undermining of scientific authorities and simultaneous demands for a humanity-saving intervention from them in time for the November election. Yet, Warp Speed's multi-billion-dollar investment program looks poised to deliver a vaccine product to US citizens far sooner than anyone would have initially thought possible. And in this context, we must dare to ask ourselves: what can Canadian science learn from the international response to COVID-19?

Among the many opining about masks, pandemic preparedness, and the role and importance of public health in our national response to transmissible illness, there is a larger point about Canadian innovation that few people have set their critical sights on. We Canadians are entirely reliant on international investment for clinical development of the numerous vaccines, drugs, and other types of medical inventions that originate here. Like many of our natural resources, Canada extracts a primary intellectual resource and sells it to be refined, only to buy the final product back at a premium in order to

supply it to Canadians. We have never developed the type of robust biomedical science sector that would see translational medicine flourish outside of academia, and see our own inventions developed within its infrastructure.

Until now, that hasn't been a very big problem. Our proximity to the US–the largest economy and innovation engine in the world–has always guaranteed a level of interest in Canadian inventions. So, our clinical development strategy has always relied upon US investment and industry to purchase or license the rights to develop those inventions. The idea that Canadian medicines will be invented here and developed for the US market is so ingrained in us that we rarely question it. But, in times of crisis the importance of supply chains is magnified and our reliance on other nations to provide resources has a higher cost. Now, Canada is facing an unprecedented intellectual property supply chain problem, and its cost may transcend mere dollars and cents.

While we may provide a great deal of intellectual property to the international scientific community, we cannot rely on others to give back as freely in the midst of pandemics. However, it seems as though our government's current plan for a COVID-19 vaccine relies entirely upon generosity of other nations given that we are not investing in advance doses of any therapeutic candidates. Furthermore, the option to do so may not even be on the table for a prolonged period of time, given our allies' accountability to their own voters. Eliminating the risk of the pandemic and restoring their economies as soon as possible is an important priority indeed.

In our current situation, Prime Minister Trudeau has left us hoping that the terms of the agreement with CanSino Biologics will be honored by the Chinese government despite discouraging early warnings. Since this is our only agreement for rapidly obtaining a vaccine candidate, a failure of any kind means we could be left with little more than hope until we come together to accomplish testing a Canadian vaccine in Canada. However, this will come at the cost of thousands of Canadian lives and livelihoods given the prolonged timeline.

Had we prioritized developing our biomedical science sector prior to the pandemic, perhaps our own vaccine development response would have been able to ramp up and meet the challenge of the pandemic more effectively. Maybe we would have been able to establish timely access to multiple vaccine candidates (including our own) as other leading scientific nations have done. In this series of hypotheticals, perhaps Canada would have even taken a leadership role in rapidly distributing vaccines to less advantaged nations, rather than writing about it in the Washington Post. (17)

It is clear that Canada is behind the rest of the developed world in the search for securing doses of an effective COVID-19 vaccine, while it is becoming increasingly likely that the endgame of the pandemic will be vaccination. COVID-19 has taught us that now is the time to strengthen our scientific infrastructure, so that we can more effectively bring therapeutics from bench to bedside in case other nations–our supposed partners–turn inward in times of crisis. Given that it is too late to strengthen this infrastructure for a COVID response, we call upon the Canadian government to make the required investments in vaccine candidates and increase our likelihood of securing the health of Canadians beginning in 2020, and onward. We must make sure that we do not cause unnecessary Canadian deaths by extending the pandemic, while ensuring that we are not left behind as the rest of the world restores normalcy in the post-pandemic period. Strengthening the Canadian biomedical science sector will guarantee that Canada has the infrastructure to more effectively safeguard its own population, and even those of other countries, in future health crises. 75 million syringes are fine and dandy, but only if there is an effective vaccine to put in them.

REFERENCES

1. Rabson M. Federal government orders supplies to give two doses of COVID-19 vaccine when it's ready [Online Article]. CBC News2020 [Available from: https://www.cbc.ca/news/politics/feds-preparing-for-covid-vaccine-1.5654801.

2. HHS. Fact Sheet: Explaining Operation Warp Speed 2020 [Available from: https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html.

3. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Prelim-

inary Report. N Engl J Med. 2020.
4. AstraZeneca. AstraZeneca to supply Europe with up to 400 million doses of Oxford University's vaccine at no profit 2020 [Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-to-supply-europe-with-up-to-400-million-doses-of-oxford-universitys-vaccine-at-no-profit.html.
5. Smout A. U.K. secures 90 million potential COVID-19 vaccine doses from Pfizer and BioNTech alliance and Valneva The Globe and Mail2020 [Available from: https://www.theglobeandmail.com/business/international-business/european-business/article-uk-secures-90-million-potential-covid-19-vaccine-doses-from-pfizer/.
6. Zhu F-C, Guan X-H, Li Y-H, Huang J-Y, Jiang T, Hou L-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. 2020.
7. WHO. Draft landscape of COVID-19 candidate vaccines 2020 [Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
8. Reuters. Israel signs agreement with Moderna for potential COVID-19 vaccine: Reuters; 2020 [Available from: https://financialpost.com/pmn/business-pmn/israel-signs-agreement-with-moderna-for-potential-covid-19-vaccine.
9. EgyptToday. Egypt signs deal to receive Oxford University's COVID-19 vaccine 2020 [Available from: https://www.egypttoday.com/Article/1/88839/Egypt-signs-deal-to-receive-Oxford-University-s-COVID-19.
10. IndiaToday. Oxford Covid vaccine trials to be conducted in India soon, Serum Institute seeks DGCI nod 2020 [Available from: https://www.indiatoday.in/science/story/coronavirus-oxford-covid-vaccine-india-human-trial-serum-institute-dgci-lancet-study-1702675-2020-07-21.
11. Medicago. Medicago begins Phase I clinical trials for its COVID-19 vaccine candidate 2020 [Available from: https://www.newswire.ca/news-releases/medicago-begins-phase-i-clinical-trials-for-its-covid-19-vaccine-candidate-803210228.html.
12. Reuters. CanSino's COVID-19 vaccine candidate approved for military use in China 2020 [Available from: https://www.reuters.com/article/us-health-coronavirus-china-vaccine/cansinos-covid-19-vaccine-candidate-approved-for-military-use-in-china-idUSKBN2400DZ.
13. NRCC. The National Research Council of Canada and CanSino Biologics Inc. announce collaboration to advance vaccine against COVID-19: National Research Council Canada; 2020 [Available from: https://www.canada.ca/en/national-research-council/news/2020/05/the-national-research-council-of-canada-and-cansino-biologics-inc-announce-collaboration-to-advance-vaccine-against-covid-19.html.
14. Clinicaltrials.gov. Phase I/II Clinical Trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) in Canada 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT04398147.
15. Pinkerton C. Canada yet to receive vaccine candidate from Chinese developer it reached an agreement with in May iPolitics.ca2020 [Available from: https://ipolitics.ca/2020/07/06/canada-yet-to-receive-vaccine-candidate-from-chinese-developer-it-reached-an-agreement-with-in-may/.
16. Jones R. Trudeau pens op-ed with world leaders calling for equal access to coronavirus vaccine CBC News2020 [Available from: https://www.cbc.ca/news/politics/op-ed-world-leaders-vaccine-access-1.5650939.
17. Justin Trudeau S-WZ, Moon Jae-in, Jacinda Ardern, Cyril Ramaphosa, Pedro Sánchez Pérez-Castejón, Stefan Lofven and Elyes Fakhfakh. The international community must guarantee equal global access to a covid-19 vaccine. Washington Post. 2020.