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By Students, For the World

THE AGING ISSUE

"A New Lens to Look at Aging"
Feature Article by Dr. Roger Wong

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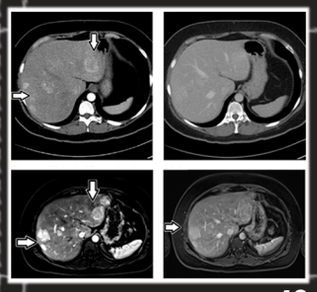

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On the cover

"Grandma" (2006),
oil on canvas

Matthew Kennedy,
MD Class of 2014,
University of Toronto

"*Grandma* is a portrait of my grandmother at 96, shortly before she passed away. I really focused on the beautiful character that age added to her face, sculpting her wrinkles and age marks with thick oil paint. This painting also captures the innocence, peaceful simplicity and endearing helplessness which developed as she moved into the last phase of her life without diminishing her dignity or beauty."

-M. Kennedy

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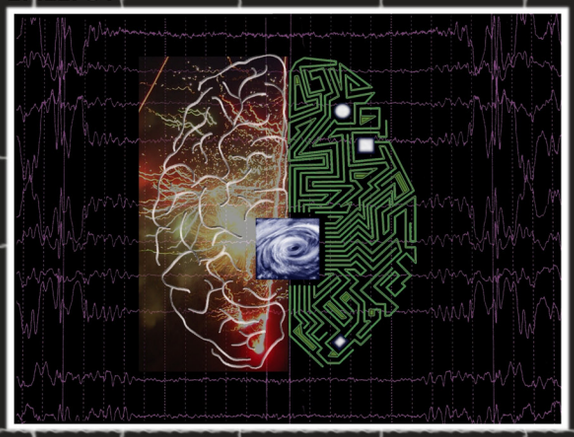

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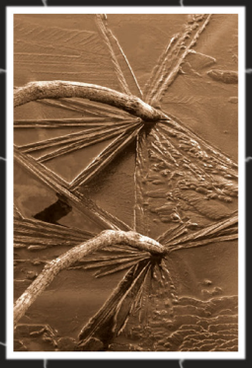


TYLER HICKEY

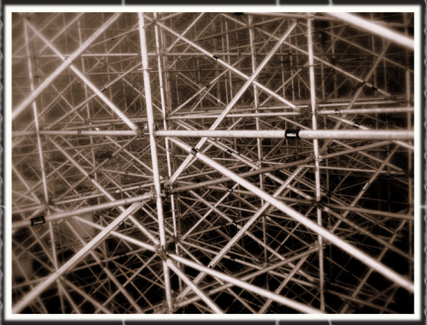
A YOUTH PERSPECTIVE*

TAYLOR SWANSON

PYRAMIDAL DECUSSATION

ALVIN CHEUNG

THALAMIC MAZE



TYLER HICKEY

THE FOG OF DELIRIUM

KRISTY WILLIAMS, CALIB DURAND

*This graphic is a compilation of descriptive words that were written by high school students when posed the question: "What words come to mind when you think of mental illness?" A collection of responses from 36 students--each word's size is proportional to the number of times it was repeated.

Adapting Canadian Healthcare to an Aging Population

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The baby boomers, born between 1946 and 1964, account for approximately one-third of Canada's population. The first of the baby boomers will turn 65 this year,[1] and it is estimated that by 2025 there will be more people in Canada over the age of 65 than there will be under the age of 14.[2] Healthcare systems in Canada as well as other Western nations are in the process of adapting to this unprecedented growth of elderly populations. The challenges of meeting the needs of the elderly have become prominent topics of discussion within the healthcare community and beyond. Research and clinical experiences continue to provide our discussions with new insights into the unique set of healthcare needs of the elderly.

Aging is characterized by a progressive decline in physiological functioning that ultimately challenges both psychological and social functioning.[3] As such, the needs of the elderly cannot be adequately addressed through medical approaches alone; for high quality care, a holistic biopsychosocial model of health must be considered. Moreover, geriatric medicine is complicated by polypharmacy, by a tendency for patients to have multiple comorbidities, and by presentations and prognoses of illnesses that often differ substantially from younger populations.[2] With increasing recognition of the importance of these issues, Canadian medical schools are beginning to implement curricular components that emphasize the specialized care of the elderly as a discrete population. For example, at UBC, students get exposure as early as first year when they visit nursing homes to interview elderly patients. Furthermore, five of the 17 Canadian medical schools have already instituted mandatory geriatrics rotations.[2]

The *UBCMJ* believes that exposure to geriatric care early in medical training is essential to equipping future physicians with the skill set necessary to manage the demands of our expanding elderly population. In this issue, Dr. Roger Wong, Vice President of the Canadian Geriatrics Society and Head of the Geriatric Consultation Program at the Vancouver Acute Health Service Delivery Area, reflects on geriatric medicine through the lens of a medical student. In his letter to future doctors, Dr. Wong reflects upon his experiences in geriatrics and offers pearls of clinical wisdom to students. "The pre-requisite of good clinical care in the older patient," writes Dr. Wong, "involves a thorough understanding of the interactions among complex medicine, cognition, physical function, and psychosocial support." These words speak to the importance that Dr. Wong places on a holistic approach to geriatric care.

This issue of the *UBCMJ* also includes articles by our staff writers that explore new ideas in specific areas of geriatric medicine: potential new treatments for Alzheimer's disease, means for encouraging seniors to stay active, and current research in age-related macular degeneration. Moreover, our staff writers report on two opportunities for students to learn more about geriatric care: the UBC Geriatric Dentistry Program and Canada's Summer Institute in Geriatrics. Furthermore, this issue provides insights into the some of the molecular causes of the aging through the review article "Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome."

It is expected that geriatric medicine will become an increasingly prominent issue in healthcare as today's students progress through their training. As a student-run journal whose goal is to promote dialogue within the academic community and to encourage students to engage in research, the *UBCMJ* recognizes the impact that students have on the future of healthcare. As is revealed through the articles in this issue, medical students are already actively collaborating with one another and physicians alike to drive research focused on improving the health outcomes of our aging population. Whether we students choose to practice family medicine or to go on to focus on a specialty, we will all inevitably have a role to play in healthcare's changing approach to medicine. Readers can rest assured that geriatrics is not a subject matter at risk of fading into the background but rather one of priority for both the current and future medical community.

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FEATURE

A New Lens to Look at Aging: Clinical Pearls that I Wish I Knew when I was a Medical Student

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The year 2011 marks the beginning of a momentous transition as the first cohort of the baby boomers turns 65 years old. While many people have spoken of the economic, social, and healthcare implications of the demographic imperative for quite some time now,[1] it is finally happening right in front of our eyes. I am delighted to learn that this issue of the *UBCMJ* is devoted to aging. Indeed, it is timely for us to rethink our approach to the aging phenomenon; rather than resorting to highly theoretical constructs and complex scientific arguments, I propose that we explore the fundamental aspects of this topic through the lens of a medical student, our most junior colleague in the medical field.

As a clinical professor in Geriatric Medicine, I encounter on a regular basis many young and enthusiastic medical students who rotate through our clinical service. I am always encouraged to see how they enjoy working with the older patient. At the same time, however, it is unfortunate to see how some of them struggle with the complexity of the older patient, whether due to the coexistence of multiple health conditions, the interplay of cognitive and physical deficits, or the impact of declining social determinants of health. It is not uncommon for students to feel lost and frustrated when they are forced to modify their usual clinical approach, which works well in a younger person but does not necessarily work well in an older person.[2] I, too, went through this stage when I was a medical student, and I must confess that I was not really turned on when I did my student rotation in Geriatrics. It was during residency and fellowship when my career interests took roots and blossomed. I have always thought that it would have been handy to know some clinical pearls about aging as a medical student, and hence I am writing this article.

Currently there is no single accepted theory of aging. The more popular biomedical theories involve immunologic modulation, accumulation of undesirable metabolites such as free radicals and other oxidative stressors, and programmed longevity at the level of cell division including telomere shortening.[3] The psychological theories are often cited to explain changes in cognition, and the social theories of aging are far too complex to delineate in detail here.[3]

We should also remember that the physiological age of an older person may not be equivalent to the chronological age. Different older people follow different aging trajectories, which are in part determined by their physiologic make-up and in part by environmental factors. There are many older people who remain highly functional without significant disease and many more who age with a few chronic diseases that do not necessarily affect their activities of daily living. Historically, the patterns of aging in these two groups of older people are described as successful aging and usual aging respectively,[4] and together they account for the majority of people over the age of 65.

In healthcare, we are more likely to encounter older people who are laden with multiple chronic diseases such as coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, arthritis, and chronic obstructive pulmonary disease to name just a few. Some of these older people may also have cognitive impairment such as dementia, and some have physical disabilities in carrying out their day-to-day activities. These older people are described as frail and are heavy users of healthcare services and resources.[5] We must remember, however, that frail, older people represent a relatively small cohort in terms of absolute numbers. The physiologic basis of frailty is complex and beyond the scope of this discussion.[6] It is definitely one of the hottest areas of scholarly inquiry in the field.

A good practical understanding of the physiology of aging is essential to provide proper clinical care to older people. I am referring to the importance of recognizing the various aging-related physiologic changes in the body's organ systems so that we can confidently distinguish aging changes from the pathologic changes of diseases. In the clinical setting, it is common to see aging changes mixed in with pathology. The corollary is that the goals of care should target on reversing what is potentially reversible rather than aging itself, which is not reversible based on the available scientific evidence, despite the numerous commercial claims from anti-aging products.

The concept of geriatric syndromes, also known as the geriatric giants, is worth some explanation. These health conditions are commonly seen in the older patient and represent a

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collection of symptoms and signs with a unique list of differential diagnoses.[7] They include dementia, delirium, depression, drug related issues, falls and mobility problems, incontinence (urinary, fecal, or both), dizziness, and homeostatic disturbances. There is a huge body of scholarly literature available on each of the geriatric syndromes. Several of these syndromes may present in the same patient concurrently, and the situation can be made more complex by the co-existence of other chronic diseases.[8]

Older people are heterogeneous in terms of diseases they may present. For instance, although pneumonia is a common disease, the presenting complaint in the older patient can be very different, ranging from dyspnea to atypical chest pain to dizziness to falls to delirium. This illustrates another clinical pearl, that atypical presentation of common diseases is more common than typical presentations of uncommon diseases. This should be carefully considered when formulating a clinically relevant differential diagnosis, which in turn should be tailored to the older patient one person at a time.

The prerequisite of good clinical care in the older patient involves a thorough understanding of the interactions among complex medicine, cognition, physical function, and psychosocial support. The problem list in any clinical encounter often includes multiple items in these domains. I like to summarize the essence of Geriatric Medicine as the studying of three kinds of interactions (drug-drug interactions, drug-disease interactions, and disease-disease interactions) and the solving of problems arising from these interactions. This is commonly the source of frustration for the junior clinician; however, more practice with appropriate mentorship does make things easier.

Similarly, the therapeutic plan must be individualized. On one hand, the older patient has been shown to be more likely to benefit from proven effective therapies compared to the younger adult.[9] On the other hand, we should be careful to avoid over-treatment as polypharmacy is prevalent in older patients and can have multiple detrimental effects.[10] This explains why traditional, single-streamed clinical care maps or pathways do not work well for seniors, although recently there seems to be a resurgence of standardized order sets that reflects the heterogeneity of older patients. In addition, the application of evidence-based practice in the older patient can be challenging because many clinical studies do not have adequate older subject representation and definitely not of the frail elderly. In the right clinical context, nevertheless, it is reasonable to make extrapolations and inferences from the available evidence based on younger cohorts.

Last but not least, one of the most important clinical pearls about geriatric care is the philosophy of practice in a team setting. Geriatric care is the prototype for interprofessional collaboration.[11] This is true for a variety of geriatric services, such as comprehensive geriatric consultation, geriatric evaluation and management unit, acute care for elders unit, geriatric rehabilitation unit etc.

It is my sincere hope that my article will spark the interest of many young and motivated colleagues in healthcare to pursue a career dedicated to the care of older people. It can be an exciting and rewarding career. If I were given the opportunity to make my career decision all over again, I would gladly make the same choice of becoming a geriatrician.

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Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome: Clinical Signs, Molecular Causes, Treatments, and Insights into the Aging Process

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is a condition characterized by signs of accelerated aging that present within the first year of life. Notable characteristics of children with HGPS include prominent superficial veins, failure to thrive, alopecia, as well as various skeletal and cardiovascular pathologies normally associated with advanced age. The discovery of the lamin A (C to T) gene mutation at position 1824 of the coding sequence has ushered in a greater understanding on the essential role of lamin A protein processing. In normal cells, processing prelamin A to mature lamin A is complete following the cleavage of end terminal amino acids. In HGPS, gene mutation results in the deletion of a Zmpste24/FACE1 splice site in prelamin A, preventing end terminal cleavage. Thus, prelamin A remains anchored due to C-terminal farnesylation. Lamin A eventually accumulates within the inner nuclear membrane of cells, resulting in disease pathology. The generation of experimental mouse models to understand the role of lamin A in normal, and HGPS cells have fostered the development of prospective HGPS treatments. Clinical trials investigating farnesyltransferase inhibitors (FTIs), statins, and bisphosphonates as HGPS treatments are currently underway. HGPS and the relationship to lamin A has also shed light on normal aging as accumulation of prelamin A has been revealed in aged (non-HGPS derived) cells.

KEYWORDS: *progeria, lamin A, laminopathy, farnesylation, aging*

INTRODUCTION

Aging is an inevitable process of bodily changes that eventually results in decreased physiologic capacity, decreased ability to maintain homeostasis, and increased vulnerability to disease processes. These changes generally occur later in life. However, in one out of every four to eight million births, children are born with HGPS and symptoms of age-related diseases such as skin thinning, low bone density, and cardiovascular complications that occur within the first decade of life. This early onset of aging in HGPS is different from other inherited accelerated aging disorders such as Werner's syndrome, which typically presents later in life (after puberty).

CLINICAL FEATURES OF HGPS

First described in 1886 by Dr. Jonathan Hutchinson,[1] Dr. Hastings Gilford subsequently expanded on Hutchinson's observations and derived the word "progeria" from ancient Greek origins ("pro" from the Greek word for "before" or "forward" and "geron" meaning "old person") to describe this accelerated aging syndrome.[2]

As of December 2010 there were approximately 78 known children with HGPS in the world, two living in Canada.[3] Children with HGPS are born with normal appearance and weight.[4] Within 12 months, clinical symptoms appear sporadically and continue to appear throughout life (Figure 1). The first noticeable signs of HGPS are circumoral cyanosis (a blue tint to the skin surrounding the lips) and a visible vein across the nasal bridge.[4,5] Children present initially with failure to thrive, and in their first to third of year of life, skin complications, hair loss (also known as alopecia), and joint deformities become apparent.[4,5] Auditory and endocrine dysfunctions are eventually noted.

Within the first year, growth is disturbed, with weight more affected than height. Pitting edema (slight swelling due to fluid build-up in the tissues) is seen in the lower abdomen, upper gluteal area, genitalia, and anterior thighs.[4,5] Pitting edema can arise anywhere from one and a half months to two years, taking on

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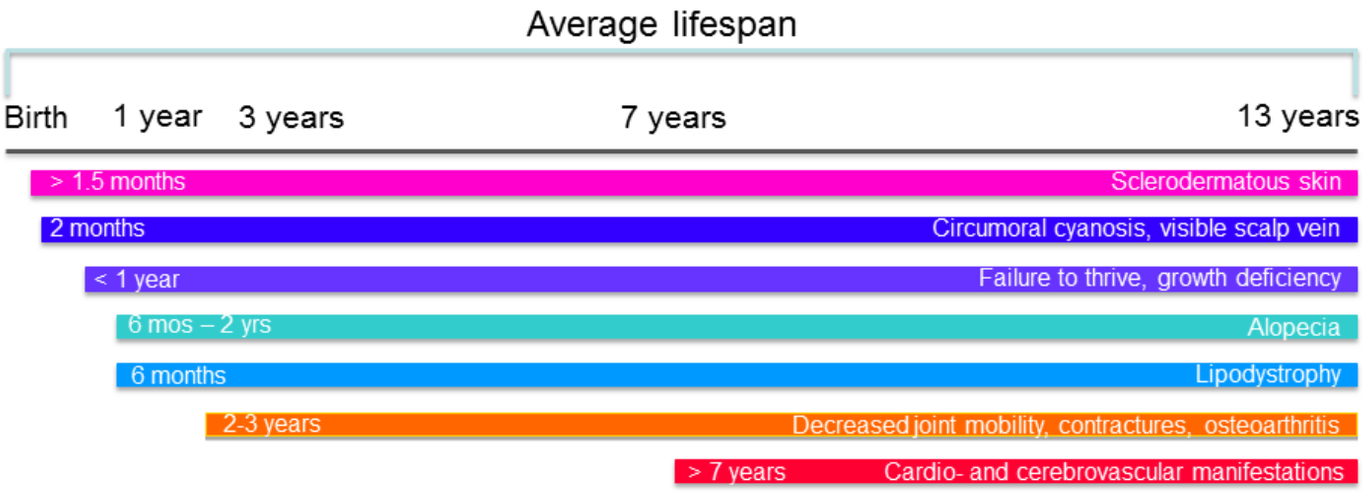

Figure 1. Common clinical signs of HGPS and typical time of presentation.

a thick, tight, stiff quality with time.[5] Alopecia usually takes place within six months to two years, and between the ages of two and three years, most children become bald with the exception of fine, downy hair.[4,5] Lipodystrophy, the disappearance of subcutaneous fat and thinning of the skin, is noted at as early as six months and contributes to the appearance of prominent veins throughout the child's body. This is first seen over the nasal bridge, then the body and infraorbital regions, giving rise to the appearance of prominent eyes.[5] Progressive resorption of bone, also known as osteolysis, of the distal phalanges tends to start between one and two years of age in the index and little fingers. Skin overlying the fingertips becomes red and swollen without pain.[5] Osteolysis of the acromial ends of the clavicles and upper ribs eventually results in characteristic narrow shoulders and pear-shaped thorax.[5] Joint range of mobility declines around age two or three years. Children with HGPS eventually possess a wide-based, shuffling gait resulting from hip deformities and knee joint stiffness.[4]

HGPS-affected children have normal mental and motor development, display age-appropriate behaviour, and are very alert and cheerful.[5] Low-conduction hearing loss and endocrine dysfunction occur later in life.[4] Children with HGPS fail to develop secondary sexual characteristics. Insulin resistance occurs in about 50 % of affected patients without progression to diabetes mellitus.[6]

Although the onset of specific abnormalities varies considerably, the major health concern for children with HGPS is progressive atherosclerosis of the coronary and cerebrovascular arteries.[4,5,7–9] Stiffness of the blood vessels manifests clinically as elevated systolic and diastolic blood pressure. Chest pain or congestive heart failure can also occur.[6] Demise is largely a result of cardiac or cerebrovascular-related events, such as myocardial infarction or stroke.[4] These events tend to occur after age seven,[10] although strokes and transient ischemic attacks, or 'mini-strokes', have occurred in children with HGPS as young as age four.[6]

Other early distinguishing physical features include the following: sleeping with eyes open, thin lips, a small and receding lower jaw, nearly normal neurocranial growth paralleling brain growth, and a narrow nasal bridge with a sharp nasal tip.[5,6] Ultimately, diagnosis is based on recognition of the aforementioned clinical features and is confirmed with molecular genetic testing.[6]

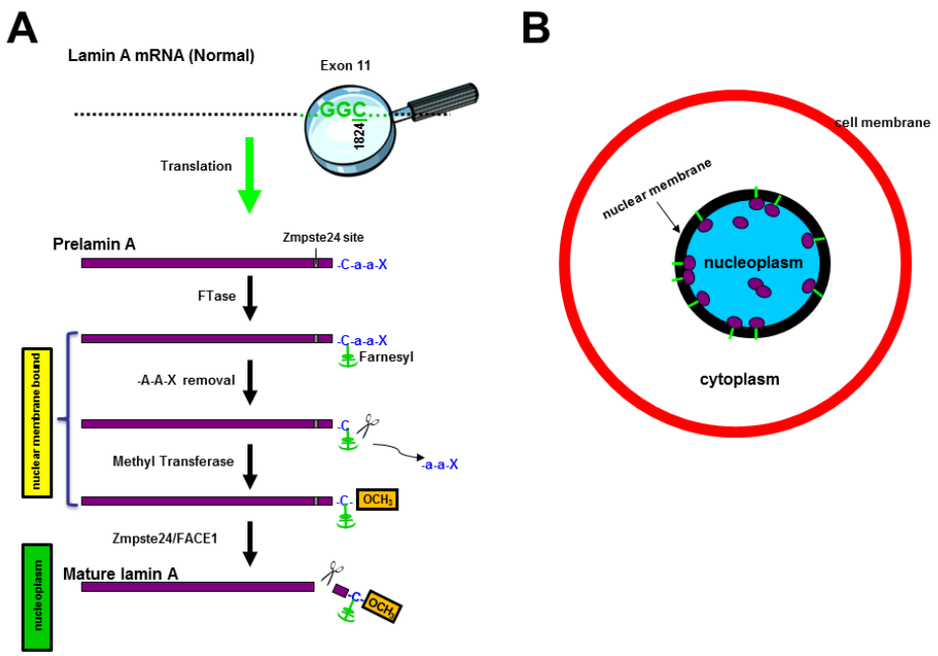

Figure 2. Normal processing of lamin A from mRNA to mature lamin A. (A) Normal lamin A mRNA is translated to prelamin A. Prelamin A becomes farnesylated resulting in anchoring to the inner nuclear membrane. Zmpste24/FACE1 cleavage of terminal amino acids results in release from the nuclear membrane and localization to the nucleoplasm. (B) In normal processing, prelamin A exists anchored to the nuclear membrane and is finally cleaved by Zmpste24/FACE1 to produce mature lamin A which localizes to the nucleoplasm.

MOLECULAR BACKGROUND OF HGPS

Lamins are intermediate filament proteins

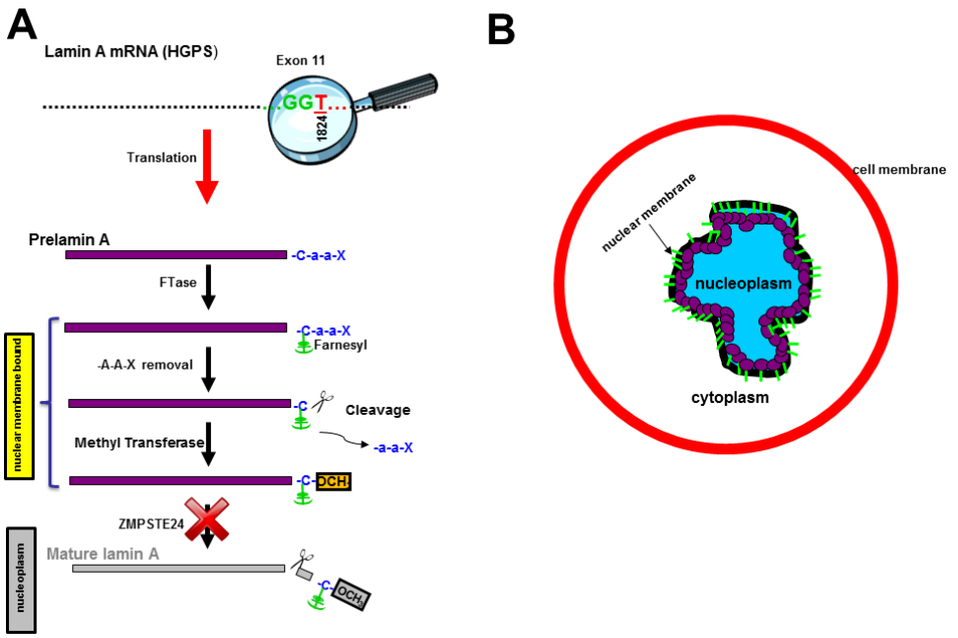

Figure 3. Processing of lamin A in cells from patients with HGPS. (A) Mutated laminA mRNA is translated to prelamin A that does not contain Zmpste24/FACE1 cleavage site. PrelaminA then becomes farnesylated resulting in anchoring to the inner nuclear membrane. The absence of Zmpste24 cleavage of terminal amino acids results in the inability to generate mature lamin A. (B) In cells from patients with HGPS prelamin A remains farnesylated, accumulates at the inner nuclear membrane, and results in misshapen nuclei.

forming a network in the inner nuclear membrane. They not only play an essential role in maintaining the structural integrity of the nucleus but are also involved in chromatin organization, DNA replication/transcription, and RNA processing.[11] There are type A (lamin A) and type B (lamin B) lamins. In contrast to lamin A, which is only expressed in differentiated tissues, lamin B is expressed throughout development, including gastrulation. Thus, defects in lamin B are generally lethal.[12] Various defects in lamin A can result in a wide variety of laminopathies. HGPS is the most severe of the (at least) sixteen laminopathies. In terms of HGPS classification,[13] HGPS falls into a group of systemic laminopathies that includes other diseases such as Werner's syndrome. These particular laminopathies affect a variety of tissue types. On the other hand, non-systemic or tissue-restricted laminopathies are classified based on the specific tissue affected. Muscle type laminopathies, such as in Emery-Dreifuss muscular dystrophy, are characterized by muscle wasting. Lipodystrophy laminopathies, including Dunnigan familial partial lipodystrophy, are characterized by abnormal fat distribution. Neuropathic laminopathies, such as Charcot-Marie-Tooth disease type 2B1, affect nerves. The molecular causes of the various laminopathies are quite diverse with over 340 unique mutations from over 1000 different patients. These mutations affect genes encoding lamins, associated with lamin post-translational modification, or proteins that interact with lamins. Specifically in HGPS, there is aberrant lamin A protein maturation.[14]

In normal lamin A maturation, the newly translated prelamin A protein undergoes a series of post-translational modifications to form mature lamin A (Figure 2a).[15] The C-terminal end of prelamin A contains a cysteine-aliphatic-aliphatic-any amino acid (CaaX) motif prompting prenylation, a process of C-terminal lipidification. Prenylation generally occurs through the addition of a farnesyl group to the cysteine residue in CaaX via farnesyltransferase (FTase). Subsequently, the –aaX tripeptide is enzymatically released. The remaining farnesylcysteine is then methylated through methyl transferase. The addition of a farnesyl– and methyl– group increases the hydrophobicity of lamin A,[16] which aids in prelamin A association with the nuclear membrane. In the last step of maturation, the end 15 amino acids of prelamin A are cleaved by a zinc metalloproteinase (Zmpste24; also known as FACE1), and mature lamin is formed. The removal of the terminating 15 amino acids allows for lamin A detachment from the nuclear membrane.[17]

While numerous causal mechanisms exist in HGPS, 90 % of affected children have a de novo heterozygous single cytosine to thymine point mutation (GGC to GGT) in exon 11 at position 1824 of the coding sequence (Figure 3a).[14,18] The mutation generates a cryptic splice site, resulting in a transcript 150 base pairs shorter than normal and 50 fewer amino acids translated. The necessary sites for Zmpste24 cleavage are among the 50 amino acids not translated. Farnesylated prelamin A consequently anchors to the nuclear envelope. However, full maturation is incomplete as Zmpste24 cleavage of the end terminal amino acids does not occur. Ultimately, prelamin A accumulates in the nuclear envelope, disrupting nuclear integrity and nuclear shape (Figure 3b). Nuclei appear larger, distorted, blebbed, and have a thicker nuclear lamina.[19] The mechanical properties of the nuclear lamina in HGPS cells are compromised. The nuclei are stiffer, have reduced deformability,[20] and do not respond to mechanical force in the same manner as normal cells.[21] Consequently, cell proliferation, differentiation, and gene expression are affected in HGPS cells.[22,23] Such marked deficiencies in general cellular processes caused by aberrant lamin A may explain how a single mutation affects various tissues. As well, studies in skin,[24] bone,[25] and cardiovascular tissues,[5,8,26,27] further exemplify the importance of normal lamin A regulation in specific tissue homeostasis.

POTENTIAL TREATMENTS FOR HGPS

Prior to the HGPS gene discovery, treatments were limited and unsuccessful. For instance, nutritional and growth hormone therapy resulted in only transient improvements in individuals with HGPS.[28] More recently, various mouse models have been generated, allowing for an enhanced general understanding of lamin A as well as providing insights into potential HGPS treatments.

Mouse lines absent in the lamin A Zmpste24 cleavage sites or Zmpste24 deficient mice demonstrate HGPS-like symptoms,[29,30] illustrating the importance of Zmpste24 cleavage and the deleterious effects of sustained farnesylated prelamin A. Thus, a potential therapeutic approach involves treatment

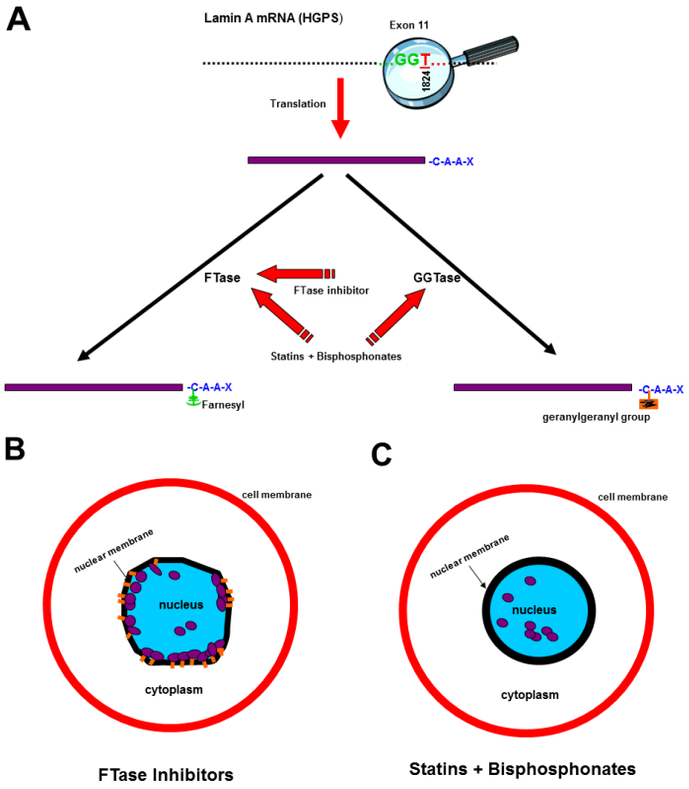

Figure 4. Prelamin A has alternative routes of prenylation. (A) Prelamin A can become farnesylated via farnesyltransferase (FTase) or geranylgeranylated via geranylgeranyltransferase (GGT). Farnesyltransferase inhibitors are able to inhibit farnesylation but not geranylgeranylation and results in (B) an overall improvement in nuclear membrane shape in HGPS (or HGPS-like) cells. (C) Statins and bisphosphonates are able to inhibit farnesylation and geranylgeranylation and may result in a greater improvement of nuclear membrane organization.

with farnesyltransferase inhibitors (FTIs) to prevent prelamin A anchoring to the nuclear membrane. Interestingly, exposure of HGPS cells to FTIs appeared to prevent prelamin A from anchoring to the nuclear membrane. Rather, FTI treatment localized prelamin A to the nucleoplasm and resulted in improved nuclear shape (Figure 4a, b)[31,32] as well as recovered nuclear stiffness in HGPS cells.[21] Additional studies reveal that in mouse models of HGPS, FTIs improved bone quality, growth, and survival.[33–35] Such findings have led to the first HGPS treatment clinical trials with the FTI, lonafarnib (Sarasar), to investigate the efficacy of FTIs as treatments for HGPS.[36] Lonafarnib is not commercially available in Canada or the United States and can only be administered in approved clinical trials.

Though FTIs appear to prevent the farnesyltransferase-based prenylation (lipidification) necessary to anchor prelamin A to the nuclear membrane (Figure 2), some concern arises with the finding that FTI treatments may result in an alternative route of prelamin A prenylation known as geranylgeranylation. Geranylgeranylation is a process by which a lipophilic geranylgeranylisoprene unit is added to the C-terminal of proteins via geranylgeranyltransferases (GGTase; Figure 4a).[37] Thus, geranylgeranylation is an alternative form of prenylation which may reduce the efficacy of FTIs. Treatment of HGPS mice with statins and bisphosphonates inhibits both farnesylation and geranylgeranylation and improves nuclear shape (Figure 4a, 4c). The utilization of statins and bisphosphonates resulted in reduced lipodystrophy, reduced hair loss, improved bone defects, and enhanced longevity.[37] Pravastatin (a statin) and zoledronic acid (a bisphosphonate) are being studied in a second set of clinical trials as treatments for patients with HGPS. Pravastatin and zoledronic acid are commercially available in Canada and have been used in the prevention of cardiovascular disease and osteoporosis, respectively. A third set of trials has also been initiated in 2009 which examines FTI, pravastatin, and zoledronic acid in combination.[36]

HGPS GIVES INSIGHT INTO NORMAL AGING

Understanding HGPS and HGPS-related disorders (not discussed in this article) yields insight into general aging. Lamin A gene mutations exemplify the importance of the nuclear lamina in disease pathology to specific, but not all, tissues. For instance, brain function and development do not appear affected in HGPS, while cardiovascular, bone, fat, and skin pathology appear commonly. For affected tissues, it comes into question whether lamin A processing becomes awry during normal aging in unaffected individuals. Indeed, skin biopsies from elderly individuals exhibited prelamin A protein accumulation, while accumulation of prelamin A was less detected in young individuals.[38] This was despite translation of normal prelamin A that included the sequence required for Zmpste24 cleavage,[38] suggesting possible defects in Zmpste24 activity. Interestingly, vascular smooth muscle cells (VSMCs) from aged or artherosclerotic lesions also accumulated prelamin A.[39] It was revealed that prelamin A accumulation in VSMCs correlated with downregulated Zmpste24 mRNA levels. Therefore, it appears that lamin A misregulation, through a lack of or faulty post-translational modification, is associated with the normal aging process.

CONCLUSION

Despite being described in as early as 1886, it was not until this last decade that the precise cause of HGPS has been elucidated. Gene discovery paved the way for a greater understanding of HGPS, exploration of treatment options, as well as insight into the potential role of prelamin A in the general aging process.

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Management of Chronic Kidney Disease and End-Stage Renal Disease in Diabetes

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ABSTRACT

Diabetic nephropathy occurs in 20–40 % of patients with diabetes mellitus and is the leading cause of End-Stage Renal Disease (ESRD) in North America. This review outlines the evidence-based approach to the management of progressive Chronic Kidney Disease (CKD) and ESRD in diabetes with the objective of guiding future physicians. In addition to patient education on diabetes management, vigilant annual screening for microalbuminuria and increased serum creatinine is the first step towards ensuring early treatment of CKD, well before the onset of frank proteinuria. In addition to controlling hyperglycemia, issues of hypertension and dyslipidemia should be addressed to prevent onset and progression of CKD, with Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers being the drugs of choice for controlling hypertension in these patients and statins being the pharmacological mainstay for dyslipidemia. Furthermore, clinicians must address the consequences of CKD, particularly anemia, hyperphosphatemia, and vitamin D deficiency. Lifestyle modifications such as a low protein diet, smoking cessation, and cardiovascular and resistance exercises could help prevent progression and morbidity in CKD. When patients progress to irreversible kidney failure or ESRD, early (pre-emptive) transplantation before the initiation of dialysis has been shown to maximize survival. Owing to lower risk and better preservation of residual kidney function, peritoneal dialysis is now recommended as the initial modality of dialysis in most ESRD patients in the absence of a kidney transplant. Ultimately, effective management of kidney disease in diabetes relies on the collaborative efforts of the patient, their support system, and their multi-disciplinary healthcare team.

KEYWORDS: *diabetes mellitus, diabetes complications, diabetic nephropathy, kidney diseases, kidney failure, chronic*

INTRODUCTION

Diabetes mellitus, a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion and/or defective insulin action, has become a worldwide pandemic affecting over 285 million people.[1,2] With devastating complications in the absence of effective management, it is vital that patients with diabetes be managed in a consistent and evidence-based manner.[3]

Of all the microvascular complications of diabetes, chronic kidney disease (CKD) is especially concerning owing to its debilitating nature.[4] Specifically, diabetic nephropathy occurs in 20–40 % of patients with diabetes mellitus and is the leading cause of end-stage renal disease (ESRD) in North America.[5,6]

While clinical guidelines for the care of patients with progressive CKD and ESRD have been developed with good consensus in the nephrology community, existing data indicates that much work remains to achieve acceptable levels of recommended care in these patients.[7]

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MANAGEMENT OF CHRONIC KIDNEY DISEASE

CKD is clinically defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2 body surface area, with or without evidence of kidney damage, for 3 months or longer.[8] The conventional method to keep track of the various aspects of CKD management in diabetes involves using the GFR to differentiate between the different stages of CKD as each successive stage necessitates further steps in management additional to those at the previous stage.[5]

Screening

The assessment of microalbuminuria (defined as an elevated albumin excretion rate in the range of 30–300 mg/24h) and an elevated urine albumin-creatinine ratio (ACR) ratio (defined as > 2.0 mg/mmol in males or > 2.8 mg/mmol in females) are both important indicators of diabetic nephropathy as it is an early clinical manifestation that presents several years before changes in GFR.[2,5,9] Overexcretion of albumin typically increases at a rate of 15 % per year, eventually culminating in macroalbuminuria (> 300 mg/24h).[10] The distinction between microalbuminuria and macroalbuminuria is significant: while non-proteinuric CKD

patients are at high cardiovascular risk, they have a much slower progression to ESRD.[11] Macroalbuminuria, on the other hand, is a strong risk factor for progression from CKD to ESRD.[9,11–12]

The American Diabetes Association recommends that both microalbuminuria and serum creatinine levels be assessed annually in patients with diabetes to screen for diabetic nephropathy.[12] Risk profiles in persons with diabetes are also important, as genetic influence (positive family history and ethnicity) is considered the most important factor for diabetic nephropathy.[6,13]

Hyperglycemia

Guidelines continue to recommend a target Hemoglobin A1c (HbA1c) level < 7 %, though there is little evidence that this improves outcomes.[14–16] Although the mechanism is not fully understood, a positive correlation exists between elevated HbA1c and the development and progression of microalbuminuria.[14–16] For instance, in the six years following the landmark Diabetes Control and Complications Trial, 4.5 % of the intensive treatment group with an average HbA1c of 7.2 % developed microalbuminuria compared to 12.3 % of the conventional treatment group with an average HbA1c of 9.1 %.[17]

Hypertension

Persons with diabetes and insufficient blood pressure control are at a high risk for both developing cardiovascular disease and progressing further with their nephropathy.[4] Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are the drugs of choice for controlling hypertension in patients with diabetes and albuminuria, but additional antihypertensive drugs should be prescribed if blood pressure remains over 130/80 mmHg despite lifestyle interventions and the use of an ACEI/ARB.[18–21]

It is currently recommended that adults with diabetes and persistent albuminuria receive an ACEI/ARB to delay progression of CKD, even in the absence of hypertension.[22–24] Thiazide-like diuretics should also be considered, with the addition of furosemide (Lasix®) for those who fail monotherapy.[2]

Despite current consensus in management, less than 20 % of patients with CKD actually meet their blood pressure goals.[25] The use of selective endothelin A receptor antagonists (potent vasodilators) for the treatment of resistant hypertension in CKD has been recently examined in clinical trials, proving effective in reducing blood pressure and improving proteinuria.[26–28] However, their use is currently limited by a significant side effect profile including increased sodium retention.[26]

Dyslipidemia

Continual screening and correction for dyslipidemia are major requirements in management of diabetic nephropathy, aiming for a low-density lipoprotein (LDL) level of < 2.59 mmol/L.[5] Statins are the preferred drug for lowering LDL levels and have been found to lower the incidence of cardiovascular events in this population.[14,28] If the patient also has a triglyceride level > 5.64 mmol/L, then fibrates are the recommended medication, although the dosage must be reduced appropriately to accommodate the decreased renal function.[28] It is important to note the increased risk of adverse effects such as rhabdomyolysis when both statins and fibrates are used in patients with GFR < 30 mL/min/1.73m^2, more so with gemfibrozil than fenofibrate.[29,30] When these drugs are used together, it is prudent to limit the statin dosage and monitor creatine kinase concentrations to identify individuals with myositis.[30]

Vitamin D Deficiency and Hyperphosphatemia

Reduced GFR leads to reduced renal excretion of phosphate, which in turn activates the release of parathyroid hormone from the parathyroid glands in addition to inhibiting activated vitamin D synthesis.[28,31] Consequences of hyperphosphatemia include deficiency of active vitamin D and secondary hyperparathyroidism with associated calcium disturbances. These are linked to abnormalities in bone homeostasis (known as renal osteodystrophy), vascular and soft tissue calcification, increased cardiovascular events, and death.[32–34]

The first treatment of choice for managing abnormalities in mineral metabolism is dietary restriction of phosphorus, although judicious use of phosphate binders and activated vitamin D can also be used to alleviate hyperphosphatemia.[28,35]

Anemia

Although the prevalence of anemia is much higher among patients with a GFR < 30 mL/min/1.73m^2, its treatment in CKD is a topic of much controversy and ongoing research.[36] As per the Kidney Disease Outcomes Quality Initiative guidelines, the goal for hemoglobin levels is 100–120 g/L, and it is recommended that patients be treated with erythropoiesis-stimulating agents (ESAs) if hemoglobin is found to be less than 100 g/L.[2,28,37] However, there is evidence suggesting that such aggressive treatment of anemia may increase CKD progression.[37,38] For instance, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial investigators found that more patients assigned to complete correction of anemia versus partial correction progressed to dialysis at the end of the study.[39]

Additionally, as many as 45 % of patients with CKD have been shown to be iron deficient.[40] Treatment involves small repeat doses of intravenous iron, which have been shown to be more effective than infrequent, large doses for maintaining levels of hemoglobin and reducing the need for ESAs.[41]

Lifestyle Modifications

Loss of renal function is also prevented by lifestyle factors: low protein diets and discontinuation of smoking have been shown to delay the progression of diabetic nephropathy.[42] Additional evidence in support of smoking cessation in persons with diabetes comes from a recent study showing reduced development of macroalbuminuria.[43]

Decreased physical activity has also been associated with an increase in mortality, particularly among patients on dialysis.[44] Exercise training not only improves physical performance-based measures but also decreases the risk of cardiovascular disease, increases protein uptake into skeletal muscles, and improves dialysis efficiency.[45] While androgens and growth hormone have been shown to improve lean body mass and strength, longer-term studies of safety and efficacy are needed before recommending their use in ESRD patients.[45]

MANAGEMENT OF END STAGE RENAL DISEASE

ESRD, a continuum of CKD, is defined as irreversible kidney failure treated with dialysis or transplantation.[46] Active participation from the patient and family is required for successful treatment of ESRD as involvement has been shown to promote non-emergent initiation of dialysis, lower morbidity and improved rehabilitation, less frequent and shorter hospital stays, and improved survival.[47]

Kidney Transplantation

A large body of literature attests to the survival benefits of patients undergoing kidney transplantation compared to those remaining on dialysis.[48] Several recent studies have demonstrated significantly improved patient and allograft survival as well as lower rates of delayed graft function or acute rejection episodes in those with preemptive transplants versus those who were on dialysis for a period of time before transplantation.[49] Recent evidence also suggests that simultaneous pancreasckidney transplantation is highly superior to kidney transplantation alone, with survival benefit already visible after five years of follow-up.[50] However, it has been hypothesized that intensified glycemic control (HbA1c < 6.5 %) may be the true differentiating factor for survival in patients with diabetes undergoing either combined or kidney only transplantation, although adverse events including hypoglycemia have been reported with the achievement of such difficult targets.[51]

Hemodialysis

Hemodialysis is found in two variants in which the primary mechanism of both is solute removal via diffusion: conventional hemodialysis, where patients receive hemodialysis in a clinic three times a week for 4 hours/session, and nocturnal hemodialysis, where patients are trained to do their own hemodialysis while they sleep, 5–6 nights/week.[52] Hemodialysis is a relatively safe procedure, but there are several complications that can occur including hypotension, cardiac arrhythmias, muscle cramps, anaphylaxis, and Restless Leg Syndrome.[52] However, with proper monitoring and prompt treatment, many of these complications can be avoided. Of note, better glycemic control (HbA1c < 7.5 %) has been shown to predict better survival of diabetic ESRD patients starting hemodialysis treatment.[53]

Peritoneal Dialysis

Compared to hemodialysis, peritoneal dialysis offers lower risk of death across all subgroups for the first 1–2 years of dialysis and is now recommended for use as the initial modality of dialysis in the majority of ESRD patients due to the lower prevalence of infections and better preservation of residual renal function.[54] The two common choices for peritoneal dialysis are Continuous Ambulatory Peritoneal Dialysis and Automated Continuous Cycling Peritoneal Dialysis, both of which function by infusing peritoneal dialysis fluid in the peritoneal cavity and draining it 4–6 hours later with the number of exchanges varying according to patient size, peritoneal membrane permeability, and residual kidney function.[52]

Benefits of using peritoneal dialysis include that of self-discipline for the patient, a sense of ownership and responsibility for disease and self-management, and lower morbidity and mortality.[52] An important caveat here for the diabetic patient is to avoid using high-glucose peritoneal dialysis solution, as this has been associated with worsening diabetes mellitus, lower serum albumin, and lower residual renal function.[54,55] The most common complication with peritoneal dialysis is peritonitis, which can be treated empirically with intraperitoneal antibiotics.[52]

CONCLUSION

Kidney disease is a serious complication of diabetes that requires intensive management and treatment. While the ultimate goals of renal therapy in patients with diabetes and kidney disease include prevention of progression to ESRD, reversal of uremic symptoms, and maximization of quality of life, this cannot be accomplished without the cooperation and active participation of the patient, their support system, and members of the healthcare team.

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Assessing the Value of Preventive Ophthalmologic Care in Ghana

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ABSTRACT

Glaucoma is the second leading cause of blindness in Ghana. At Emmanuel Eye Centre in Accra, Ghana, a large portion of glaucoma patients do not receive glaucoma treatment until the disease has progressed to an advanced stage. To identify the possible barriers between glaucoma patients and ophthalmologic care, patients who arrived at the clinic with both early and late stages of glaucoma were selected for semi-structured interviews. This Institutional Review Board-approved study had three targets: knowledge of what glaucoma is, perception of the need for eye care before treatment, and specific barriers to glaucoma care. The findings suggest that the "invisibility" of early stage glaucoma is a significant barrier to care. Rather than a lack of funds, patients did not see the value in seeking preventive ophthalmologic care.

KEYWORDS: *glaucoma, prevention, ghana, aging*

The Ghanaian people are a social and warm group. They do not need maps, menus, or price lists as everything is spoken. In the capital, Accra, the best place for Ghanaian hospitality is at "He Is Mighty," a small chop bar. The owner will accommodate a group of visitors to steaming fried rice topped with a scrambled egg on the family's porch behind the store with a candle lit to eliminate the darkness. It is these small, pleasant interactions that reflect the Ghanaian life style and their intense focus on making the present meaningful. But, in a country where roughly 44.8 % of the population lives on less than $ 1 per day, implementing expensive necessities like medical care is a challenge.[1] As the government of Ghana and various other non-governmental organizations attempt to make medical care available for more people, it is important to assess the value of medical care perceived by the people. Efforts to establish an effective medical care system in Ghana hinge on the system's ability to both provide the treatment needed by its people and create an incentive to receive medical care, in large part by stimulating trust that health services are indeed valuable.

This focused research project involved studying preventive ophthalmologic care in Ghana while volunteering with Unite For Sight during the summer of 2010. Unite For Sight supports local eye clinics in Accra to deliver ophthalmologic care to the rural poor. While participating in this outreach program, I found medical care did not exist in much of the rural areas in Ghana. Dr. Michael Gyasi, a glaucoma ophthalmologist working at Emmanuel Eye Centre in Accra, found that 96 % of patients diagnosed with glaucoma in this rural setting already had moderate to advanced disease.[2] He also found that 76 % of his glaucoma patients in the urban capital setting already had an advanced case of glaucoma.[2] Even in a setting with available ophthalmologic care, patients were not receiving glaucoma treatment soon enough. Glaucoma affects about 8 % of people over the age of 40 in Ghana.[3] For comparison, the prevalence of glaucoma in the United States hovers around 2 % for people over the age of 40.[4] Throughout the world, it is also the second leading cause of blindness.[5] Glaucoma, usually associated with increased ocular pressure, is characterized by progressive damage to the major optic nerve inside the eye that transmits light generated signals from the retina to the brain. Optic nerve damage generally causes a subtle loss of peripheral vision initially with gradual loss of central vision if left untreated. Increased ocular pressure is generally caused by ineffective drainage of aqueous humor fluid in the anterior chamber of the eye through the trabecular meshwork.[6] Glaucoma treatment is focused on lowering and controlling ocular pressure. Eye drops, generally beta-adrenergic antagonists, can effectively manage the disease by decreasing the production of aqueous humor. However, some cases require surgery, such as a trabeculectomy, to open up the trabecular meshwork and decrease the pressure. Oddly, there are rarely symptoms until vision has already begun to decline.[6] Preventive management of the pressure inside the eye is critical in blindness prevention, especially since the vision loss is irreversible.

> "...the people in Ghana culturally do not seek medical care unless there is a foreseeable problem. If something is hurting or broken, then they will seek a physician.

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While working at Emmanuel Eye Centre, an Institutional Review Board-approved exploratory study was conducted to investigate why a significant number of glaucoma patients seek vision treatment late. The goal was to gain insight through patients and their stories by exploring the barriers between them and their ophthalmologic care. The conversations had three goals: 1) gain patient knowledge about glaucoma; 2) understand the reluctance for preventative treatment; and 3) define the barriers to glaucoma care with the intention of developing a solution. While talking to glaucoma patients, more than half expressed feeling no need to seek care from an eye doctor until they noticed a problem. Several patients commented about seeing a doctor for a broken arm and a dentist for teeth cleaning, but never to see an eye doctor with seemingly perfect vision. Moreover, patients had a strong grasp about the most popular mechanism of glaucoma, elevated ocular pressure, but few noted its fearful outcome: blindness. Even when specifically asked about difficulties in affording medical care, patients did not identify an inability to afford ophthalmologic care as a significant barrier.

These exploratory findings suggest that the "invisibility" of early stage glaucoma clouds a patient's perception about seeking ophthalmologic care, which is directly caused by the lack of glaucoma symptoms. This invisibility, an inability to perceive glaucoma, hinders a patient's ability to see the value of routine eye exams. Another special finding from the investigation was the overwhelming affirmative answer to the following question: would you recommend seeing an eye doctor to your friends and family? Even when probed to see if the patients would recommend a friend or family member to see a doctor without a problem and simply for an eye exam, they still responded affirmatively. This demonstrated that after being diagnosed and receiving glaucoma treatment, patients then saw the value of preventive ophthalmologic care.

"Although coupled with the structural constraint of the lack of support of glaucoma care, individual responsibility is ultimately the challenge facing effective glaucoma treatment.

One patient who participated in the study was a pastor at an Accra church being treated for late stage glaucoma. He was an intelligent, soft-spoken yet determined and passionate man. He spelled out the problem the study slowly uncovered. He told his story about how the people in Ghana culturally do not seek medical care unless there is a foreseeable problem. If something is hurting or broken, then they will seek a physician. He now has taken action to reverse this; the pastor invites health professionals to speak to his congregation about basic healthcare and the need for certain kinds of preventive care.

The healthcare system in Ghana does not currently provide enough incentive for people to seek regular ophthalmologic care. It is both a private and public operation, largely supported by the government national health insurance. The system focuses on dealing with infectious diseases caused, generally, by unsanitary conditions. An estimated 52 % of Ghana's population lives in an urban city area compared to 30 % for the rest of Africa.[7] The national insurance largely supports projects to build health centres that will expand treatment for communicable diseases such as malaria and tuberculosis (TB).[8] While enhancing the availability of health clinics, this policy does not effectively address other types of disease in Ghana, including glaucoma and AIDS, that require a different strategy for treatment: one that focuses instead on prevention. This preventive strategy treats with the objective of stopping the disease from occurring, while the current healthcare system is supporting treatment of infectious disease. When a health system is desperately scrambling to manage the heavy burden of infections disease like HIV, TB, and malaria, basic health promotion and primary prevention of other illnesses are often neglected. Glaucoma is a prime example of an illness that, with appropriate prevention and early diagnosis, can be treated successfully.

Although coupled with the structural constraint of the lack of support of glaucoma care, individual responsibility is ultimately the challenge facing effective glaucoma treatment. The 76 % of patients in the urban setting who arrive late for glaucoma treatment do have access to ophthalmologic care unlike the 96 % in the rural areas where there is no access to ophthalmologic care.[2] An increase in the access to ophthalmologic care does not significantly increase its perceived value. Intertwined with the efforts needed to expand the structure of care should also be a motive to demonstrate the value of the care. One plausible option for this is pursuing the vision of the pastor, namely medical screenings for local communities. By measuring the major risk factor of glaucoma, elevated eye pressure, those who may be glaucoma suspects can be referred to see a glaucoma ophthalmologist like Dr. Gyasi. These screenings not only provide the necessary early treatment but also demonstrate the

value and awareness that will hopefully give patients the motivation and incentive to seek routine eye screenings.

As the medical system in Ghana becomes a greater priority, the ability to treat the needs of the population is critical. The African Glaucoma Summit, a conference of ophthalmologists from around the continent meeting to discuss glaucoma care, was held in Accra in August 2010. Two of their main goals for glaucoma vision care were to both improve the ability to provide glaucoma care through more trained personnel to screen for the disease and to increase public awareness about the sight-stealing disease.[9] The population of Ghana, in terms of glaucoma treatment, needs support from the structure of their healthcare system as well as motivation to seek treatment. The interviewed glaucoma patients did associate value with receiving vision care for their glaucoma. They saw the connection between quality of life and their vision. Considering the significant prevalence of glaucoma in Ghana, there is a need to expand the focus of the healthcare system to reduce the numbers. In remembering the words, stories, and smiles of the glaucoma patients interviewed, the goal is not to just to treat the numbers but to treat each individual person.

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A Continuum of Oral Care for the Aging Baby Boomers – the UBC Geriatric Dentistry Program

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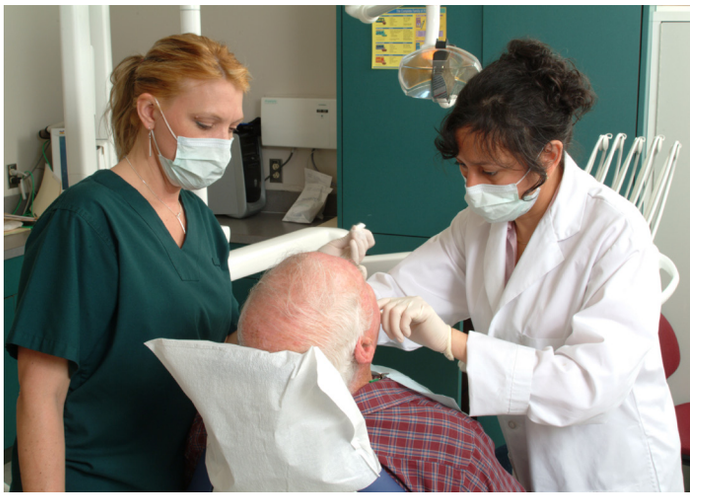
On the frontlines to meet the coming wave of baby boomers is the University of British Columbia's Geriatric Dentistry program—a pioneer in serving the needs of a rapidly emerging niche by providing much needed dental services in residential care and hospital settings.

The profile of the geriatric population is ever changing. Canada has a healthy aging population living longer than ever before, which means doctors and dentists are encountering patients who are frailer, more cognitively impaired, and require increasingly high-maintenance dental work. This summates to very complex, compromised patients, who are often difficult to care for in community practice.

The UBC Geriatric Dentistry Program is addressing oral health problems in the geriatric population according to its three-fold mission: to provide education, research, and service. Patients, families, nursing staff, care aides, students, and community dentists are educated to ensure a continuum of oral care, particularly during the transition to residential care. Ongoing research is being done to examine current problems in geriatric care, look for ways to manage and prevent these problems, and understand various models of care. The program brings dental service to patients in long-term care facilities, extended care hospitals, and the UBC Specialty Dental Clinic to accommodate the unique needs of this population.

One vision of the program is to foster a holistic, team approach among healthcare professionals in tending to the overall health of the patient. A geriatric patient's healthcare provider team can be extensive and may include a nutritionist, geriatric psychiatrist, social worker, as well as physicians and nurses. The Geriatric Dentistry Program is an advocate for the integration of dental treatment into the medical care of a patient and pushes for more liaising between physicians and dentists for consultations and treatment coordination. It hopes to empower medical professionals with more knowledge about oral health and encourage them to proactively identify problems that need assessment by a dentist. Program Manager Shunhau To explains:

> What we're trying to do is promote awareness that oral health can impact your overall health... I think it's more important for the population that we see because they're so much more compromised, and often, if they're not getting proper oral care, they're not going to feel like eating, and so their body weight and everything else is [sic] impacted. Their ability to socialize, their self-confidence level, all of that comes into play, and I think a lot of times, that starts in the mouth.



Dr. Chris Wyatt, Head of the Division of Prosthodontics and Dental Geriatrics in the Faculty of Dentistry emphasizes that:

> Physicians are key to ongoing care and reassessment. Physicians and nurses should look in the mouth and at least be aware of what's going on, because that may be the first sign[] that the patient has other systemic problems going on.

As Shunhau To points out:

> Many of these patients have so many other medical conditions that their mouth often gets neglected. So where the medical students or physicians could really help is promote that message and awareness. They could certainly help by making the referral to the patient that they should see a dentist. And I think that message, coming from a physician, would go a long way[].

While elderly people in long-term care may be well looked after in the event of a dental emergency, visiting the dentist may be difficult for those living at home. This makes them an especially vulnerable population, one whom the Geriatric Dentistry Program hopes to reach in collaboration with the medical community.

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The Future Treatment of Alzheimer's Disease – an Interview with Dr. Song

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Dr. Weihong Song is the Canada Research Chair in Alzheimer's Disease and the Director of the Townsend Family Laboratories at UBC. He has extensive training in psychiatry, psychobiology, neurobiology, and medical genetics. Dr. Song's research team focuses on the molecular basics behind Alzheimer's disease, the leading cause of dementia in Canada.[1] Alzheimer's disease represents 63 % of all causes of dementia and currently affects approximately half a million people in Canada.[1] Here Dr. Song discusses his research interests and the new developments being made by his research team.

Dr. Song's interest in Alzheimer's disease developed when he was working as a clinical psychiatrist where he saw patients presenting with agitation who were being misdiagnosed with psychiatric illnesses when in fact they had dementia.

> This is one of the diseases that has exemplified how basic research can really contribute ... to ... how we understand [dementia]. In Alzheimer's disease there is [sic] unique neuropathology and features of the disorder ... We have plaque formation and tau tangles. When we see that [sic], with memory loss, this is absolutely Alzheimer's disease. (Dr. W. Song, personal communication, March 15th, 2011)

As Dr. Song explains, the three major neurophysiological hallmarks of Alzheimers disease are amyloid plaque formation, neurofibrillary tangles, and neuronal death. His lab has contributed significantly to the research in this field.

Neurofibrillary tangles are formed as a result of hyperphosphorylation of tau proteins.[2] It is now believed that neurofibrillary tangles play a major role in the formation of amyloid plaques.

> Neurofibrillary tangles actually consist of the amyloid beta peptide (Aβ), cleaved from a large protein called the Aβ peptide precursor (APP) by two secretases, β and γ. Our lab actually contributed very significantly to the understanding of how those secretases cleave the APP to generate Aβ. (Dr. W. Song, personal communication, March 15th, 2011)

Dr. Song describes one hypothesis for the pathophysiology of Alzheimer's disease which states that Aβ plaque formation in the brain could lead to neuronal death.

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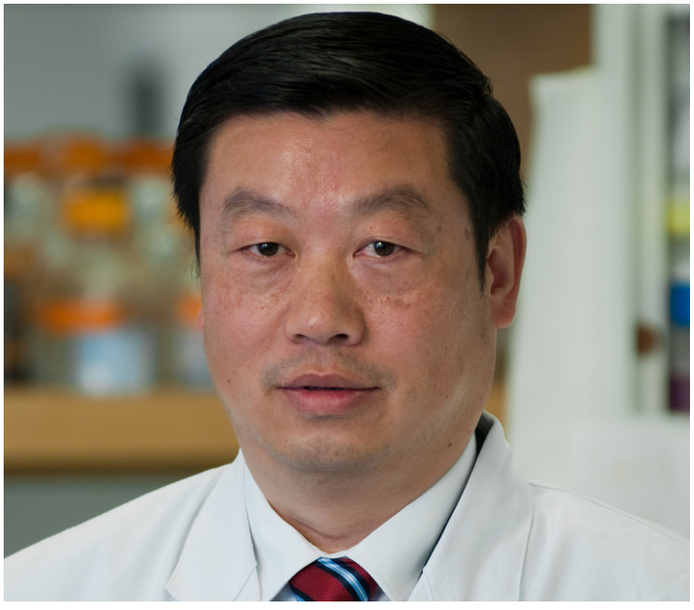
Furthermore, there is a strong link between Alzheimer's disease and Down syndrome:

> Down syndrome is very related to Alzheimer's disease so almost all the Down syndrome kids, if they can survive and grow up past the middle age, they all become very typical Alzheimer's disease patient[s]. (Dr. W. Song, personal communication, March 15th, 2011)

Down Syndrome is a condition in which the individual has three copies of chromosome 21 (trisomy 21). The *APP* gene is located on chromosome 21; therefore, the *APP* gene is over-expressed.

Dr. Song explains that when looking at post-mortem brain tissues of Alzheimer's patients, some had increased levels of RCAN1 protein. Further research revealed that RCAN1 is pro-apoptotic, and its over-expression can trigger the activity of one of the major molecules involved in neuronal apoptosis.

Dr. Song's lab discovered the *RCAN1* gene, originally called the Down Syndrome Critical Region 1 gene (*DSCAR1*). The *RCAN1* gene is also located on chromosome 21. While this helps to explain why individuals with Down syndrome develop Alzheimer's disease, we are left to wonder how individuals with two copies of chromosome 21 have increased *RCAN1* expression.



In this photo: Dr. Weihong Song.

Continued on page 24

UBC MEDICAL JOURNAL SUBMISSION GUIDELINES

The *University of British Columbia Medical Journal (UBCMJ)* is a student-run academic journal with a goal to engage students in dialogue in medicine. Our scope ranges from original research and review articles in medicine to medical trends, clinical reports, elective reports, and commentaries on the principles and practice of medicine. We strive to maintain a high level of integrity and accuracy in our work, to encourage collaborative production and cross-disciplinary communication, and to stimulate critical and independent thinking.

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Articles are submitted online (**http://ojs.library.ubc.ca/index.php/ubcmj**) via our online submissions system, OJS. Please refer to the complete online version of the *UBCMJ* Guide to Authors which can be found at **www.ubcmj.com.**

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Authors must acknowledge and declare any sources of funding or potential conflicting interest, such as receiving funds or fees by, or holding stocks and benefiting financially from, an organization that may profit or lose through publication of the submitted paper.

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Formatting should conform strictly with the ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals (**http://www.download.thelancet.com/flatcontentassets/authors/icmje.pdf**), also known as the Vancouver Style. Manuscripts should be written in clear, grammatical English, with 12-point font and double-spaced formatting. Manuscript pages must be numbered consecutively with the title page constituting page 1 and include continuous line numbers. All identifying information from the manuscript must be removed.

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Reviews provide an overview of a body of scientific work or a medical trend. Reviews may outline a current medical issue or give insight into the principles of practice of a clinical field. Authors may choose to review the etiology, diagnosis, treatment, or epidemiology of a specific disease. Articles may also provide a survey of literature dealing with philosophy or social sciences.

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Global Health

This section deals with specific experiences or issues in global health; these generally fit into the WHO definition of global health as "the health of populations in a global context that transcends the perspectives and concerns of individual nations." Articles should reflect on current or historical issues of international relevance. Articles should correspond to one of the following formats:

1. Editorials are well-researched submissions that outline a current or historical global health issue or expose and explore aspects of global health.
2. Reflections are subjective, anecdotal pieces of personal insight upon a global health related issue.
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Abstracts are not required for News and Letters submissions. There are two main types of submissions:

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The aim of this section is to provide a platform for intellectual dialogue on topics relevant to the study and practice of medicine. Articles submitted to this section should correspond to one of the following descriptions. An abstract is required.

1. Subjective pieces relevant to medical studies, life as a future physician, or the current social context of medicine.
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Case Reports describe notable clinical encounters with patients in a public health setting. The case should provide a relevant teaching point for medical students.

Patient consent

Submissions must include consent from the patient in order to be considered for publication. A copy of the written consent obtained from the patient must accompany the submission.

SOAP note

In addition to the standard submission criteria, case reports are strongly encouraged to include a brief inset summarizing the findings in the form of a standard medical history SOAP note (Subjective, Objective, Assessment, Plan).

Elective Reports aim to increase student exposure to a variety of medical specialties and training opportunities both locally and internationally. Reports give a specific description of the scope of a practice in a medical specialty and/or training program and recall a student's impressions and reflections during and upon completion of the elective. They should highlight the student's clinical experiences and the unique features offered by the program. Examples of Elective Reports can be found at the Lancet Student (**http://www.thelancetstudent.com/category/electives/**).

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Dr. Song's research team is currently developing a hypothesis to elucidate the relationship between stress, such as oxidative stress, and an increase in *RCAN1* expression. Aβ increases with increasing *RCAN1* expression as well. Therefore, there are two major hypotheses for the development of Alzheimer's disease: the first is the Aβ hypothesis, where amyloid plaque formations deposit in the brain cells, and the second is the *RCAN1* gene hypothesis, where neuronal cell death occurs as a result of increased *RCAN1* expression. Dr. Song's lab is now focusing on pharmacological agents to inhibit neuronal loss. He elaborates that regardless of the presence of plaques or tau tangles, in the end it is the loss of neurons that causes Alzheimer's disease.

Dr. Song's research highlights the importance of going back to basic science in order to make advances in the field of Alzheimer's disease research. While it is likely that years will pass before these pharmacological agents are being used in clinical trials, we are hopeful that these new developments will one day prevent this devastating disease from affecting our patients. Dr. Song strongly encourages all students to think critically and to do research. By doing so, we can impact more people than just our own patient population.

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Why Geriatrics is Important to You

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It has been well documented that the geriatric population is rapidly growing with an estimation that people 65 years and older will comprise 23 % of the population by 2041.[1] This aging population translates into an increasing demand for geriatric care, yet currently, Canada has just half the required geriatricians.[2] Furthermore, there are only 22 hours of formal teaching within the UBC undergraduate curriculum centred around geriatric care, with no mandatory clinical rotations during third or fourth year. The bottom line is that demand is much greater than supply, and solutions to balance out the equation are required in order to ensure that the care and needs of older adults can at least come close to being met.

The Summer Institute in Geriatrics was created 22 years ago to enhance knowledge of geriatric principles and to stimulate interest in pursuing careers in geriatric medicine and research. This five-day conference provides medical students, who are presently in their first or second year of medical school, with an exciting opportunity to gain exposure to clinical work and academia in geriatric medicine. Course activities include interactive presentations, patient/problem-based learning workshops, and exposure to a variety of geriatric services including site visits to clinic programs. The 2011 Summer Institute in Geriatrics was hosted by the University of Western Ontario from June 20th–24th. Twenty-nine medical undergraduate students from across the country met in London, Ontario to learn more about geriatric care. The week covered common topics such as physical activity and successful aging, biology of aging, falls as an example of geriatric syndromes, cognition, dysphasia, medication reviews, and ophthalmology. There was a strong focus on clinical skills with stations teaching students how to assess confusion, transfer a patient, examine a patient with parkinsonism and/or tremor, and assess gait and mobility. Students also spent half a day shadowing geriatricians or nurse practitioners involved in care of the elderly. The conference also ensured balance with leisurely activities including an afternoon watching a play at the famous Stratford Shakespeare Festival. Overall, the Geriatric conference was not only a phenomenal way to learn more about caring for the elderly, but also a fantastic opportunity to network with other medical students from across Canada, and an opportunity to have in-depth conversations with geriatricians about their careers.

Regardless of what specialty one chooses, aside from pediatrics and obstetrics, the geriatric population will inevitably make up a significant portion of his or her patient demographic. Having a stronger understanding of the complex care required by the elderly will ensure we are better prepared to meet their needs. There are numerous opportunities for students to expand their knowledge of geriatric care: UBC organizes its own one-day Summer Institute event with talks and case-based discussions facilitated by clinicians and residents. The UBC Geriatric Interest Group will also have events throughout the year to provide similar experiences and opportunities to medical students.

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The Night Shift: A Talk by Dr. Brian Goldman

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Dr. Brian Goldman delivered an exciting talk at the UBC Life Sciences Centre on March 27th, 2011. It was also broadcast to distributed sites at Prince George, Terrace, and Victoria. This talk was hosted by Dr. Carol-Ann Courneya and Dr. Andrew Seal. According to Dr. Courneya, the aim of the talk was to "focus on maintaining a love of and passion for arts and humanities throughout [medical and dental] training and practice." Humanities were reported to nurture and maintain empathy, professionalism, and self-care in students and physicians.[1] The talk was strategically scheduled on the day after the highly anticipated Spring Gala 2011, which celebrated the astounding artistic talents of UBC medical and dental students.

Dr. Goldman is an Emergency Room (ER) physician working at Mt. Sinai Hospital in Toronto, ON. Besides medical practice, he has a passion for journalism. He is a CBC radio broadcaster on the show "White Coat, Black Art" and author of the book entitled "The Night Shift", both of which take listeners and readers on to "[his] side of the gurney."

Dr. Goldman began the talk by sharing his training in medicine and how his passion of writing intertwined with his undergraduate and medical studies. During his residency training, his passion in journalism landed him in a continuing education course in writing which began his career in journalism.

Working in the ER is not only a vocation for Dr. Goldman. He also gets his inspiration for writing there, thus providing him the opportunity to be an effective journalist. His goal is to bring out the voices of nurses, paramedics, physicians, and other healthcare providers through his radio show.

Authenticity, brutal honesty, and medical futility were the three main purposes for Dr. Goldman's broadcasting career. He discussed the challenges in satisfying two types of listeners of his show: patients and healthcare providers. He played recordings from his radio show to illustrate how he, in presenting the different perspectives, could carry out his three missions.

Competency in reflective practice is valued as one of the essential attributes of physicians, and Dr. Goldman highlighted its importance in one's medical career.[2] In our interview after the talk, Dr. Goldman elucidated that

> It is never too early to develop reflectiveness in our work… there is a general lack of reflection in postgraduate training and in practice. There has been a bias against reflection [because some physicians] equate reflectiveness as self doubts. We have developed an unhealthy shame around our feelings, our thoughts, and human frailty.

In this photo: Dr. Brian Goldman (Left) and Dr. Carol-Ann Courneya (Right).

Physicians with literary careers have the privileges to include candid medical stories in their work.[3] Dr. Goldman explained that they needed to write without violating patient confidentiality. When writing his book, his strategy to protect patient confidentiality was to use stories which were inspired by real people with disguised details, thus being unrecognizable by the patients and their families. Dr. Goldman also warned the audience about publishing on social networking sites where patient confidentiality could easily be breached. Having dual roles as "a compulsive storyteller" and "a sworn guardian of [his] patient confidentiality," he is still trying to figure out where the balance lies.

Dr. Goldman closed his talk by asking us to continue to nurture our artistic endeavors in our future careers. Although it was hard work alongside his other responsibilities, he still made journalism possible around his busy schedule. Dr. Goldman also left UBC medical students with an important advice: "Be true to yourself, be honest. Keep doing what makes you feel passionate. But above all, find the truth in what you do, and follow that."

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Endurance Exercise, the Fountain of Youth, and the Mitochondrial Key

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Scientists have been searching for the proverbial fountain of youth for centuries, hoping that a newly discovered drug or exotic plant would hold the key to anti-aging riches. However, a recent study from Canada provides powerful evidence that the key was within each and every one of us the entire time.

Led by Dr. Mark Tarnopolsky, Professor of Pediatrics and Medicine, a team of researchers from McMaster University's Michael G. DeGroote School of Medicine recently published a study that found endurance exercise can prevent the signs of premature aging in virtually every tissue and organ system in the body. Published in the Journal of Proceedings of the National Academy of Sciences of United States of America, the study found that mice that were genetically engineered to age faster were protected against the phenotypic and biologic changes of aging by engaging in regular endurance exercise.[1] In an era that has seen the epidemic emergence of chronic diseases—likely a result of increasing sedentary behaviour, excess caloric intake, and obesity—this study should help promote the benefits of exercise for all those searching to stay forever young.[2]

Epidemiological evidence has established that endurance training greatly reduces the risk of chronic diseases and decreases mortality in humans; however, little is known about how endurance training affects aging.[3–14] The mitochondrial theory of aging postulates that lifelong accumulations of mitochondrial DNA mutations lead to a cellular energy crisis, resulting in progressive decline in tissue and organ function, and ultimately accelerating the aging process. Based on this theory and known evidence that exercise can induce mitochondrial biogenesis and metabolism, Dr. Tarnopolsky and his team of researchers set out to prove that endurance exercise could help prevent premature aging in mice.[15–19]

The study used mice with genetically modified dysfunctional mitochondria which caused them to age prematurely. Starting at three months of age, or about 20 human years, the mice were randomly assigned to moderate intensity endurance exercise three times per week for 45 minutes or to a sedentary group. The mice were studied over the next five months until the age of eight months, or approximately 60 human years, with startling findings.[1]

Although both groups of mice were genetically disadvantaged to prematurely age, the mice that engaged in endurance exercise looked as healthy as normal mice while the sedentary group showed many phenotypic features of aging, including hair loss, greying, physical inactivity, and social isolation. Furthermore, the exercised mice were protected against early mortality and multi-system organ degeneration, such as hearing loss, cataracts, sarcopenia, brain atrophy, cardiomyopathy, anemia, and infertility. Compelling evidence revealed that endurance exercised mice had decreased accumulations of mitochondria DNA mutations, increased mitochondrial biogenesis, and decreased mitochondrial apoptosis,[1] further highlighting the potential role of mitochondria in the aging process.

These findings strengthen the mitochondrial theory of aging, providing evidence that endurance exercise may prevent premature aging through the maintenance and recovery of mitochondrial function, which is crucial for organ health. "Every part of the body was protected by exercise," said Dr. Tarnopolsky, who believes "that exercise is the most potent anti-aging therapy available today and likely forever."[20] The poet John Gray wrote in 1716: "Rosy-complexion'd health thy steps attends, and exercise thy lasting youth defends."[21] It is interesting to think that maybe he was right all along.

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Unraveling the Role of Lipid Metabolism in Alzheimer's Disease

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Imagine the heartbreak of being unrecognizable to your spouse after 40 years of marriage or losing the capacity to remember one's only child—such are the features salient in the latter course of Alzheimer's dementia. Given that Alzheimer's Disease (AD) is estimated to affect up to 40 % of North Americans over the age of 85, it constitutes a substantial obstacle to healthy aging.[1,2]

Upon finishing her post-doctorate work with Dr. Michael Hayden at the University of British Columbia, Dr. Cheryl Wellington began investigating the link between neurodegenerative disease and lipid disorders. Given that the most important genetic risk factor for AD is apolipoprotein E (apoE), which is a major cholesterol carrier in the brain, Dr. Wellington set out to further investigate the relationship between cholesterol metabolism and AD.

One of the major neuropathological hallmarks of AD is the presence of amyloid plaques within the brain parenchyma and cerebral blood vessels. The plaques are deposits of Aβ peptide, a by-product of amyloid precursor protein that is continuously produced and then cleared from the brain. With aging, it is hypothesized that the clearance and degradation of Aβ become less effective. Dr. Wellington's lab has shown that the clearance rate of Aβ is strongly affected by how much lipid is carried on apoE.[3]

The natural function of apoE is to distribute lipids among various cell types in the brain, a function that is critical for repairing damaged neuronal membranes. The cholesterol transporter ABCA1 acts to move excess lipids from the cell surface to apoE. In humans, the polymorphic *apoE* gene is present in three different allelic isoforms (2,3, and 4), and *apoE4* has been shown to increase the risk of developing AD with each inherited copy. At least 50 % of patients with AD possess at least one *apoE4* allele.[3]

In accordance with ethical guidelines for preclinical research, Dr. Wellington has used murine models of AD to show that the whole degradation pathway of the Aβ peptide slows down in the absence of ABCA1. The mice deteriorate cognitively and develop more amyloid deposits in their brains. Dr. Wellington has also shown that lipid saturation of apoE can be increased by using genetic modifications or small molecule compounds that increase ABCA1 activity. This results in more rapid degradation of Aβ peptides and less amyloid formation. "This gives us the ability to possibly provide novel therapeutic strategies for Alzheimer's disease that can augment therapies being developed to slow the

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production of Aβ," says Dr. Wellington.[3]

Despite her progress she emphasizes that our ability to treat or prevent the illness is nascent and that we must not overlook the influence of other factors that do affect overall risk. Intriguingly, what is good for the heart is good for the brain. She explains that "the biggest piece of advice I always give to the general public is never stop exercising; that's probably one of the best things that you can do to promote healthy aging from the cardiovascular, metabolic, and neurologic perspectives."[3]

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University of British Columbia Conference on Dementia 2011

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On January 29, 2011, The University of British Columbia partnered with the Clinic for Alzheimer's Disease and Related Disorders at UBC Hospital (CARD-UBCH) to host Dementia 2011. Speakers included Jean Blake, CEO of Azheimer Society of BC, and Dr. Lynn Beattie, medical director at CARD-UBCH. The objective of this conference was to inform the public on Alzheimer's Disease (AD) diagnostic techniques, current treatments, and future treatments. AD affects 25–45 % of persons over the age of 85, and this percentage is projected to increase as the geriatric population grows. One of the event's focuses was in AD diagnostics, which is currently undergoing substantial review. AD can only be diagnosed upon post-mortem examination, leading to frustration and uncertainty over the appropriate course of treatment for patients.

Current AD diagnostic techniques primarily include assessment of medical history, cognitive examination, and neuroimaging. The Mini Mental Status Examination (MMSE) is an especially important cognitive exam to conduct; the MMSE tests a patient's cognitive capacity through a series of basic questions and tasks. It has high sensitivity but only moderate specificity, occasionally resulting in false positive diagnoses. Part of the difficulty in using the MMSE is that it is a highly subjective test and depends on the age and educational level of the patient. Magnetic resonance imaging (MRI) has also been a useful diagnostic tool, especially when considering the decrease in hippocampal volume. However, a decrease in hippocampal volume is common in many forms of dementia other than AD and therefore does not provide a definitive diagnosis. This is problematic because many AD treatments are most effective when implemented at early stages of the disease. Furthermore, a compounding problem is that the most advanced diagnostic tools are restricted to urban areas resulting in inaccessibility for rural populations.

A relatively newer diagnostic tool used in clinical trials measures the ratio of beta amyloid 42 (Aβ-42) to phosphrylated tau (p-tau) protein as biomarkers in the cerebrospinal fluid (CSF). Biomarkers are measurable biological substances which indicate the presence or absence of a particular disease state. Studies have indicated that Aβ-42 concentration diminishes as AD progresses while p-tau concentration increases with disease severity. Therefore, when the biomarkers are used together, clinicians can accurately assess both disease severity and stage.

The most promising solution is to develop a non-invasive, accessible, and accurate technique such as blood testing which would detect AD at an early stage. Although this field of research is still in its infancy, recent reports have found possible blood biomarkers which could lead to definitive AD diagnosis. AD diagnostics has progressed significantly in the past decade. Looking forward, physicians will increasingly rely on biomarkers found in the CSF and blood plasma to diagnose AD and hopefully to provide patients and their families with some peace of mind.

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A Sight for Old Eyes: Front-line Research of Age-Related Macular Degeneration

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Age-related macular degeneration (AMD), a degenerative disease of the central retina associated with aging, is the leading cause of blindness in the elderly of North America.[1] The majority of patients have the "dry" form of AMD, presenting with varying degrees of central vision loss, and can progress to the "wet" form where neovasculatures generate in the retina.[2] These fragile vessels leak blood and fluid, displacing the macula from its natural position, causing damage, rapid vision loss, and perceived image distortions.[2]

We spoke with two experts in the field of AMD—Dr. David Maberley, a Vancouver ophthalmologist sub-specializing in the retina and vitreous humour, and Dr. Joanne Matsubara, a researcher at the UBC Eye Care Centre investigating connections between amyloid-β, a pro-inflammatory peptide, and AMD pathogenesis.

Dr. Maberley is the founder and director for the Canadian Retinal Trials Group, a national clinical trials group conducting multi-centred randomized control trials. Concerning AMD, Dr. Maberley has led trials examining the roles of intraocular steroids in the context of Visudyne laser treatment of AMD and of intra-vitreal injections of anti-vascular endothelial growth factor (VEGF) therapy with or without steroids for AMD.[3] Looking to the future, Dr. Maberley foresees much potential for AMD-related research, explaining that there are effective treatments for the wet form of AMD but not so for the dry form. As such, further investigations need to be conducted on the latter.

As for wet AMD, Dr. Maberley believes the first step to increasing therapeutic efficiency would be to develop devices or medications with a more sustained release profile, thus decreasing patients' total number of administrations and time spent in treatment. Furthermore, he commented that it would be worthwhile to examine other neovascularisation triggers of wet AMD, such as tumour necrosis factor (TNF), as well as other upstream mediators, such as complement factors, to uncover targets for early intervention.

Also along the frontlines of AMD research is Dr. Joanne Matsubara, working in her laboratory to further understand the pathophysiology of this disease. Specifically, she described, "We are studying how amyloid-β, recently discovered to be a constituent of drusen [accumulations of ocular extracellular material], may affect cells in the outer retina." Regarding the aetiology and potential therapeutic targets, Dr. Matsubara commented,

In this photo: Dr. David Maberley

> Our studies show that amyloid-β oligomers cause the RPE [retinal pigment epithelium] cells to up-regulate pro-inflammatory cytokines such as IL-1β and IL-8. We know that low levels of these cytokines can trigger apoptotic cascades in neurons, and specifically at risk are the photoreceptor cells that sit adjacent to the RPE.[4]

In addition to the use of monoclonal antibodies against angiogenesis in AMD, cytokine inhibition and neuroprotection are being explored as other methods of remedy.[5] She concluded that the clinical application of her findings could potentially include anti-amyloid-β drugs, or blocking pro-inflammatory cytokine secretion in the retina, leading to a resultant reduction in photoreceptor apoptosis.

We are thankful for the work of Dr. Matsubara and Dr. Maberley and hope to see more exciting findings about the aetiology and treatment for AMD in the near future.

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Playing for Fitness – Helping Seniors Stay Active

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This past December, Gladys Burrill of the United States of America completed the Honolulu Marathon in nine hours and 53 minutes. Through exercising into her senior years, 92-year-old Burrill cemented herself in history as the oldest female to ever complete a marathon.[1] She also lowered her risk of osteoporosis, cognitive impairment, and cardiovascular disease,[2] conditions that affect longevity and independence. What can be done to encourage other seniors to stay active?

Jennifer Slater works as the Recreation Coordinator at Terraces on 7th, an independent and assisted living facility for seniors in Vancouver's South Granville area. Slater coordinates a variety of events to encourage the facility's residents to stay active. Twice per week, she leads an hour-long group fitness class where residents develop their strength, endurance, and balance in order to prevent falls and improve mobility. When working with seniors, Slater notes that it is important to modify exercises to suit an individual's functional abilities. She also encourages residents to "work at their own pace and not to look around but to look at themselves" as they participate in her classes, noting improvements in their personal skills over time.

In this photo: Jennifer Slater (right), Recreation Coordinator at Terraces on 7th, created a "Fitness Stars" program to encourage participation in physical activity. Residents received a star for each program they attended. Claire Alderberg (left) achieved a Fitness Star award in March 2011.

In this photo: Irene Denny won the "curling" game during the "Terraces Olympics".

Other successful programs at Terraces include Tai Chi classes, personal trainer sessions, a walking program, and gardening sessions. One of the biggest hits with the residents, however, is the Wii™, a video-gaming system. This device allows residents to physically mimic bowling, boxing, golf, cycling, kayaking, and tennis with a handheld controller. This is especially beneficial for residents who cannot participate in

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the real-life versions of these sports due to health or mobility concerns. Although less physically taxing than a real tennis game, for example, Slater feels the Wii™ helps develop residents' hand-eye coordination skills. It also allows residents to connect with young family members who regularly use the technology.

"Targeting programming to the wants of residents" and "always making things fun" are two keys to helping seniors stay active, according to Slater. During the 2010 Olympic and Paralympic Winter Games, Slater coordinated a variety of social events to encourage activity. There was a "torch relay" where residents proudly wore red and white while they passed a homemade torch from the fifth floor to the main socializing area on the first floor. Residents also participated in an indoor "curling" session with balls instead of rocks and took part in "hockey drills" around pylons amongst other sports.

At Terraces, it seems that the secret to staying active lies in play. So encourage your older patients to pick up a hockey stick or a basketball; to put on their gardening gloves or grab hold of a Wii™ controller; and, of course, to find a friend or family member to join in on the fun. For, as the saying goes, "We do not stop playing because we grow old. We grow old because we stop playing."

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The Federation of Medical Women of Canada

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In 1924, six distinguished female physicians lead by Dr. Maude Abbott, an internationally-respected pathologist, came together at the Canadian Medical Association's Annual General Meeting and founded the Federation of Medical Women of Canada (FMWC). The organization was founded both to support the "professional, social, and personal advancement of women physicians" in Canada and to promote the "well-being of women both in the medical profession and in society at large."[1] After over nearly a century of dedication, the FMWC continues to advocate for women physicians by providing them with a unified public voice, mentorship, and the opportunity to network with peers.

At UBC, we have a student-run branch of the FMWC, which enthusiastically supports this tradition of advocating for women physicians and medical students. Last year, the UBC FMWC created a mentor group of medical student mentees and physician mentors. The group met over a warm meal and discussed issues such as choosing a specialty, family planning, and the changing atmosphere of healthcare in Canada. After the physician mentors had divulged their pearls of wisdom to the eager mentees, the roles were reversed as the mentors became mentees on the topics of surviving the technological onslaught of internet networking. Later in the year, the mentor group met again to share one another's life passions.

Other previous UBC FMWC events have included talks on career information and updates concerning women's health. During their "Women in Medicine" talk, the UBC FMWC invited special guests including a pediatric infectious disease specialist and a plastic surgeon who specializes in the treatment of burns. The talk provided an intimate evening of advice about future careers and the opportunity for questions. The UBC FMWC subsequently held an "Updates in Women's Health" talk that featured experts in the field of gynecological cancers, global issues in women's health, and naturopathic medicine in women's health. The talk was an informative educational experience on women's health.

In mid-September, the FMWC will have its Annual General Meeting in Vancouver. The conference will bring FMWC members from across Canada to meet for a weekend of fascinating talks, great food, and networking. Topics that will be covered range from healthcare team leadership and people management to pertinent issues of women's health such as contraception, post-menopausal fracture risk, and cervical cancer. Interspersed amongst these talks will be breaks for yoga and tai-chi as well as discourses highlighting self-care, self-improvement, and overall life balance for women physicians. The weekend will end with an uplifting examination of women as a catalyst for change, focusing on how women are shifting the curve for cancer survival through their participation in integrated cancer care services.[2]

For UBC FMWC members who would like to attend the Annual General Meeting, the UBC branch is offering a subsidy of $ 25, cutting the attendance fee to just $ 25. For more information, contact Kristin DeGirolamo at kdegir@gmail.com. For those

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that are eager to get involved with the FMWC, their website can be found at http://www.fmwc.ca. On the website are details for joining the organization. To get involved with the local UBC student-run branch of the FMWC, contact Teresa Liang, president of the UBC branch of the FMWC, at afteresa@interchange.ubc.ca. The UBC FMWC is an ever-growing branch of the FMWC and is always looking for new enthusiastic members.

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Why We Should All Edit Wikipedia

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AN OVERVIEW

Wikipedia, as most are aware, is the free online encyclopedia that covers nearly everything. Almost anyone can edit it, and nearly everybody reads it. As of June 2011, it had over 3.6 million articles in the English language of which approximately 23,000 pertained to the practice of medicine, and 6,700 discussed aspects of pharmacology. The medical pages in a given month receive between 150 and 200 million page views[1] while the pharmacology content receives approximately 35 million.[2] For the entire encyclopedia, 40,000 people make more than five edits each month,[3] though a much smaller number of editors are actively involved with medicine. However, users involved with WikiProject Medicine are a dedicated group of volunteer physicians, students, and non-professionals with the goal of providing people with free access to reliable, understandable, and current health information.[4]

WIKIPEDIA'S AUDIENCE

Wikipedia has become extensively used by medical professionals and the lay public alike. It was ranked the fifth most popular website on the Internet according to Google in 2011[5] after becoming one of the 10 most popular sites in 2007.[6]

In Europe, a 2011 survey found that 60 % of physicians used Wikipedia for professional purposes,[7] which is similar to estimates of physician usage in other developed countries.[4] In 2009, 35 % to 72 % of United States pharmacists admitted to its use,[8,9] and over half of e-patients consulted it.[4]

While Wikipedia provides information of significant quality, further efforts are needed. Of the top 100 most viewed medical articles, only 24 % where deemed high quality and had passed a semi-formal review; for the medical project as a whole, this was less than 1 %.[10] Still, in 2005, when Wikipedia was only four years of age, it compared favourably with the Encyclopaedia Britannica on a selection of scientific articles.[11]

REASONS TO EDIT

So why get involved? There are many reasons and a few that have played a role for me are expanded on below.

As Wikipedia is written for a general audience, it has given me practice communicating complicated ideas in language that is easily accessible. In addition, it has forced me to explore the literature behind my clinical practice: I have frequently found what I was taught in medical school is more nuanced than I may have been led to believe. At the same time, Wikipedia has taught me critical reading, which has made me better equipped to deal with less reliable sources of information such as pharmaceutical representatives.

Also, I have had the opportunity to join people interested in medicine and to maintain an academic practice far from an academic centre. As Wikipedia is what many of my colleagues and patients are using, I feel an obligation to ensure the content is of high quality. What I write on Wikipedia matters as it is freely and easily accessible, due in part to its open source license and non-profit foundation.

As an added bonus to UBC health science students, Wikimedia Canada, the Canadian chapter of Wikimedia Inc, is offering a scholarship to whomever makes the most significant contribution to Wikipedia's medical content. Application for the first award will hopefully begin in the fall of 2011 and will be awarded in early 2012. Applications will be found at http://wikimedia.ca/wiki/Scholarship_application.

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HOW TO EDIT

Learning how to edit is relatively easy with few technical hurdles. Learning the community norms can take a little more time when one starts, but most are intuitive. A more in-depth look at how to edit has been published in the journal *Public Library of Science*, but I will provide a short overview here.[12]

Wikipedia's content creation is based on three core principles: verifiability, a neutral point of view, and no original research. The first, the principle of verifiability, means that every point that is added needs to be referenced. A neutral point of view implies that appropriate attention needs to be given to competing ideas, and the "no original research" rule reinforces the first point that attribution is required. As encyclopedia writers, we are here to reflect the current state of knowledge on a topic as presented by significant sources. For medicine, these sources are typically review articles published in peer reviewed journals within the previous five years or statements by major national or international organizations.[13]

Once you have found a suitable reference on PubMed or Google Scholar, summarize the content, and click the blue [edit] button for the section to which you wish to add. Simply enter the text, click on the "cite" arrow, pull down the "journal" tab, and add the PubMed ID (PMID). The tool will automatically format the reference based on the PMID. You can follow the same process with the ISBNs of books.

ADDRESSING CRITICISM

Wikipedia has been criticized as much of its content originates from anonymous authors. Anonymity has both positive and negative aspects. On the positive side, it forces one's sources to stand on their own. On the negative side, readers remain unaware of potential editor biases; for example, there were issues with pharmaceutical companies removing "negative" material pertaining to medications they produced.[4] Anonymous editing, however, is optional: some, including myself, edit under their own name. Wikipedia is currently encouraging greater transparency in the editing community.

Wikipedia has received criticisms for its non-peer reviewed process.[14] However, this is not entirely true. Wikipedia has an article grading scale, and for an article to be included in the two highest grades (good article and featured article), it must pass review standards. The good article status requires an independent review by a single other editor to verify that it is has no obvious problems. For featured article status, a review by multiple editors is required to verify that the article reaches a professional standard. Out of all medical articles as of June 2011, only 62 were featured articles, and 106 were good articles.[10] These can be determined by a gold star or green plus in the right upper corner of the article respectively.

Some have questioned Wikipedia's reliability as a source of medical information, including a 2009 paper which concluded that it was unsuitable for use by medical students.[15] On the other hand, a 2011 analysis found that Wikipedia was appropriate for nursing students since many articles were well referenced to the peer reviewed literature.[16] Regardless, Wikipedia is what people are using, for better or for worse. Rather than complain about reliability, we can take this opportunity to improve its quality.

CONCLUSION

Wikipedia is a frequented source for medical information, a fact often under-appreciated by academia, and has yet to reach its full potential. Greater involvement of the broader medical community is required to make sure our colleagues and patients get the quality content they deserve. The volunteers at Wikipedia Medicine would love to see our healthcare professionals join us. Come write with us: the next printed article your patient comes in with may be yours.

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Understanding Integrated Care: The Aboriginal Health Initiative Heads North

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ABSTRACT

With an increasing emphasis on holistic and culturally appropriate healthcare, a community in the Yukon has set a new standard for serving the needs of its specific population. Whitehorse General Hospital has collaborated with representative Yukon First Nations elders to create the First Nations Health Program, a program dedicated to allowing Aboriginal people to access Traditional practices, which are integrated alongside Western healthcare. This program has successfully demonstrated the importance of incorporating culture into the healing process.

KEYWORDS: *first nations, rural, elders, cultural healing, holistic*

This year, the Aboriginal Health Initiative, a student interest group operated through the University of British Columbia's Faculty of Medicine, traveled to Whitehorse, Yukon to tour the community-led First Nations Health Program (FNHP) at Whitehorse General Hospital. As part of our mandate to promote Aboriginal health through improving the cultural competency of future health practitioners, we wanted to learn from this working model of culturally competent, community-led care. We hoped that from this we would find a model to illustrate to fellow students how a program grounded in an indigenous world view can work harmoniously within a conventional western hospital.

Unacceptable health disparities exist between Aboriginal and Non-Aboriginal Canadians, and the cultural competency of physicians has been promoted as a means of addressing these.[1] As medical students, we are interested in learning how to adapt our own practices to promote Aboriginal health and reduce barriers to care for Aboriginal people. However, we recognize that the determinants of health for Aboriginal people extend far beyond the doctor's office and that in order to make meaningful progress, we must support Aboriginal communities in their broader journeys toward health. Chandler and Lalonde have identified several indicators of cultural continuity important for strong Aboriginal communities that we feel physicians are capable of supporting. These include community control over health services and facilities for the transmission of cultural practices.[2] As future physicians, we will have the opportunity to support these indicators of cultural continuity by welcoming, and advocating for, community control over health services and for facilities within hospitals for traditional healing practices.

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> **Unacceptable health disparities exist between Aboriginal and Non-Aboriginal Canadians, and the cultural competency of physicians has been promoted as a means of addressing these.**

The FNHP at Whitehorse General Hospital is a result of several agreements forged in the early 1990s. In 1990, the Yukon Hospital Corporation (YHC) was formed in preparation for the First Phase Transfer Agreement in which the Federal Government handed over responsibility for health services to the Yukon Territorial Government.[3] This was an opportune time for the Council of Yukon First Nations (CYFN) to develop an agreement with the YHC and Yukon Government to create a First Nations Health Committee on the hospital Board of Trustees and negotiate for the FNHP in the new transfer. This agreement enabled the Council to respond to the needs of the 14 First Nations it represents and develop a health program conceived, developed, and delivered by Yukon First Nations.

In April 1993, Whitehorse General Hospital was officially transferred to the YHC.[3] The First Nations Health Committee currently oversees the program and constitutes four of the 14 YHC Board members nominated by the CYFN. This is approximately representative of the Yukon population, 25 % of which are Aboriginal.

The mission of the FNHP is to "promote provision of quality, culturally-sensitive holistic healthcare to Aboriginal people" through advocacy, social and spiritual support, education of healthcare practitioners, and recognition of the effects of

> “Patients benefit by accessing holistic care that has traditionally been integral to Aboriginal health and healing.

residential schools and colonialism on the health of Aboriginal people.[4] Program services include Health and Social Liaison Workers, access to traditional medicines and healing practices, a traditional diet program, Child Life Workers, and Community Liaison Discharge Planners.

Health and Social Liaison Workers connect with Aboriginal patients on admission to help them navigate the system and ensure diagnosis, treatment, and palliation options are fully understood. They provide culturally sensitive support to patients and their families who are often far from home. Since traditional clan systems remain an integral part of Yukon Aboriginal identity, Heath and Social Liaison Worker knowledge around clan protocols is essential in matters of death, dying, and grieving. First Nations patients also have access to traditional medicines, a traditional healer, and the healing room Na Ku. Na Ku is a dedicated space within the hospital, built under the guidance of Elders, where patients can hold ceremonies and tend to their cultural needs. The traditional diet program serves donated traditional foods harvested from the territory such as moose, caribou, and salmon. Child Life Workers support families of hospitalized children while Community Liaison Discharge Planners coordinate a smooth transition from hospital to community care.

The benefits of the FNHP extend from patients to staff and physicians who work under this model. Patients benefit by accessing holistic care that has traditionally been integral to Aboriginal health and healing. Patient advocacy by liaison workers has helped reduce miscommunication between patients and their healthcare team. This ensures that physicians receive accurate information from patients and that patients actively participate in their recovery. The traditional diet program respects First Nations’ knowledge that traditional foods are healthy foods and eliminates the stress of a foreign diet during recovery.

Staff and physicians benefit by learning to adapt their care to the population they serve as workshops offered through the FNHP provide them with the resources to become culturally competent practitioners. The program has increased understanding and acceptance of cultural norms of local First Nations, and in the words of one Whitehorse GP, has “increased respect for all patients.”

While the FNHP continues to successfully operate and grow, there are still some challenges that exist. Although the YHC undergoes accreditation every three years, the FNHP has never been formally studied. Program staff indicated that the lack of evaluation is due to time constraints on staff as well as a lack of funding for an external evaluation.

After visiting the Whitehorse FNHP, our group members returned to Vancouver feeling inspired and convinced that this quality of care should be available in more hospitals. It was remarkable to see a hospital adapt its culture to care for Aboriginal patients, as so often it is Aboriginal patients who are expected to adapt to the culture of the hospital in order to receive basic care. As we are being educated as doctors in the era of patient-centred care, it makes perfect sense to us that the health services in a community should be guided by the values of that community, work to achieve the goals of that community, and be equipped to support the holistic health of that community. We are grateful to the staff and patients at the Yukon FNHP for allowing us to learn from their example and share it with our colleagues.

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Providing Quality End-of-Life Care: A Look at the Essentials of Care and the Adequacy of Instruction in Canadian Medical School Curricula

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ABSTRACT

Most Canadian medical students are interested in learning about end-of-life care. Recent research has explored the key elements involved in providing quality care to terminally ill patients and their families. Despite these new insights, limitations surrounding the provision of end-of-life teaching in medical curricula have left many residents feeling unprepared and uncomfortable in clinical encounters with patients that are near life's end. Various medical programs have effectively augmented their curricula to deal with this issue. We hope that Canadian medical students and educators will reassess the quality of their end-of-life care instruction.

KEYWORDS: *end-of-life care, medical education, terminal illness*

The overwhelming majority of today's medical students will be involved in a patient's end-of-life (EOL) care. Fortunately, both medical students and residents have positive attitudes towards caring for EOL patients and believe that these interactions provide meaningful learning experiences.[1,2] Medical education deans also consider EOL care education to be "very important" and support its incorporation into undergraduate curricula.[3] Since our understanding of what constitutes quality EOL care continues to evolve,[4–6] so too should the implementation of these insights into medical school curricula. With this in mind, our objectives are to outline the essentials of quality EOL care, to assess the adequacy of instruction in Canadian medical curricula, and to discuss programs that have made steps towards addressing this vital issue.

A recent study has highlighted key factors for medical professionals to consider when approaching clinical encounters in EOL care.[4] The most important element identified by doctors, patients, and families in the provision of quality EOL care is being able to trust and have confidence in their doctors. Other factors have also been ranked highly by both parties: patients should not be kept on prolonged and unnecessary life-support, honest communication should occur between doctors, patients, and their families concerning the disease process, and finally, patients should be given adequate time to resolve conflicts, say their goodbyes, and prepare for life's end.

Effective communication techniques can minimize the distress experienced by families of terminally ill patients. While prognostic discussions may be uncomfortable, they are necessary to provide a shared understanding among patients and family members regarding the patient's outlook and to guard against the unnecessary grief arising from unrealistic expectations. It is the responsibility of the healthcare professional to create an environment where these discussions can occur in an honest and direct manner.[5]

> "The most important element identified by doctors, patients, and families in the provision of quality EOL care is being able to trust and have confidence in their doctors.

Finally, the value of having a physician with a kind and caring attitude should not be taken for granted. Informal, everyday conversations with patients and families help create some sense of normalcy and humaneness in an otherwise alien situation. Indeed, patients and families, aware of their vulnerability in such settings, strive to maintain good relationships with their doctors, often fearing that complaints may damage the quality of their care.[6] It is thus a top priority for doctors to promote and maintain a comforting environment where patients and family members will feel satisfied with the memorable interactions that occur at life's end.

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It is unfortunate that many junior physicians find dealing with EOL situations to be the most uncomfortable and unknown area in their medical practice.[7] Medical residents value learning from terminally ill patients; however, lack of training and supervision can contribute to emotional distress.[2] Barriers to comprehensive teaching of palliative care in Canadian undergraduate medical education include competition for time, resources, and lack of faculty expertise and leadership.[8] Students often feel that medical culture is not supportive of EOL education, perhaps because physicians feel unprepared to teach EOL care.[4] Although EOL-related instruction has increased over the past two decades, its implementation in undergraduate education tends to be fragmented, inconsistent, and rarely formally assessed.[7] The Educating Future Physicians in Palliative and End-of-Life Care (EFPPEC) Project is a unique initiative undertaken to increase and standardize EOL care instruction in Canadian medical education.[9] By 2008, this nationwide, interdisciplinary team had developed a complete undergraduate EOL curriculum; however, its effectiveness has not yet been formally assessed.

While we are not in the position to make specific recommendations, there are several examples of medical schools that have implemented successful EOL programs, resulting in increased confidence perceived by their students when caring for patients at the end-of-life.[10–12]

In New Zealand, medical undergraduate students are required to complete intermittent visits with a hospice patient and his/her caregivers over a period of at least one month.[10] These visits are followed with personal reflection regarding the student's emotional responses, thoughts on spirituality, and self-identified areas of improvement for providing care to terminally ill patients in the future. Many students find the program's emphasis on treating the whole person, instead of individual parts of the disease, to be both personally and professionally enriching.

In contrast, a program in New York has focused on teaching EOL care through multiple small group discussions and interactive lectures.[11] The curriculum is split into four main topics: pain alleviation, management of distressing symptoms, communicating bad news, and advanced directives. Students then practice effective communication through videotaped interviews with standardized patients. Co-facilitation of the discussions by physicians and ethicists provides an ideal team-teaching model to address decision-making, legal, and ethical issues related to EOL care. Students appreciated the opportunity to practice delivering difficult news to standardized patients before encountering potentially uncomfortable real-life situations.

> "Barriers to comprehensive teaching of palliative care in Canadian undergraduate medical education include competition for time, resources, and lack of faculty expertise and leadership.

The University of Alberta has received generally positive student feedback by integrating both of the aforementioned techniques into its instruction.[12] It splits palliative care teaching into six classroom sessions, involving both small group discussions and didactic lectures. These are followed by a hospice visit and post-visit discussion led by a palliative care expert. The classroom sessions provide an opportunity to clarify information and ask questions before attending the hospice session while the hospice visit provides reinforcement and integration of lecture content.

It is worthwhile noting that virtually any amount and type of educational intervention, especially those with multiple methods of instruction, can improve students' knowledge and competence when encountering EOL situations.[2,13] Our hope is that this commentary will provide areas of focus for medical schools to enhance the teaching of EOL care in medical curricula and that graduating students may be adequately prepared to meet the needs of terminally ill patients and their families in our aging population.

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How Low Can It Go? Trends, Benefits, and Risks of Expanding the Definition of Hypertension

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ABSTRACT

Hypertension is a strong risk factor for cardiovascular disease. However, the current criterion for hypertension in British Columbia was only recently established, and the international medical community has seen a push toward lowering blood pressure thresholds even closer toward normal levels. Is redefining this threshold truly beneficial in reducing the associated health risks? After examining the evolution of the definition of hypertension and weighing the major benefits and concerns, we support a definition based on a value where the benefits of lowering blood pressure threshold for hypertension have been proven to outweigh the harms.

KEYWORDS: *hypertension, prehypertension, cardiovascular disease, aging, trends*

INTRODUCTION

In 2009, an estimated 19 % of Canadians had hypertension or elevated blood pressure (BP).[1] Hypertension is strongly correlated with an increased risk of many adverse cardiovascular events such as myocardial infarction, stroke, and mortality.[2] Since aging is correlated with increased BP, and the number of seniors is expected to significantly increase over the next decade in BC, the anticipated increase in prevalence of hypertension poses a major healthcare concern.[3] Currently, in the 2008 BC guidelines for hypertension, the BP diagnostic threshold is 140/90 mmHg over three office visits.[2] This criterion, however, was only agreed upon within the last decade.

Guidelines for the treatment of hypertension have changed dramatically over time.[4] Results from clinical trials, epidemiological studies, and drug reviews have prompted its re-evaluation, usually toward lowering the blood pressure threshold deemed hypertensive. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure proposed a series of recommendations in 1977, setting a threshold of 160/95 mmHg and above for individualized drug treatment.[5] The next major re-evaluation in 1984, also supported by the World Health Organization and International Society for Hypertension,[6] lowered the threshold recommended for treatment to 140/90 mmHg based on epidemiological data linking BP to increased risks of mortality and morbidity.[7] Canada, however, conservatively continued even in 2002 to define hypertension as 160/100 mmHg out of concern that the recommendation changes would increase the number of anti-hypertensive drug prescriptions.[8] It was only in 2005 that the Canadian guidelines recommended therapy for those with 140/90 mmHg or above.[9] That same year, new American standards were proposed to expand the definition, arguing that other risk factors have been ignored.[10] This expansion may result in pre-hypertensive patients, between 120/80 and 139/89 mmHg, to also receive hypertension treatment. Whether this trend is beneficial for patients remains to be seen.

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EARLY TREATMENT AS PREVENTION?

The potential health risks of pre-hypertension may warrant early treatment, especially due to the high risk of developing hypertension and related complications.[11] Cardiovascular and cerebrovascular diseases have also been correlated with pre-hypertension; starting at 115 mmHg, an increase of 20 mmHg in systolic BP is associated with a two-fold increased risk of ischemic heart disease and stroke,[12] while for diastolic BP, every 5 mmHg increase starting at 70 mmHg is associated with a 20 % increase in coronary risk.[13] The Framingham Risk Assessment Chart also shows how increases in systolic BP above 120 mmHg translates to a higher risk of coronary heart disease within 10 years.[2] Taken together, these studies suggest that pre-hypertension, a risk factor for heart disease, should be reduced as close as possible to 120/80 mmHg.[11]

However, will treating for pre-hypertension—in effect lowering the BP threshold for hypertension—improve patients' health outcomes? After all, medical professionals are concerned about the health of their patients, and treating pre-hypertension when unnecessary is unethical as well as dangerous. For instance, if diabetics undergoing insulin treatment are also given anti-hypertensive beta-blockers, then they are at an increased risk of developing severe hypoglycemia.[15] Thus, if the BP goal for diabetics is lowered to below the current target of 130/80 mmHg,

> **“However, will treating for pre-hypertension—in effect lowering the BP threshold for hypertension—improve patients’ health outcomes?**

then a greater number of diabetics will be potentially harmed by anti-hypertensive drugs. As well, the top anti-hypertensive drug covered by Pharmacare, ramipril (Altace®),[16] has potential side effects; as an angiotensin-converting enzyme inhibitor, it may cause acute renal failure, hyperkalemia, dry cough, and angiodema.[17] Hence, unwarranted treatment of pre-hypertension may expose patients to unnecessary harms.

Even if the side effects were minimized, treating for pre-hypertension has not yielded the same benefits as has treating for hypertension. Authors of the Trial of Preventing Hypertension study suggested that treating pre-hypertension with angiotensin receptor blockers would prevent the progression of hypertension, implying that hypertension-related diseases were also prevented.[18] However, the study has been criticized for having inappropriate endpoint criteria and potentially overestimating the benefits of preventing hypertension using anti-hypertensive drugs. In a New England Journal of Medicine editorial, Schunkert highlighted that greater than 50 % of participants in both the control and treated groups in the study eventually developed hypertension.[19] Furthermore, the Cochrane intervention review on hypertension concluded that lowering the BP target below 140/90 mmHg does not reduce mortality or morbidity.[20] Even so, the Cochrane review was unable to find appropriate randomized controlled trials (RCTs) comparing systolic BP targets; only RCTs comparing diastolic BP thresholds were available for analysis.[20] Because systolic hypertension has a stronger association with cardiovascular diseases than diastolic hypertension, more studies may be necessary to confirm that lowering the systolic BP target below 140 mmHg does not benefit patient health outcomes.[21] Consequently, the benefits of lowering the BP minimum for hypertension are debatable.

Changing the definition of hypertension could have a large impact on epidemiological health and resource management.[22] Anti-hypertensive drugs are already one of the most frequently prescribed drugs in BC; for example, ramipril (Altace®) had the second highest number of Pharmacare beneficiaries in 2007 and 2008.[16] However, if pre-hypertensive Canadians, comprising 20.1 % of the population, are added to the 19 % of the population who are hypertensive, we may see a doubling of those prescribed anti-hypertensive drugs, which will greatly burden the cash-strapped healthcare system. Furthermore, the World Health Organization has been concerned with studies whose authors are associated with pharmaceutical companies.[23] It is troubling that those advocating for more prescription of anti-hypertensive drugs may also benefit from their usage. Thus, given the limited resources of our health care system, we should question whether prescribing these drugs to 40 % of the population is the most effective method of improving patients’ cardiovascular health.

CONCLUSION

We have explored the evolution of defining hypertension and examined the literature on pre-hypertension and hypertension to find potential arguments for and against lowering the threshold. Definitions of hypertension have tended towards lowering thresholds and there have been recent efforts to push this even lower. Arguments for lowering BP thresholds generally revolve around decreasing cardiovascular risks associated with pre-hypertension whereas counterarguments point to the lack of benefits of treating pre-hypertensive patients. We believe that decreasing the BP threshold for hypertension under 140/90 mmHg is not warranted unless randomized controlled trials show that doing so confers more benefit than harm to patients.

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Focal Nodular Hyperplasia: A Case Report of Rare Multiple Ruptures of a Common Liver Tumour in a Single Patient

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ABSTRACT

Focal nodular hyperplasia (FNH) is one of the three most common benign solid liver tumours along with hemangiomas and adenomas.[1] FNH is considered a vascular abnormality that usually follows an uneventful course after accidental discovery on CT or MRI for an unrelated medical problem and rarely requires any treatment.[1] These lesions are stable in nature with minimal risk of rupture and essentially no risk for malignant degeneration.[1] The general recommendations for an asymptomatic FNH are observation only, regardless of size of the mass.[1] However, the consequences of a ruptured liver mass can be very serious as abdominal bleeding may be catastrophic, so accurate diagnosis is essential.[1] Here we present the only known case of a patient with multiple FNH nodules and subsequent rupture of two of the lesions; the first treated with a left hepatectomy and the second with embolization. A discussion of the management of the ruptured tumours follows and highlights how little evidence is available for the treatment of multiple ruptures of FNH or for properly risk stratifying patients.

KEYWORDS: *focal nodular hyperplasia, ruptured tumor, liver resection and radiofrequency ablation*

INTRODUCTION

Benign liver tumours are predominantly found in women with the most common usually being categorized as one of the following: hemangioma, adenoma, or focal nodular hyperplasia (FNH).[1] Out of these three, adenomas are most notable for their risk of rupturing and malignant degeneration.[1] FNH is characterized by its benign course, and generally no treatment is recommended.[1] Hemangiomas follow a similar benign course, and again, observation only is recommended.[1] FNH is the second most common benign solid liver tumour, makes up 8 % of all primary hepatic tumours, and is present in up to 3 % of the general population.[1] However, spontaneous rupture and subsequent bleeding is very rare.[1]

The pathophysiology of FNH is not well understood although it is thought to be caused by polyclonal hyperplasia of liver cells as a result of locally enhanced blood flow due to vessel malformations.[2] Lesions that typically present are well-circumscribed with a central scar and are noted most often during X-ray computed tomography (CT) on the arterial phase contrast rather than venous, distinguishing FNH from adenoma.[2] It is important to use imaging to diagnose FNH so as not to miss a more serious diagnosis of a potential malignancy. Using magnetic resonance imaging (MRI) after gadolinium administration, the lesions are hyperintense but then become isointense on later images.[3] The MRI will also show the characteristic central scar of FNH more readily than CT and will often also demonstrate sulfur colloid imaging uptake by Kupffer cells, which does not have the sensitivity and specificity to confirm or refute FNH but is usually not seen in malignancy.[3,4] Unlike adenomas, FNH does not seem to increase in oral contraceptive users but can occur more often in older women.[5] Classically, these lesions remain stable in size, do not rupture, and do not have malignant potential.[5]

> “Prophylactic ablation, embolization, or surgical excision could be considered in high-risk patients.

CASE REPORT

Here we present a case report of a 37-year-old First Nations woman with multiple FNH lesions who first presented to the Emergency Department (ED) with right upper-quadrant abdominal pain and a vague history of back, flank, and abdominal pain of two months duration. Upon ultrasound, a 4 cm solid lesion was detected in

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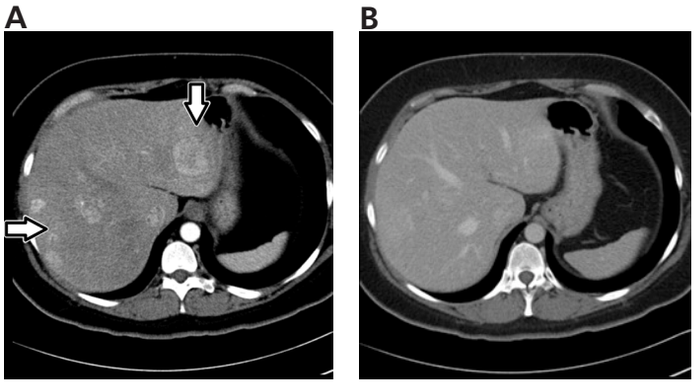

Figure 1. Biphasic CT scan showing typical dynamic phase imaging of an FNH. Arterial phase image (1A) demonstrates early arterial enhancement with portal phase image (1B) demonstrating portal venous washout.

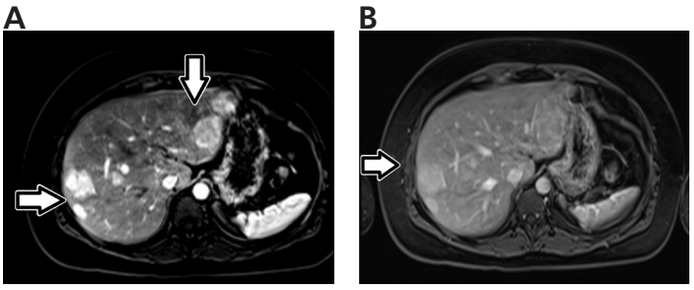

Figure 2. Contrast enhanced MRI also demonstrating similar features as CT scan with arterial enhancement (2A) and portal venous washout (2B).

the left lobe of the liver along with a smaller lesion in the same region. A triphasic CT was performed which showed multiple lesions in her liver seen only in the arterial phase with the largest lesion being 5 cm. The lesions were thought to be consistent with FNH, adenoma, or hepatocellular carcinoma.

This patient had no history of Hepatitis B or C infection or significant alcohol intake. Her past medical history was unremarkable except for a hospitalization for a Caesarean section and a previous laparoscopy for ovarian pain.

At one-month follow-up, CT scanning, MRI, and nuclear medicine imaging were done. The imaging was highly consistent with FNH including arterial phase hypervascularity, the presence of a central scar, and concordance with sulfur colloid uptake indicating the presence of Kupffer cells within the lesions. These features together are considered pathognomonic of FNH.[3] The largest nodule was in liver segment 7/8 and measured 4.9 cm X 3.5 cm. In segment two, another large nodule measuring 3.8 cm X 3.2 cm was present as well as several other smaller scattered lesions. See Figure 1 for a biphasic CT scan showing typical dynamic phase imaging of FNH. The arterial phase image (1A) demonstrates early arterial enhancement and the portal phase image (1B) demonstrates portal venous washout. See Figure 2 for a contrast-enhanced MRI that also demonstrates similar features as the CT scan with arterial enhancement (2A) and portal venous washout (2B).

Further laboratory work was unremarkable and negative for Hepatitis A Virus, Hepatitis B Surface Antigen, and antibodies to Hepatitis C Virus (anti-HCV). Alpha feto protein levels were also normal. Her pain was attributed to irritable bowel syndrome.

The patient continued to have right upper-quadrant pain for several more months when she presented with sudden increased abdominal pain. Imaging demonstrated evidence of hemoperitoneum and rupture of one of her liver masses. She was taken to the operating room on urgent basis where a left hepatectomy was performed. Pathology confirmed the diagnosis of FNH with a ruptured 7.5 cm nodule. Her postoperative course was uneventful. Specimens were sent to pathology with the results shown in Figure 3 and Figure 4, both demonstrating the classic pathology for FNH: a central scar and surrounding non-dysplastic hepatocytes. A subsequent abdominal sonogram was done that showed three new lesions in the right lobe of the liver with the rest of the exam unchanged.

At her follow-up appointment six months later, she was still complaining of intermittent aches and pains. Discussions ensued regarding the utility of prophylactic embolization or ablation of her remaining lesions. This was not recommended due to lack of evidence and follow-up imaging in six months was the recommended course of action.

The patient remained stable for another six months when she again presented to the ED for recurrence of right upper-quadrant

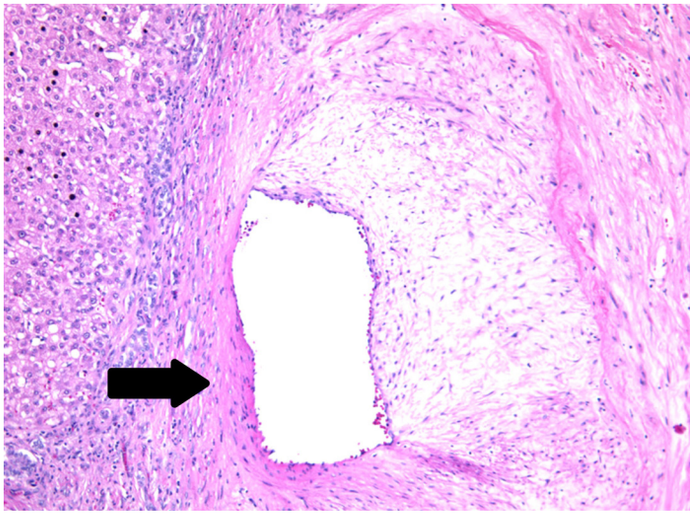

Figure 3. Central scar in the middle of the lesion. Note the vessel partly occluded by organized thrombus. Medium Power (X100) H&E stain.

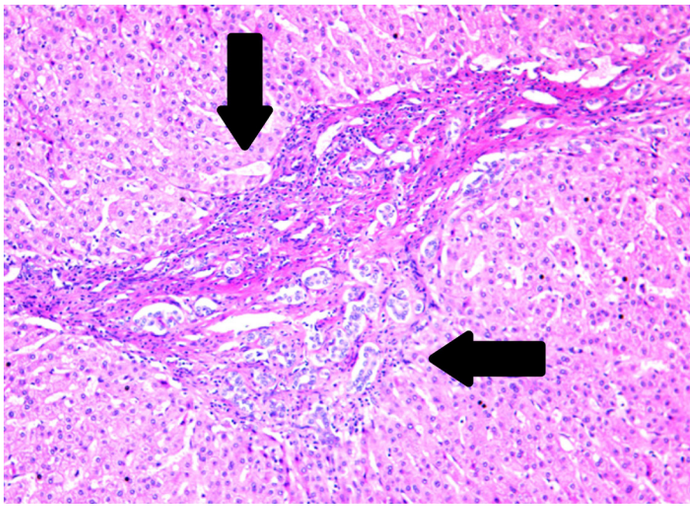

Figure 4. Scarred focus demonstrating bile ductular proliferation with surrounding non-dysplastic hepatocytes. Medium Power (X100) H&E stain.

pain and was investigated on suspicion of a second rupture of one of her smaller FNH lesions. After confirmation by imaging and core biopsy, the recurrent bleed was treated with embolization. Currently the patient is still experiencing ongoing stable non-specific abdominal pain. The plan is for her to undergo sequential ablations of her remaining lesions with repeat imaging.

DISCUSSION

FNH remains a largely asymptomatic disease that patients often only discover after vague abdominal symptoms or from imaging for another medical concern.[1] The current hypothesis is that FNH occurs from a vascular origin, which is supported by the presence of associated bile ducts, veins, and the hyperperfused area of parenchyma. In comparison, a liver cell adenoma has only hepatocytes and no associated structures such as bile ducts are seen.[6] FNH also has an association with hemangiomas, as do hepatic adenomas, but only FNH and hemangioma are associated with vasculature.[6,7]

Accurate diagnosis is important in FNH as it dictates the course of treatment. It is particularly important to distinguish the diagnosis of FNH from liver cell adenomas as larger liver cell adenomas (> 4 cm) are at increased risk for bleeding or malignant degeneration.[1,4] Fortunately, FNH lesions can be identified on imaging as they are well circumscribed with a central scar.[1] Confirmation can be made on contrast-enhanced MRI or a CT scan with MRI having the highest sensitivity and specificity (70 % and 98–100 %, respectively).[2,3,6] On MRI, an important differentiating factor of FNH from malignant hepatic tumors is that FNH often shows strong homogenous activity in the hepatic parenchyma due to the Kupffer cells phagocytosing the dye.[1,3] Malignant tumours will usually have no uptake at the focal defects.[1,3]

The unknown pathology of FNH grouped with its benign nature has resulted in a lack of research into the best treatment for FNH.[6] The accepted recommendations are for observation only. After a literature review, less than 10 cases of FNH ruptures have been reported and no cases of multiple ruptures were found. The rupture of any liver tumour, including FNH nodules, can lead to serious medical consequences, but the factors that increase the risk of rupture in a patient with an FNH are unknown. Routine imaging may be beneficial following discovery of larger or multiple lesions. Prophylactic ablation, embolization, or surgical excision could be considered in high-risk patients. The obvious question is, "What constitutes high-risk?" as no data exists to define this group of patients.

CONCLUSION

The consequences of a ruptured FNH nodule can be very serious for patients, especially those who may not have immediate access to tertiary centres if surgical intervention is needed. Patients that have a high risk of rupture may be considered for prophylactic hepatic resection, ablation, or embolization where appropriate. However, the benefits of these procedures must be weighed against the generally low incidence of ruptured nodules in patients with FNH, and the invasive nature of these treatments as preventative measures. Complications related to FNH resulting in ruptured nodules are rare. As a result, it is unclear as to which patients with FNH require more frequent follow-up versus those whose nodules will never rupture. Surveillance protocols for FNH patients are required so that risk factors for a rupture can be identified. The paucity of literature on this topic makes it difficult to provide specific recommendations that are evidence-based. Patients have to be individualized in their approach to therapy, risk factors, and potential benefits.

SOAP Note

Subjective
- 37-year-old woman presented with increasing vague abdominal pain and enlarging mass in the left lobe of the liver
- History of progressive, vague, chronic upper abdominal and back pain for 1 year, including a visit to the ER and a CT scan showing multiple FNH-like nodules
- Patient denies history of blood transfusions, tattoos, IV drug use, HIV, or significant alcohol intake
- No fevers, chills, or significant weight loss
- Presents again 6 months later for increasing right upper quadrant pain

Objective
- No palpable mass on examination, no palpable hepatomegaly
- AFP ranged from 1.9–2.4 ng/mL over the course of hospital stay (N < 11 ng/mL)
- Hepatitis A and B serology negative
- Carcinogenic Embryonic Antigen 0.8 µg/L (N 0–5 µg/L)
- CBC unremarkable with the exception of MCV 81 fL (N 82–100 fL)
- Liver function tests unremarkable
- Lipase 42 U/L (0–60 U/L)
- Hemoperitoneum
- Pathology results from first rupture indicate central scar in the middle of the lesion and a scarred focus demonstrating bile ductular proliferation with surrounding non-dysplastic hepatocytes
- Follow-up MRI 6 months after second rupture, MRI report showed little change to the numerous hepatic nodules consistent with focal nodular hyperplasia and a central area of necrosis/calcification

Assessment
- History, pathology, lab results, and imaging confirm FNH with multiple ruptures

Plan
- Stabilization of vitals (transfusion if required) and intervention
- Hepatic resection after first rupture, embolization after second rupture
- Continue to follow with imaging and prophylactic ablation of larger lesions to prevent further rupture

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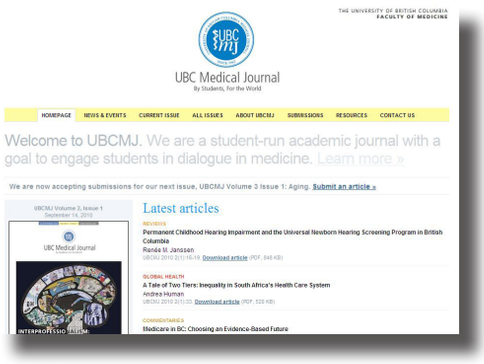

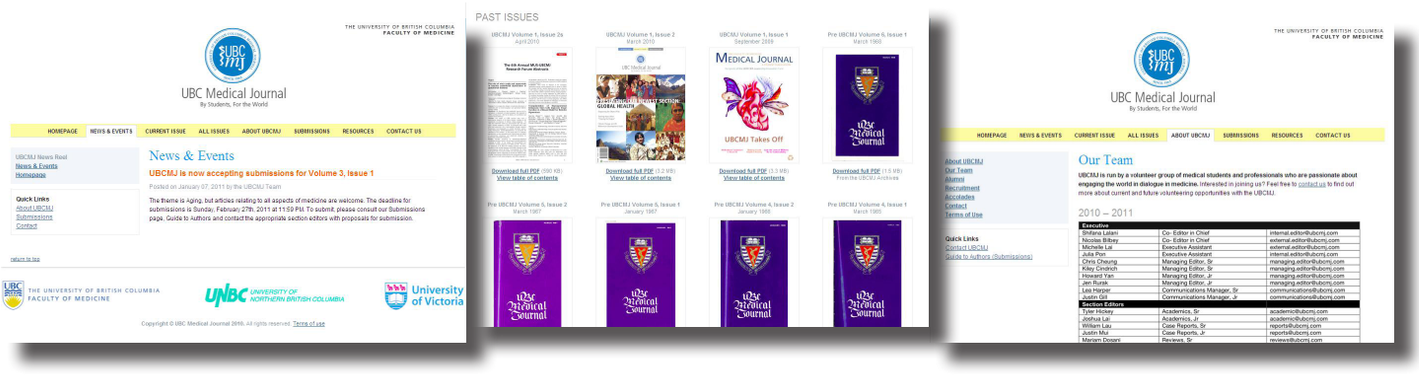

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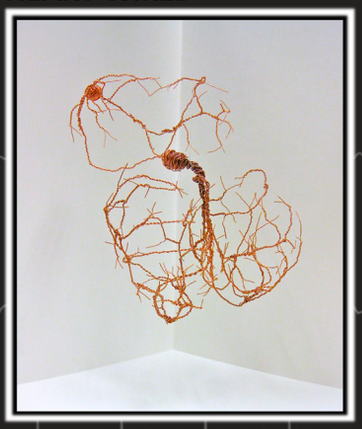

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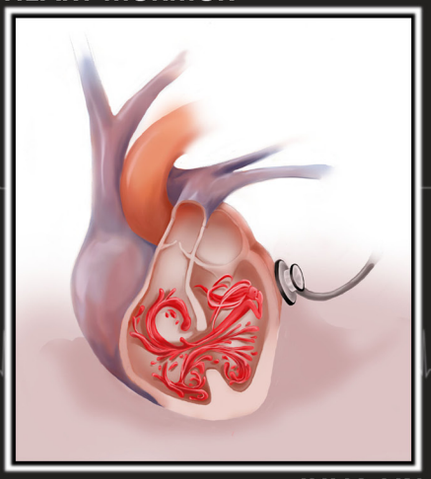

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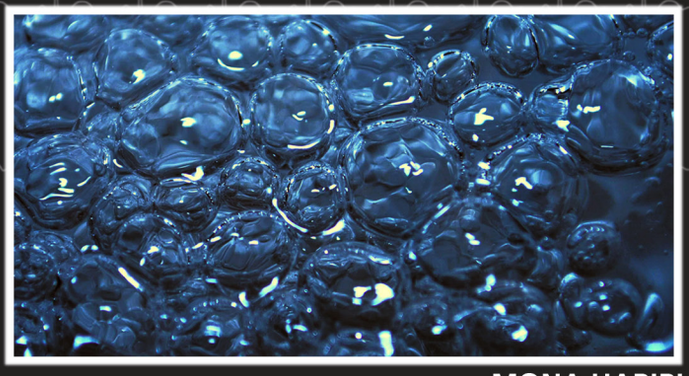

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