

# UTMJ

University of Toronto Medical Journal

## Maternal Care Practices and Perceptions of Birth Defects in Central India

## The Uterus and Female Illness

Western Uterine Medicine from the Classical Period to the Renaissance



*Also in this issue:*

Sudden Cardiac Death:  
Small Plaques, Big Problems

The Palliative Care Unit:  
Does room design matter?

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**Cover Artist: Heidi Richter, B.A.** Heidi received her undergraduate degree in biology and visual art from Minot State University in North Dakota where she did research on salamander osteology and development. She is currently in her second year as a graduate student in the Master in Biomedical Communications program in the Faculty of Medicine at the University of Toronto. Her research project is a Flash animation of the locomotion and growth stages of the dinosaur *Massospondylus carinatus*, a prosauropod that, similar to humans, walked on four legs as a hatchling and two as an adult.

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## Preface from the Editors

As the 2006-2007 academic year draws to an end, and another edition of the University of Toronto Medical Journal (UTMJ) comes to a close, we would like to take a moment to reflect on the year that was. This year, the Journal underwent a revitalization of its design and layout through an exciting collaboration with the talented students in the Biomedical Communications Program in our own Faculty of Medicine. Furthermore, we were fortunate enough to receive outstanding contributions from our peers in places as diverse as our own doorsteps in the Medical Sciences Building to the Neurology Unit at the University of Nigeria. Thanks to the outstanding effort of our junior and senior editorial teams, we were able to present to you, our readers, a myriad of fascinating and stimulating articles meant to ignite, or re-ignite, our collective passion for the medical sciences.

In this issue, we approach the topic of Women's Health from two decidedly different disciplines in the hopes of broadening our perspectives on the topic. In the International Health feature article, *Maternal Care Practices and Perceptions of Birth Defects in Central India*, Minhas and Hilliard explore the common beliefs about birth defects in the rural population of Madhya Pradesh, India. Meanwhile,

in the Historical Review feature article, *The Uterus and Female Illness: Western Medicine from the Classical Period to the Renaissance*, Lam delves into Western medicine's preoccupation with the uterus and the subsequent *hysteria* that ensues. Moreover, you will find an enlightening review of image-guided cardiovascular intervention by Toma *et al.* in the Technology Review feature article, as well as an informative Morning Report on sudden cardiac death by Yanagawa and Butany.

As always, we are grateful to our patrons for their continuing support and our wonderful editorial team for a job well done. It has been an honour to serve as the Editors-in-Chief of the UTMJ this year. We sincerely hope that you have enjoyed reading the Journal as much as we have enjoyed publishing it for you, our loyal readers.

With many thanks,

Janice Kwan and Justine Chan  
Editors-in-Chief

## News at a Glance

Marat Slessarev, M.Sc. (1T0), Faculty of Medicine, University of Toronto

### Opening Windows and Doors Reduces the Risk of Airborne Infections

(PLoS Med. 2007 Feb; 4(2): e68)

Results of a recent study from Lima, Peru suggest that the use of natural ventilation methods (i.e. opening windows and doors), as well as the architectural design of older hospital wards, which feature large windows and high ceilings, may be better at reducing the transmission of airborne infections than modern rooms with mechanical ventilation. The study compared different rooms, including tuberculosis wards and isolation rooms, in old-fashioned and modern hospitals. Surprisingly, opening windows and doors provided more than double the ventilation seen in the mechanically ventilated negative pressure isolation rooms. Moreover, the level of ventilation in the mechanically ventilated rooms was below the expected standard, possibly due to improper maintenance. Strategies that increase natural air-flow, such as natural ventilation and room design, may provide cost-effective alternatives to mechanical ventilation systems. This may be especially useful in less developed countries, where such systems may be expensive to install and properly maintain, or during periods when the isolation capacity of healthcare facilities are overwhelmed, for example, during an influenza pandemic.

### Smoking Addiction – Do We Finally Have a Solution?

(Science 2007 Jan; 315(5811):531-4)

Researchers from the Universities of Iowa and Southern California have identified the insula, a region of the brain implicated in conscious urges, as a potentially important mediator of smoking addiction. They showed that smokers who sustain damage to the insula are very likely to quit smoking easily and without relapse. Moreover, accounts of individual patients from the study suggest that the insula may play a role in the modulating the feeling that smoking is a bodily need and may therefore be involved in the persistent urge to smoke. It is interesting to speculate that drug therapies directed towards modulating insula function may one day solve the problem of smoking addiction.

### AIDS Prevention Delivered Another Blow

(Nature Med. 2007 Mar; 13(3): 230)

Phase 3 trials of the microbicide, Ushercell have been prematurely terminated in Africa and India because of paradoxical results showing that the therapy actually increases the rate of HIV infection. Ushercell is a vaginal gel that is intended to act as a contraceptive that is able to protect females from sexually transmitted HIV. Since earlier trials showed that Ushercell was both effective and safe, there is currently no official explanation for this trial failure.

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## The CD28/CTLA-4/B7 Pathway in Immunological Regulation: The Basis of Disease and the Promise of Therapy

Kaylyn Kit Man Wong, H.B.Sc. (0T9), Faculty of Medicine, University of Toronto

### Immunological Regulation and Disease

The immune system is essential in the protection of organisms against infectious foreign pathogens. It is orchestrated by a highly complex, yet harmoniously integrated ensemble of molecular and cellular players that appropriately mediate both innate and adaptive immune responses. Normally, a foreign agent initiates the immune response, which leads to a cascade of stimulatory molecular signals, resulting in the activation of many effector cell types that cooperate in their varied functions, ultimately culminating in the destruction of the foreign agent. At the same time, inhibitory signals are equally important in terminating immunological activity once the threatening infectious agent has been successfully eradicated. In fact, a sustained immune response may even damage host tissues. Moreover, the ability of the immune system to regulate itself plays a key role in self-tolerance. Thus, the immune system is constantly under tight regulation by the intricate interplay of stimulatory and inhibitory signals, which control the overall fine balance between immunological activation and suppression.<sup>1</sup>

Immunoregulatory pathways are critical for normal immune function. Indeed, much evidence has implicated the phenomenon of immunological dysregulation, whether due to excessive stimulation or inhibition, in the mechanisms of several disease processes. Notably, an overactive immune system directed against innocuous self antigens and environmental antigens is associated with autoimmunity<sup>1,2</sup> and allergic or hypersensitivity reactions,<sup>3</sup> respectively. Likewise, an easily stimulated immune system contributes to the etiology of some chronic inflammatory disorders.<sup>1,4</sup> On the other hand, attenuated immune function promotes susceptibility to infections, as is clearly observed in both inherited and acquired immunodeficient states.<sup>5-7</sup> Given the normal role of immune surveillance in the detection and destruction of host tumour cells, immunosuppression has also been recognized as one of the factors predisposing to tumorigenesis and cancer.<sup>8,9</sup> An understanding of the precise immune pathways and other regulatory mechanisms that, when disrupted, underlie these disease states will be critical in the development of more specific molecular-based therapies.

Immunoregulatory pathways are also instrumental in allograft rejection, the primary limitation of modern transplantation, which is caused by a normal host attack against foreign donor antigens.<sup>10</sup> An approach to preventing rejection without the adverse outcomes of long-term non-specific immunosuppression is still an elusive goal. Immunological manipulation to induce suppression in a donor antigen-specific manner will be more effective than the general immunosuppressive drugs that are currently the only available hope for transplant patients.

This article will review the current knowledge and per-

spectives on one important immunoregulatory pathway involving CD28, CTLA-4 and B7, the role of this pathway in the pathogenic mechanisms of several disease states, and its manipulation in existing and future therapeutic applications.

### The CD28/CTLA-4/B7 Regulatory Pathway

With the recognition of the central importance of immune regulation and the promise of immunomodulatory therapies, there has been great interest in deciphering the molecular details of these pathways, both stimulatory and inhibitory. Some of the best-studied mechanisms that are essential in the control of adaptive responses and T lymphocyte activation involve the following cell surface proteins: CD28, cytotoxic T lymphocyte-associated-4 (CTLA-4), and B7. The CD28/CTLA-4/B7 pathway modifies the stimulatory signals mediated by the T cell receptor (TCR), which drives clonal expansion and differentiation of T cells.<sup>1,11</sup>

The T cell-specific CD28 and CTLA-4 (also called CD152) are members of the CD28 family of co-receptors, which possess a single extracellular IgV domain, a transmembrane domain, and a cytoplasmic domain. CD28 is a co-stimulatory receptor that is constitutively expressed on the surface of T cells and positively regulates immune responses. In fact, co-stimulatory signaling via CD28, simultaneous with TCR signaling by antigens, is required for successful activation of naïve T cells. In contrast, the co-inhibitory receptor, CTLA-4, exhibits low basal level expression on naïve T cells and is upregulated shortly after T cell activation.<sup>11</sup> The negative regulatory effects of CTLA-4 inhibit TCR signaling, and ensure that T cell proliferation is self-limited over the course of an immune response.<sup>1</sup>

CD28 and CTLA-4 mediate their effects by binding to the ligands of the B7 family, namely B7.1 and B7.2. These cell surface immunoglobulins are homodimers that contain extracellular IgV and IgC domains, and are specifically expressed on antigen-presenting cells (APCs) in a regulatory manner. While both B7.1 and B7.2 can interact with either receptor, CTLA-4 binds to the B7 ligands with a 20-fold greater affinity than CD28.<sup>1,11</sup>

The immune regulatory functions of the CD28/CTLA-4/B7 pathway have been well established. Indeed, it is known that defects or dysregulation of these molecular components, in particular CTLA-4, contribute to certain diseases. Their therapeutic potential has also been studied in numerous pre-clinical and clinical trials.

### The CD28/CTLA-4/B7 Pathway in Autoimmunity

There exists a strong genetic component in the development of autoimmune diseases. Although human leukocyte antigen (HLA) genes explain a significant part of this genetic link, they do not account for all of it. In fact, it was con-

firmed that CTLA-4 is a susceptibility locus that confers a genetic predisposition to multiple common autoimmune diseases, including Type 1 diabetes mellitus;<sup>12,13</sup> the CTLA-4 +49 A/G polymorphism, for example, is preferentially associated with type 1 diabetes, especially those with an earlier onset of the disease.<sup>14</sup> Similarly, meta-analyses of association studies on the CTLA-4 +49 A/G polymorphism concluded that this allele is preferentially found in patients with rheumatoid arthritis<sup>15</sup> and systemic lupus erythematosus<sup>16</sup> in the Asian population. Since CTLA-4 signaling inhibits T cell activation, it is predicted that genetic mutations resulting in a reduction or loss of function or expression of CTLA-4, thus disabling the suppressive mechanism, would promote autoimmunity.

Further evidence supporting the relationship between CTLA-4 and autoimmune diseases came from the recent discovery of sCTLA-4, the soluble form of this receptor that is normally produced by alternative mRNA splicing in CD4 and CD8 T cells.<sup>17</sup> Interestingly, sCTLA-4 has B7 binding activity, and is found at increased serum baseline levels in several autoimmune diseases, including Graves' disease, myasthenia gravis, systemic lupus erythematosus and systemic sclerosis. Thus, sCTLA-4 may represent a new biomarker for autoimmune susceptibility. One hypothesis is that increased levels of sCTLA-4, by binding to B7 on APCs, can effectively interfere with CTLA-4:B7 co-inhibitory signaling.<sup>17</sup> The soluble forms of co-stimulatory molecules, including soluble CD28 (sCD28), have also been shown to exhibit higher levels in disease states. Particularly, a recent study demonstrated a direct correlation between sCTLA-4 and sCD28 plasma concentrations and the severity of acute asthma in children.<sup>18</sup>

Further clarification of the biological, diagnostic and prognostic relevance of these new biomarkers is needed.

### The CD28/CTLA-4/B7 Pathway in Cancer

The normal immune system functions in the control of tumorigenesis by recognizing and destroying cells displaying specific tumour antigens. These antigens, which are presented by host APCs to T cells, may be of several types, including mutated cellular proteins and oncogenic viral proteins produced by infected cells.<sup>1</sup> Immunological protection against tumorigenesis requires the responses of effector T cells specific for these tumour antigens. It is expected that this function of immune surveillance would be impaired in conditions of attenuated immune activity.

However, tumours can undergo genetic alterations and acquire the ability to evade immune surveillance. Some of the mechanisms leading to evasion depend on preventing or downregulating T cell activation. For example, certain tumours reduce their cell surface expression of MHC I, thus preventing antigen binding of the TCR and subsequent T cell activation.<sup>19</sup> Others evade tumour immunity with the production and release of immunosuppressive cytokines. This phenomenon has been extensively described in the case of TGF- $\beta$ , which effectively impairs inflammatory T cell responses and cell-mediated immunity.<sup>20</sup> Collectively, these observations confirm the importance of the level of T cell responses in determining susceptibility to cancer, and lead to the notion that the induction of T cell activation might be an option for anti-cancer therapy.

Although most tumour types that increase in incidence in

immunodeficient states are associated with viral infections (e.g. cervical carcinoma due to human papilloma virus infection),<sup>1</sup> there is also evidence that the dysregulation of CD28/CTLA-4/B7 signaling contributes to the pathogenesis of neoplasia. For instance, in patients with mycosis fungoides, a low-grade lymphoma of T cells in the skin, it was shown that CTLA-4 expression, particularly in cases of progressive disease, is more easily stimulated and increased transcriptionally and translationally in peripheral blood mononuclear cells, when compared to healthy controls.<sup>21</sup> Furthermore, in breast cancer, a specific CTLA-4 promoter haplotype is preferentially associated with earlier stages of the disease and higher estrogen receptor expression, while certain promoter polymorphisms (e.g. -1661 A/A) are prognostically predictive of less lymph node involvement. This suggests that these CTLA-4 promoter variants contribute to the progression of breast cancer.<sup>22</sup>

Therefore, an imbalance in the CD28/CTLA-4/B7 pathway is one possible oncogenic mechanism. Moreover, immune-based strategies to treat cancer might be beneficial and would depend on the ability to enhance or facilitate the activation of T cell responses, such as by modulation of the CD28/CTLA-4/B7 signaling pathway. In other words, by increasing co-stimulatory CD28 signals, or decreasing co-inhibitory CTLA-4 signals, it may be possible to boost the natural host immune responses in tumour surveillance.

### The CD28/CTLA-4/B7 Pathway in Transplant Rejection

The rejection of allogeneic grafts is the primary challenge in organ transplantation. In this setting, foreign donor antigens (both major and minor histocompatibility complexes) are recognized by a normally functioning host immune system; they are presented by host APCs that subsequently trigger the activation of effector T cell responses.<sup>1</sup>

Previous studies have reported a link between the CD28/CTLA-4/B7 regulatory pathway and transplantation outcomes. For example, there was an observed association between the level of CD28 and CTLA-4 expression by T cells and the degree of alloreactivity to the donor organ in renal transplant recipients. In patients who showed stable graft function and survival, freshly isolated CD3<sup>+</sup>CD4<sup>+</sup>CTLA-4<sup>+</sup> cells expressed higher surface and intracellular CTLA-4 than in patients who developed chronic allograft nephropathy. Furthermore, after *ex vivo* stimulation, CD4<sup>+</sup> T cells from the transplant-stable group displayed a greater potential for the expression of surface CTLA-4 and the downregulation of CD28 than the rejecting group.<sup>23</sup>

Further support for CTLA-4 as a susceptibility gene in transplant rejection has come from genetic studies, which have established a linkage between certain allelic variants of the CTLA-4 gene and acute rejection of renal allografts. In one report, the -318 C/T polymorphism in the promoter region was found to occur two times more frequently in recipients with a stable graft than in those who acutely rejected.<sup>24</sup>

These and similar findings confirm the idea that the level of regulation by the CD28/CTLA-4/B7 pathway in part determines T cell activity and, consequently, the clinical course and outcome of transplantation.

### CTLA-4 and Natural Regulatory T (nT<sub>reg</sub>) Cells

In the last few years, much research in the field of immune regulation has revolved around natural regulatory (nT<sub>reg</sub>) cells. Characterized by their distinctive CD25<sup>+</sup>CD4<sup>+</sup> surface profile and their expression of the specific transcriptional factor Foxp3, which is needed for their development and function, nT<sub>reg</sub> cells are a population of T cells specialized to suppress the activity of effector T cells and to maintain self-tolerance. Indeed, a deficiency in the number or function of nT<sub>reg</sub> cells leads to autoimmune and other inflammatory diseases in both animals and humans.<sup>4</sup> The discovery of nT<sub>reg</sub> cells has revolutionized the prevailing paradigms of immune modulation and carries tremendous therapeutic promise in a variety of clinical settings.<sup>25</sup> Due to their central role in immune regulation, nT<sub>reg</sub> cells may eventually be exploited in immune-based strategies to induce tolerance to donor grafts in transplantation, suppress excessive immune responses in allergic disease, and enhance immune function in microbial and tumour immunity.<sup>4</sup> At present, much is still unknown regarding the mechanisms by which nT<sub>reg</sub> cells carry out their immunosuppressive function. However, a clear understanding of these mechanisms is a prerequisite for the use of nT<sub>reg</sub> cells in therapy, and is currently the subject of intense research.

It was previously thought that CTLA-4 was exclusively expressed on activated T cells and functioned in *cis* to inhibit their proliferation. Interestingly, it was reported that CTLA-4 is constitutively expressed on the surface of nTreg cells and, by acting in *trans* to inhibit T cell responses, may be a mechanism of nT<sub>reg</sub>-mediated suppression.<sup>26–28</sup> Additionally, CTLA-4 may play a role in the development of nT<sub>reg</sub> cells, as one study found that homozygosity for the CT60 A allele, a single nucleotide polymorphism in the 3' untranslated region of the CTLA-4 gene, correlates with a greater nTreg frequency (i.e. a 30–40% increase) in the peripheral blood of normal individuals.<sup>25</sup> CD28 is similarly important for nT<sub>reg</sub> function.<sup>29,30</sup>

The close link between CTLA-4 and nT<sub>reg</sub> cells provides evidence that, in addition to inhibiting immune responses directly at the surface of effector T cells, CTLA-4 can indirectly suppress the immune system via nTreg cells, either as part of the immunosuppressive mechanisms of nT<sub>reg</sub> cells or as a component that promotes their development. In fact, these findings may illustrate a general principle in immune regulation: there is cooperation and intersection between various immunomodulatory pathways, such that any particular regulatory player in the immune system can participate in multiple mechanisms.

### Targeting the CD28/CTLA-4/B7 Pathway: Immunomodulatory Therapy

The well-established role of CD28/CTLA-4/B7 in immune regulation and many disease processes has made this pathway an attractive therapeutic target. Depending on the nature of the dysregulation underlying a certain pathological state, this pathway may be manipulated using molecular agonists or antagonists to enhance or suppress its activity, in order to prevent, treat, or slow the progression of disease. For instance, there is emerging interest in the exploitation of CTLA-4 and other co-inhibitory molecules as a strategy to induce peripheral T cell tolerance to  $\beta$ -pancreatic cells to pre-

vent the onset of type 1 diabetes in susceptible individuals.<sup>32</sup> At the same time, enhancing these co-inhibitory signals, whether in isolation or synergistically with other therapeutic approaches, may be helpful in preventing islet allograft rejection in type 1 diabetes patients.

Many of the immune-based therapeutic approaches previously studied are aimed at inhibiting T cell activation by targeting CTLA-4. One of the best-studied strategies involves CTLA4Ig, a recombinant fusion protein of the extracellular domain of CTLA-4 and the Fc region of IgG1.<sup>11</sup> Soluble CTLA4Ig inhibits immune responses by binding to B7.1 and B7.2, thereby blocking their interactions with CD28 and preventing T cell activation, as demonstrated in several preclinical models of autoimmune and inflammatory disorders.<sup>33</sup> The effectiveness of CTLA4Ig has also been investigated in clinical trials. Therapeutic CTLA4Ig was first tested in patients with psoriasis vulgaris, in which some benefit was observed.<sup>34</sup> More recently, in a clinical trial for rheumatoid arthritis, CTLA4Ig was administered in a combination therapy with methotrexate (MTX). The results showed promise: after six months, those who received CTLA4Tg/MTX had greater improvement in clinical outcomes than those on MTX alone.<sup>35</sup>

However, an important limitation in the application of CTLA4Ig is the possibility of an unanticipated exacerbation of autoimmune diseases, as previously seen in some preclinical trials.<sup>33,36</sup> This may be due to several reasons. By binding to B7 ligands, CTLA4Ig might lead to unintended interference in CTLA-4:B7 interactions and hence, downregulating inhibitory effects. Alternatively, increased autoimmunity in the presence of CTLA4Ig might result from a blockage of CD28 signaling on nT<sub>reg</sub> cells that functionally depend on such co-stimulation, in the process impairing their immunosuppressive properties.<sup>11</sup> Therefore, the exact outcomes of CTLA4Ig immunotherapy are likely affected by multiple host and disease factors, such that its therapeutic effects are difficult to predict.

In the domain of cancer therapy, where the goal is to enhance immune surveillance and responses to tumour antigens, monoclonal antibodies to CTLA-4 have been tried, especially in conjunction with anti-cancer vaccines.<sup>37</sup> These blocking antibodies may prevent CTLA-4:B7 interactions, thus allowing for greater T cell activation and immune function. Indeed, anti-CTLA-4 was shown to promote tumour rejection and tumour immunity in murine tumour models.<sup>38</sup> Similarly, anti-CTLA-4 effectively suppressed the growth of lung tumour xenografts in severe combined immunodeficient mice, in a way that is dependent on T and natural killer (NK) cells.<sup>39</sup> The success of cancer immunotherapy requires the ability to induce T cell responses against antigens exclusive to tumour cells, while leaving normal host cells intact. This therapeutic approach may be most effective when there is a concurrent induction of a positive immune response against the tumour itself, which may be achieved with an anti-tumour vaccine.<sup>37</sup> In clinical trials involving stage IV melanoma patients, anti-human CTLA-4 was used in conjunction with a gp100 melanoma-associated antigen peptide vaccine. Although there was evidence of tumour regression, the benefits were outweighed by unwanted manifestations of autoimmune and inflammatory responses in the skin, liver

and gastrointestinal tract.<sup>40,41</sup> Therefore, a complication in the use of anti-CTLA-4 to remove co-inhibitory signaling is that it poses a real risk of autoimmune disease in non-cancerous organs.

The manipulation of the CD28/CTLA-4/B7 regulatory pathway in the context of preventing allograft rejection has mainly been studied in rodent models. CTLA4Ig was shown to prolong the survival of cardiac allografts in mice, possibly by the induction of tolerance to donor antigens.<sup>10</sup> However, more research is warranted before its application in humans.

Due to limitations in the use of CTLA4Ig or anti-CTLA-4 (i.e. the possibility of enhanced autoimmunity), there is a benefit to exploring and targeting alternate ways of manipulating the CD28/CTLA-4/B7 signaling pathway. These alternative immunomodulatory strategies have not been as well-studied. Nevertheless, the use of anti-B7 antibodies that may block CD28:B7 or CTLA-4:B7 interactions has shown favourable results in primate models of transplantation, as well as in rodent models of inflammatory and autoimmune diseases.<sup>11,33</sup> Moreover, in the presence of human carcinoembryonic antigen (CEA), a B7-1/Ig fusion protein was found to promote *in vitro* anti-CEA responses and tumour rejection.<sup>42</sup> On the other hand, the study of CD28 in immunotherapy is still at an early stage, partly due to the difficulty in identifying anti-CD28 blocking antibodies that do not cross-link CD28<sup>11</sup> or affect the essential co-stimulatory CD28 pathway in nTreg cells.<sup>29,30</sup> Clearly, further research is needed before new immunomodulatory therapies targeting the CD28/CTLA-4/B7 pathway will emerge.

### The Future of Immunotherapy

Great promise lies in understanding the precise mechanistic details of immunoregulation, such as those of the CD28/CTLA-4/B7 pathway. This knowledge will not only yield insights into the pathogenic basis of disease states, but most importantly, it will also offer the hope of effective therapies for a variety of disorders caused by an immune system gone awry. However, the complexity of the intersecting networks and cascades of the immune system makes it a real possibility that any immunological manipulation could bring about unanticipated adverse effects. Thus, the success of immune-based treatments will ultimately depend on a clear understanding of the immunoregulatory signaling pathways involved and their myriad downstream effects, as well as the specific mechanisms of action of therapeutic agents.

### References

- Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology: the Immune System in Health and Disease 5th edition. New York: Garland Publishing; 2001.
- O'Garra A, Steinman L, Gijbels K. CD4+ T-cell subsets in autoimmunity. *Curr Opin Immunol.* 1997 Dec;9(6):872-83.
- Romagnani S. The role of lymphocytes in allergic disease. *Journal of Allergy & Clinical Immunology.* 2000 Mar;105(3):399-408.
- Sakaguchi S. Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. *Nat Immunol.* 2005 Apr;6(4):345-52.
- Fischer A, Cavazzana-Calvo M, De Saint Basile G, DeVillartay JP, Di Santo JP, Hivroz C, Rieux-Laucat F, Le Deist F. Naturally occurring primary deficiencies of the immune system. *Annu Rev Immunol.* 1997;15:1593-124.
- Hill AV. The immunogenetics of human infectious diseases. *Annu Rev Immunol.* 1998;16:593-617.
- Badley AD, Dockrell D, Simpson M, Schut R, Lynch DH, Leibson P, Paya CV. Macrophage-dependent apoptosis of CD4+ T lymphocytes from HIV-infected individuals is mediated by FasL and tumor necrosis factor. *J Exp Med.* 1997 Jan 6;185(1):55-64.
- Jaffee EM, Pardoll DM. Murine tumor antigens: is it worth the search? *Curr Opin Immunol.* 1996 Oct;8(5):622-7.
- Robbins PF, Kawakami Y. Human tumor antigens recognized by T cells. *Curr Opin Immunol.* 1996 Oct;8(5):628-36.
- Lechler RI, Sykes M, Thomson AW, Turka LA. Organ transplantation—how much of the promise has been realized? *Nat Med.* 2005 Jun;11(6):605-13.
- Carreno BM, Carter LL, Collins M. Therapeutic opportunities in the B7/CD28 family of ligands and receptors. *Current Opinion in Pharmacology.* 2005 Aug;5(4):424-30.
- Holmberg D, Cilio CM, Lundholm M, Motta V. CTLA-4 (CD152) and its involvement in autoimmune disease. *Autoimmunity.* 2005 May;38(3):225-33.
- Pearce SHS, Merriman TR. Genetic progress towards the molecular basis of autoimmunity. *Trends in Molecular Medicine.* 2006 Feb;12(2):90-8.
- Mojtahedi Z, Omrani GR, Doroudchi M, Ghaderi A. CTLA-4 +49 A/G polymorphism is associated with predisposition to type 1 diabetes in Iranians. *Diabetes Research and Clinical Practice.* 2005 May;68(2):111-6.
- Han S, Li Y, Mao Y, Xie Y. Meta-analysis of the association of CTLA-4 exon-1 +49A/G polymorphism with rheumatoid arthritis. *Hum Genet.* 2005 Oct;118(1):123-32.
- Lee YH, Harley JB, Nath SK. CTLA-4 polymorphisms and systemic lupus erythematosus (SLE): a meta-analysis. *Hum Genet.* 2005 Apr;116(5):361-7.
- Pawlak E, Kochanowska IE, Frydecka I, Kielbinski M, Potoczek S, Bilinska M. The soluble CTLA-4 receptor: a new marker in autoimmune diseases. *Arch Immunol Ther Exp (Warsz).* 2005 Jul-Aug;53(4):336-41.
- Ip WK, Wong CK, Leung TF, Lam CWK. Plasma concentrations of soluble CTLA-4, CD28, CD80 and CD86 costimulatory molecules reflect disease severity of acute asthma in children. *Pediatr Pulmonol.* 2006 Jul;41(7):674-82.
- Bodmer WF, Browning MJ, Krausa P, Rowan A, Bicknell DC, Bodmer JG. Tumor escape from immune response by variation in HLA expression and other mechanisms. *Ann NY Acad Sci.* 1993 Aug 12;690:42-9.
- Tada T, Ohzeki S, Utsumi K, Takiuchi H, Muramatsu M, Li XF, Shimizu J, Fujiwara H, Hamaoka T. Transforming growth factor-beta-induced inhibition of T cell function. Susceptibility difference in T cells of various phenotypes and functions and its relevance to immunosuppression in the tumor-bearing state. *J Immunol.* 1991;146:1077-82.
- Wong HK, Wilson AJ, Gibson HM, Hafner MS, Hedgcock CJ, Berger CL, Edelson RL, Lim HW. Increased expression of CTLA-4 in malignant T-cells from patients with mycosis fungoides—cutaneous T cell lymphoma. *J Invest Dermatol.* 2006 Jan;126(1):212-9.
- Erfani N, Razmkhah M, Talei AR, Pezeshki AM, Doroudchi M, Monabati A, Ghaderi A. Cytotoxic T lymphocyte antigen-4 promoter variants in breast cancer. *Cancer Genetics & Cytogenetics.* 2006 Mar;165(2):114-20.
- Kosmaczewska A, Magott-Procelewska M, Frydecka I, Ciszak L, Bocko D, Szeblich A, Kusnierczyk P, Patrzalek D, Szyber P. CD40L, CD28, and CTLA-4 expression on CD4+ T cells in kidney graft recipients: A relationship with post-transplantation clinical course. *Transplant Immunology.* 2006 Jun;16(1):32-40.
- Wisniewski A, Kusztal M, Magott-Procelewska M, Klinger M, Jasek M, Luszczyk W, Nowak I, Kosmaczewska A, Ciszak L, Frydecka I, Gorski A, Kusnierczyk P. Possible association of cytotoxic T-lymphocyte antigen 4 gene promoter single nucleotide polymorphism with acute rejection of allogeneic kidney transplant. *Transplant Proc.* 2006 Jan-Feb;38(1):56-8.
- Atabani SF, Thio CL, Divanovic S, Trompette A, Belkaid Y, Thomas DL, Karp CL. Association of CTLA4 polymorphism with regulatory T cell frequency. *Eur J Immunol.* 2005 Jul;35(7):2157-62.
- Manzotti CN, Tipping H, Perry LC, Mead KI, Blair PJ, Zheng Y, Sansom DM. Inhibition of human T cell proliferation by CTLA-4 utilizes CD80 and requires CD25+ regulatory T cells. *Eur J Immunol.* 2002 Oct;32(10):2888-96.
- Read S, Malmstrom V, Powrie F. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+)CD4(+) regulatory cells that control intestinal inflammation. *J Exp Med.* 2000 Jul 17;192(2):295-302.
- Takahashi S, Kataoka H, Hara S, Yokosuka T, Takase K, Yamasaki S, Kobayashi W, Saito Y, Saito T. *In vivo* overexpression of CTLA-4 suppresses lymphoproliferative diseases and thymic negative selection. *Eur J Immunol.* 2005 Feb;35(2):399-407.
- Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S. Immunological self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte antigen 4. *J Exp Med.* 2003 Jul 14;196(5):593-602.

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- phocyte-associated antigen 4. *J Exp Med.* 2000 Jul 17;192(2):303-10.
30. Tang Q, Henriksen KJ, Boden EK, Tooley AJ, Ye J, Subudhi SK, Zheng XX, Strom TB, Bluestone JA. Cutting edge: CD28 controls peripheral homeostasis of CD4+CD25+ regulatory T cells. *Journal of Immunology.* 2003 Oct 1;171(7):3348-52.
  31. Salomon B, Lenschow DJ, Rhee L, Ashourian N, Singh B, Sharpe A, Bluestone JA. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. *Immunity.* 2000 Apr;12(4):431-40.
  32. Truong W, Hancock WW, Anderson CC, Merani S, Shapiro AM. Coinhibitory T-cell signaling in islet allograft rejection and tolerance. *Cell Transplant.* 2006;15(2):105-19.
  33. Salomon B, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. *Annu Rev Immunol.* 2001;19:225-52.
  34. Abrams JR, Leibold MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, Menter A, Lowe NJ, Krueger G, Brown MJ, Weiner RS, Birkhofer MJ, Warner GL, Berry KK, Linsley PS, Krueger JG, Ochs HD, Kelley SL, Kang S. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest.* 1999 May;103(9):1243-52.
  35. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, Russell A, Dougados M, Emery P, Nuamah IF, Williams GR, Becker JC, Hagerty DT, Moreland LW. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med.* 2003 Nov 13;349(20):1907-15.
  36. Racke MK, Scott DE, Quigley L, Gray GS, Abe R, June CH, Perrin PJ. Distinct roles for B7-1 (CD-80) and B7-2 (CD-86) in the initiation of experimental allergic encephalomyelitis. *J Clin Invest.* 1995 Nov;96(5):2195-203.
  37. Waldmann TA. Effective cancer therapy through immunomodulation. *Annu Rev Med.* 2006;57:65-81.
  38. Korman A, Yellin M, Keler T. Tumor Immunotherapy: preclinical and clinical activity of anti-CTLA-4 antibodies. *Curr Opin Investig Drugs.* 2005 Jun;6(6):582-91.
  39. Sabel MS, Hess SD, Egilmez NK, Conway TF, Chen F, Bankert RB. CTLA-4 blockade augments human T lymphocyte-mediated suppression of lung tumor xenografts in SCID mice. *Cancer Immunol Immunother.* 2005 Oct;54(10):944-52.
  40. Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, Restifo NP, Haworth LR, Seipp CA, Frazier LJ, Morton KE, Mavroukakis SA, Duray PH, Steinberg SM, Allison JP, Davis TA, Rosenberg SA. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proc Natl Acad Sci USA.* 2003 Jul 8;100(14):8372-7.
  41. Sanderson K, Scotland R, Lee P, Liu D, Groshen S, Snively J, Sian S, Nichol G, Davis T, Keler T, Yellin M, Weber J. Autoimmunity in a phase I trial of a fully human anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody with multiple melanoma peptides and Montanide ISA 51 for patients with resected stages III and IV melanoma. *see comment. Journal of Clinical Oncology.* 2005 Feb 1;23(4):741-50.
  42. Chakrabarti R, Zhou ZF, Chang Y, Prud'homme GJ. A mutant B7-1/Ig fusion protein that selectively binds to CTLA-4 ameliorates anti-tumor DNA vaccination and counters regulatory T cell activity. *Vaccine.* 2005 Aug 31;23(37):4553-64.

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## A Tale of Two Remedies: All-Trans Retinoic Acid and Arsenic Trioxide in the Treatment of Acute Promyelocytic Leukemia

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### Background

Leukemia, the predominant cancer causing mortality in young people, is a group of hematological malignancies characterized by clonal expansion of hematopoietic cells, uncontrolled proliferation, decreased apoptosis, and blocked differentiation.<sup>1</sup> One particular subtype, acute promyelocytic leukemia (APL), is characterized by the arrest of myeloid progenitor cell maturation at the promyelocytic stage caused by chromosomal translocations involving the retinoic acid receptor alpha (RAR $\alpha$ ) locus on chromosome 17 and the promyelocytic leukemia (PML) gene, on chromosome 15, t(15;17)(q22;q21).<sup>2</sup> Once considered the most fatal form of acute leukemia, APL is largely unresponsive to conventional chemotherapy.<sup>3</sup> However, as a result of work done over the past 30 years, much of which was conducted at the Shanghai Institute of Hematology (SIH), APL is now potentially curable. Presently, the standard treatment is all-trans retinoic acid (ATRA) with chemotherapy for newly-diagnosed cases and arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) for patients who have relapsed. Recent studies suggest that an improved clinical outcome may be achieved when both compounds are used in combination,<sup>4,6</sup> illustrating the enormous potential of using synergistic molecular targeted therapies and the importance of modulating multiple signaling networks in the development of novel treatments for cancer.

### The Molecular Pathogenesis of APL

The pathogenesis of APL was a mystery until the late 1970's, when cytogenetic analysis revealed that a balanced reciprocal translocation between the long arms of chromosomes 15 and 17 was present in 98% of APL patient samples.<sup>7</sup> In 1990, the defect was localized to the fusion of the RAR $\alpha$  gene to a previously unknown locus, the *promyelocytic leukemia* (PML) gene, resulting in the transcription and translation of a novel fusion protein, PML-RAR $\alpha$ .<sup>2</sup>

The RARs are nuclear receptors which function as ligand-inducible transcription factors regulating many different physiological processes, including hematopoiesis.<sup>8</sup> In normal hematopoietic cells, RAR $\alpha$  forms a heterocomplex with RXR and binds to the RA response element (RARE) located on the regulatory region of target genes. Upon binding to its ligand, retinoic acid, the RAR/RXR heterodimer activates gene expression by dissociating with a histone deacetylase corepressor complex and recruiting a coactivator complex with histone acetylase activity. In APL, the PML-RAR $\alpha$  fusion protein interferes with wild-type RAR $\alpha$  function, by sequestering RXR and other cofactors and binding to RARE as a homodimer.<sup>9</sup> This complex recruits corepressors with histone deacetylase activity to inhibit gene transcription, and is insensitive to physiological concentrations of retinoids, thereby causing differentiation arrest.<sup>10</sup> PML-RAR $\alpha$  also inhibits the

normal functions of PML, a tumour suppressor with an essential role in controlling apoptosis.<sup>11</sup>

### All-Trans Retinoic Acid

While the interaction between PML-RAR $\alpha$  and corepressors is insensitive to physiological retinoid (10<sup>-8</sup> M) levels, pharmacological treatment at high concentrations (10<sup>-6</sup> M) was shown to cause release of corepressors and recruitment of a coactivator complex, thereby causing transactivation of gene expression through the fusion protein.<sup>10</sup> This process is potentiated by the ability of ATRA to induce cAMP, leading to PKA activation and subsequent phosphorylation of PML-RAR $\alpha$ , modulating its interaction with corepressors and coactivators.<sup>12</sup> Importantly, ATRA also induces PML-RAR $\alpha$  and wild-type RAR $\alpha$  catabolism via the ubiquitin/proteasome system, since ligand binding to the AF-2 domain of RAR $\alpha$  promotes recruitment of the 19S proteasome complex.<sup>13</sup> The coupling of ligand-induced transcription factor activation with degradation serves as a negative feedback mechanism used by many nuclear receptors to prevent over-expression of target genes.

As early as 1980, the SIH had already begun screening compounds to identify inducers of differentiation for APL. Achieving promising results *in vitro* with ATRA, a drug commonly used to treat acne, the team proceeded to conduct a clinical trial. All 24 APL patients treated with ATRA achieved complete remission (CR), demonstrating for the first time the effective use of differentiation therapy in treating cancer.<sup>14</sup> Subsequently, large randomized controlled studies evaluating the efficacy of ATRA plus chemotherapy were conducted around the world.<sup>15-18</sup> While results varied among studies depending on the specific treatment regimen and patient selection criteria, CR rates were generally greater than 90%. Nevertheless, 20-30% of patients eventually relapsed within 4 years, likely due to the selection of resistant clones. Salvage therapy for these patients entailed high doses of cytotoxic chemotherapy, which was often toxic though rarely curative.<sup>3</sup>

### Arsenic Trioxide

For centuries, arsenic has been used in Chinese medicine as "a poison used to treat poison," and is documented in Li Shizhen's *Compendium of Materia Medica* in the late 16th century. In recent years, As<sub>2</sub>O<sub>3</sub> has re-emerged as a treatment for relapsed APL, as a result of clinical studies first reported by the SIH in 1997.<sup>19</sup> With As<sub>2</sub>O<sub>3</sub> monotherapy, over 85% of relapsed patients achieved CR.<sup>19,21</sup> However, the disease relapsed again within 2 years in around 40% of patients.<sup>20,21</sup>

The precise mechanisms of As<sub>2</sub>O<sub>3</sub> have not been fully worked out, but are likely to involve multiple targets. As with ATRA, As<sub>2</sub>O<sub>3</sub> was shown to induce degradation of the

PML/RAR $\alpha$  fusion protein; however, it targets the PML moiety, rather than RAR $\alpha$ .<sup>22</sup> Specifically, As<sub>2</sub>O<sub>3</sub> induces sumolation of the K160 residue of PML-RAR $\alpha$  or PML, targeting the protein for degradation via the 11S proteasome of the immunoproteasome system.<sup>23</sup>

Interestingly, As<sub>2</sub>O<sub>3</sub> exerts a dose-dependent dual effect on APL cells *in vitro*.<sup>24</sup> At lower concentrations (0.1–0.5 x 10<sup>-6</sup> M), partial differentiation is induced, while at higher concentrations (0.5–2.0 x 10<sup>-6</sup> M), the cells undergo apoptosis. Unlike ATRA, As<sub>2</sub>O<sub>3</sub> is unable to induce granulocyte maturation on its own. However, *in vitro* experiments have shown that subsequent addition of cAMP pushes the cells to terminal differentiation.<sup>25</sup> The current explanation is that As<sub>2</sub>O<sub>3</sub> primes the cells for differentiation, yet, unlike ATRA, does not modulate all the necessary genes at a high enough level required for terminal differentiation. This is supported by a systems-based study showing that a smaller number of genes are affected with lower fold-change by As<sub>2</sub>O<sub>3</sub> (487) relative to ATRA (1113) treatment, though many of these genes overlap.<sup>5</sup> With regard to apoptosis induction, multiple mechanisms are activated by As<sub>2</sub>O<sub>3</sub> including, but not limited to, downregulation of Bcl-2<sup>22</sup> and Akt<sup>26</sup>, and activation of caspases,<sup>26</sup> likely in response to reactive oxygen species generation.

### East Meets West: Combined ATRA/As<sub>2</sub>O<sub>3</sub> Therapy

Though still controversial, a number of recent molecular and clinical studies support the joint use of ATRA and As<sub>2</sub>O<sub>3</sub> in the treatment of newly-diagnosed APL. Since ATRA and As<sub>2</sub>O<sub>3</sub> modulate/degrade the PML-RAR oncoprotein through distinct pathways (ubiquitin/proteasome system and immunoproteasome, respectively), it is reasonable that the combination of these agents may have synergistic effects and thereby improve clinical outcome. Cross-talk between signaling pathways activated by ATRA and As<sub>2</sub>O<sub>3</sub> may also be important. For example, the upregulation of cAMP by ATRA may act on APL cells that have been primed for differentiation by As<sub>2</sub>O<sub>3</sub>. From a systems analysis of the transcriptome and proteome in APL cells treated with ATRA, As<sub>2</sub>O<sub>3</sub>, or both combined, a complex map was generated of the signaling networks that were affected.<sup>5</sup> Synergistic/additive effects were observed in genes involved in the proteasome system, cell proliferation, and interestingly, some genes commonly involved in other human malignancies. Importantly, this study revealed that multiple signaling pathways need to be targeted for effective treatment.

In 2004, the SIH reported the first clinical trial comparing ATRA, As<sub>2</sub>O<sub>3</sub>, or ATRA+ As<sub>2</sub>O<sub>3</sub> therapy on 64 newly-diagnosed APL patients.<sup>4</sup> Although CR rates were high in all groups (greater than 90%), length of time needed to achieve CR was shortest and PML-RAR $\alpha$  transcripts decreased most significantly in the combination group. Importantly, after a median follow-up at 18 months, none of the 20 cases in the combination group, but 7 out of 37 cases in the monotherapy groups relapsed. Similar results were reported in 2006 from the M.D. Anderson Cancer Centre, with all 36 patients alive in the first CR remaining PCR-negative for PML-RAR $\alpha$  at a median follow-up of 16 months, with 9 patients followed for 24 months.<sup>6</sup> However, all patients were given the combination treatment in this study, so its efficacy could not be compared to that of either agent alone.

### Conclusions

The past three decades have yielded a large body of work establishing the effectiveness of ATRA and As<sub>2</sub>O<sub>3</sub> in the treatment of APL. Studies are still ongoing to elucidate the precise mechanisms of action of these therapeutic agents. Recently, an argument has been raised for the use of ATRA and As<sub>2</sub>O<sub>3</sub> in combination for the treatment of newly diagnosed patients, though further studies need to be conducted before definitive recommendations can be made. Nevertheless, it has become apparent that multiple signaling pathways need to be modulated in order to effectively fight the disease. A better understanding of the complex signaling networks involved in APL will provide insight into key steps that should be targeted and lead to the development of more efficacious therapies.

### References

1. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer* 2006;107:2099-107.
2. de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. *Nature* 1990;347:558-61.
3. Lengfelder E, Saussele S, Weisser A, Buchner T, Hehlmann R. Treatment concepts of acute promyelocytic leukemia. *Crit Rev Oncol Hematol* 2005;56:261-74. Epub 2005 Oct 19.
4. Shen ZX, Shi ZZ, Fang J, Gu BW, Li JM, Zhu YM, et al. All-trans retinoic acid/As<sub>2</sub>O<sub>3</sub> combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci U S A* 2004;101:5328-35. Epub 2004 Mar 24.
5. Zheng PZ, Wang KK, Zhang QY, Huang QH, Du YZ, Zhang QH, et al. Systems analysis of transcriptome and proteome in retinoic acid/arsenic trioxide-induced cell differentiation/apoptosis of promyelocytic leukemia. *Proc Natl Acad Sci U S A* 2005;102:7653-8. Epub 2005 May 13.
6. Estey E, Garcia-Manero G, Ferrajoli A, Faderl S, Verstovsek S, Jones D, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood* 2006;107:3469-73. Epub 2005 Dec 22.
7. Rowley JD, Golomb HM, Dougherty C. 15/17 translocation, a consistent chromosomal change in acute promyelocytic leukaemia. *Lancet* 1977;1:549-50.
8. Melnick A, Licht JD. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood* 1999;93:3167-215.
9. Jansen JH, Mahfoudi A, Rambaud S, Lavau C, Wahli W, Dejean A. Multimeric complexes of the PML-retinoic acid receptor alpha fusion protein in acute promyelocytic leukemia cells and interference with retinoid and peroxisome-proliferator signaling pathways. *Proc Natl Acad Sci U S A* 1995;92:7401-5.
10. Guidez F, Ivins S, Zhu J, Soderstrom M, Waxman S, Zelent A. Reduced retinoic acid-sensitivities of nuclear receptor corepressor binding to PML and PLZF-RARalpha underlie molecular pathogenesis and treatment of acute promyelocytic leukemia. *Blood* 1998;91:2634-42.
11. Rego EM, Wang ZG, Peruzzi D, He LZ, Cordon-Cardo C, Pandolfi PP. Role of promyelocytic leukemia (PML) protein in tumor suppression. *J Exp Med* 2001;193:521-29.
12. Zhao Q, Tao J, Zhu Q, Jia PM, Dou AX, Li X, et al. Rapid induction of cAMP/PKA pathway during retinoic acid-induced acute promyelocytic leukemia cell differentiation. *Leukemia* 2004;18:285-92.
13. Zhu J, Gianni M, Kopf E, Honore N, Chelbi-Alix M, Koken M, et al. Retinoic acid induces proteasome-dependent degradation of retinoic acid receptor alpha (RARalpha) and oncogenic RARalpha fusion proteins. *Proc Natl Acad Sci U S A* 1999;96:14807-12.
14. Huang ME, Ye YC, Chen SR, Chai JR, Lu JX, Zhou L, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood* 1988;72:567-72.
15. de Botton S, Coiteux V, Chevret S, Rayon C, Vilmer E, Sanz M, et al. Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004;22:1404-12.
16. Ades L, Chevret S, De Botton S, Thomas X, Dombret H, Beve B, et al. Outcome of acute promyelocytic leukemia treated with all trans retinoic

- acid and chemotherapy in elderly patients: the European group experience. *Leukemia* 2005;19:230-3.
17. Sanz MA, Martin G, Gonzalez M, Leon A, Rayon C, Rivas C, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood* 2004;103:1237-43. Epub 2003 Oct 23.
  18. Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood* 1999;94:1192-200.
  19. Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, et al. Use of arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. *Blood* 1997;89:3354-60.
  20. Niu C, Yan H, Yu T, Sun HP, Liu JX, Li XS, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999;94:3315-24.
  21. Lazo G, Kantarjian H, Estey E, Thomas D, O'Brien S, Cortes J. Use of arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) in the treatment of patients with acute promyelocytic leukemia: the M. D. Anderson experience. *Cancer* 2003;97:2218-24.
  22. Chen GQ, Zhu J, Shi XG, Ni JH, Zhong HJ, Si GY, et al. In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) in the treatment of acute promyelocytic leukemia: As<sub>2</sub>O<sub>3</sub> induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. *Blood* 1996;88:1052-61.
  23. Lallemand-Breitenbach V, Zhu J, Puvion F, Koken M, Honore N, Doubekovsky A, et al. Role of promyelocytic leukemia (PML) sumolation in nuclear body formation, 11S proteasome recruitment, and As<sub>2</sub>O<sub>3</sub>-induced PML or PML/retinoic acid receptor alpha degradation. *J Exp Med* 2001;193:1361-71.
  24. Chen GQ, Shi XG, Tang W, Xiong SM, Zhu J, Cai X, et al. Use of arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) in the treatment of acute promyelocytic leukemia (APL): I. As<sub>2</sub>O<sub>3</sub> exerts dose-dependent dual effects on APL cells. *Blood* 1997;89:3345-53.
  25. Zhu Q, Zhang JW, Zhu HQ, Shen YL, Flexor M, Jia PM, et al. Synergic effects of arsenic trioxide and cAMP during acute promyelocytic leukemia cell maturation subtends a novel signaling cross-talk. *Blood* 2002;99:1014-22.
  26. Choi YJ, Park JW, Suh SI, Mun KC, Bae JH, Song DK, et al. Arsenic trioxide-induced apoptosis in U937 cells involve generation of reactive oxygen species and inhibition of Akt. *Int J Oncol* 2002;21:603-10.



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## Trial and Error in HIV Microbicide Research

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### Background

**M**icrobicides are applied topically to mucosal surfaces to prevent transmission of viruses and bacteria. Many of these gels and creams are in development for prophylaxis against HIV and other sexually transmitted infections. Microbicides have attracted significant attention in the last few years from activists, media, and funding agencies, such as the Bill and Melinda Gates Foundation, as a method of putting HIV prevention directly into the hands of women. Multiple first-generation microbicides are currently in clinical trials around the world.

Recently, failures of several large-scale clinical trials have shed doubt on microbicide research and have raised questions on how this research is being conducted. In January 2007, the research organization, CONRAD announced the halt of Phase III trials for cellulose sulfate (Ushercell) in South Africa, Benin, Uganda, and India. Preliminary results indicated that cellulose sulfate, which was being tested for HIV prevention in women, could lead to increased risk of HIV infection. Family Health International's Phase III trial of cellulose sulfate in Nigeria was therefore also stopped as a precautionary measure based on the CONRAD trial results.<sup>1</sup>

The CONRAD trial was the third major Phase III microbicide trial to fail as of March 2007. Despite these failures, there are compelling reasons supporting why this research needs to continue.

### Support for Microbicide Research

Firstly, while condoms are still the most effective method of STD prevention when used consistently and correctly, surveys have shown that in sub-Saharan Africa, less than 7% of women used a condom during their last sexual contact with their primary partner – whether their male partner was monogamous or not. Less than 50% of women used a condom with their last casual sexual partner.<sup>2</sup> Negotiating the use of a condom is difficult for many women due to cultural norms, gender power imbalance, and economic dependence.<sup>3</sup> Unlike condom use, however, the application of a topical microbicide gel may allow women to protect themselves when they have no control over condom use in their relationships. The introduction of microbicides will therefore have a substantial impact on HIV transmission.

Secondly, renewed excitement in the field, increased funding, and multiple research group interest has meant that most pharmaceutical companies have likely pushed the first products in their pipelines towards large clinical trials, as opposed to their best, and perhaps more efficacious products. The microbicides that have currently been tested

in Phase III trials are all “first generation” products that work by making the vagina a more hostile environment to HIV. These products – which include cellulose sulfate, and the spermicide, nonoxynol-9 – have either failed or led to higher infection rates. However, microbicides that are currently in their early stages of development show more promise. These newer products contain actual antivirals that directly target HIV, such as two candidates containing non-nucleoside reverse transcriptase inhibitors, which will likely be in Phase III trials by 2009.<sup>4</sup> Therefore, it is premature to reject research into microbicides in general.

### Difficulties with Microbicide Research

Despite important reasons for continuing research, multiple failed clinical trials have led to a loss of public confidence, which may lead to reduced support and funding for microbicide research. Furthermore, recruitment of volunteers for trials may become more difficult if people believe that the product will not work or that it may harm their health.<sup>5</sup> Public confidence in HIV microbicide research is particularly important since the ethics of HIV research in developing countries is increasingly being called into question due to concerns about high prevalence of HIV, and difficulties surrounding informed consent in the context of lower education levels and language barriers.<sup>6</sup>

### Improvements to Research

Recent failures also suggest that research resources are not being used effectively. For instance, two of the failed major Phase III trials were testing products with the same active ingredient (cellulose sulfate).<sup>1</sup> Large-scale clinical trials, while necessary, are expensive and time consuming. In order to make useful progress in microbicide research, a more coordinated approach may be necessary to put the most promising candidates into clinical trials, and not just the fastest candidates. Testing a diverse product range, as opposed to variations of similar products from different companies may also help to identify the most effective compounds faster. In addition, more communication between research groups and the involvement of an impartial body may be helpful in making decisions and prioritizing drug testing.<sup>4</sup>

### Conclusion

In sub-Saharan Africa, there are 1.5-times more HIV-positive women than men. The prevalence of HIV in women rises to 3-times more than men in young adults between the ages of 15 and 24. Furthermore, young women are more biologically susceptible to HIV infection.<sup>7</sup> Since women are

often not in control of condom use, microbicides will provide an important method of HIV prevention for a particularly vulnerable population. While there have been setbacks in recent microbicide trials, this research should not be abandoned. New therapeutics that directly target the virus provide hope; however, a more integrated approach to clinical trials by the pharmaceutical research community will also be required to move the field forward. Nevertheless, it is important to remember that in addition to development of a female-controlled HIV prevention strategy, addressing the social and economic inequalities that take power away from women is also critical for slowing the rate of HIV transmission in women.

### References

1. Larkin A. Phase III Trials of Cellulose Sulfate Microbicide for HIV Prevention Closed [monograph on the Internet]. Arlington: CONRAD; 2007 [cited 2007 January 31]. Available from: <http://www.conrad.org/press/phaseIIItrials.htm>
2. Foss AM, Watts CH, Vickerman P, Heise L. Condoms and prevention of HIV. *BMJ*. 2004 Jul 24;329(7459):185-6.
3. Luke N. Age and economic asymmetries in the sexual relationships of adolescent girls in sub-Saharan Africa. *Stud Fam Plann*. 2003 Jun;34(2):67-86.
4. Check E. Scientists rethink approach to HIV gels. *Nature*. 2007 Mar 1;446(7131):12.
5. Editorial: Trial and Failure. *Nature*. 2007 March 1;446(7131):1.
6. Ramjee G, Morar NS, Alary M, Mukenge-Tshibaka L, Vuylsteke B, Ettiegne-Traore V, Chandeying V, Karim SA, Van Damme L, COL 1492 study group. Challenges in the conduct of vaginal microbicide effectiveness trials in the developing world. *AIDS*. 2000 Nov 10;14(16):2553-7.
7. UNAIDS. Facing the Future Together: Report of the Secretary General's Task Force on Women, Girls and HIV/AIDS in Southern Africa. 2004 July.



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## Redeeming the SARS Tragedy

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### Introduction

The Severe Acute Respiratory Syndrome (SARS) crisis was a global tragedy that serves to highlight the evolving risk of pandemics in our increasingly globalized world. In total, over 8,000 cases of the novel coronavirus were identified worldwide, resulting in almost 800 deaths;<sup>1</sup> 375 of the cases and 44 of the deaths were in Canada, by far the most severely affected of the western countries.<sup>2</sup> Estimates indicate that the economic cost to Toronto, in 2003 alone, was over 1 billion dollars.<sup>3</sup> Nine major conventions were cancelled and 12,000 jobs were lost. It took two years for the city's economy to return to pre-2003 levels.<sup>3</sup> Moreover, these statistics fail to capture the consequences of a paralyzed healthcare system, damage to Toronto's reputation, inconvenience to and lost productivity of the 30,000 people quarantined, and most importantly, the disastrous impact on the families of the 330 infected and the 44 who died – 72% of whom were infected at healthcare facilities and 45% of whom were health care workers.<sup>2</sup> The release of the SARS Commission's final report this January reminds us there were many systemic failures that served to prolong and exacerbate the tragedy. In honour of those who died and to prevent future outbreaks, it is our responsibility to identify and learn from these failures.

### Canada's First Exposure to SARS - in 2 cities

Within the span of 3 hours on March 7, 2003, two undiagnosed SARS patients, both originating from the same hotel in Hong Kong, each presented to overcrowded emergency rooms in Vancouver and Toronto.<sup>2</sup> The patient in Vancouver was admitted to a private room with respiratory precautions within 25 minutes of arrival, transferred to a negative-pressure isolation room two hours later, and then into the ICU with full respiratory precautions 14 hours later.<sup>4</sup> He did not transmit the disease to anyone; among himself, his wife, and two other people who acquired the virus in Hong Kong and returned to Vancouver, only one transmission occurred and there were no fatalities.

In contrast, the Toronto patient spent 16 hours in general observation in the emergency room, and was not placed in airborne isolation until another five hours had passed. Droplet and contact precautions were not instituted until days later, and by the time the World Health Organization issued the global SARS alert, four generations of spread had occurred, which resulted in 14 new cases among the patient's family and healthcare contacts.<sup>2</sup> The disastrous consequences that followed over the next 14 weeks were highlighted in the introduction.

### Were the different responses to the initial patient presentation and accompanying outcomes due to chance alone?

British Columbia had been preparing for a possible pandemic beginning as early as 1999 by setting up a pandemic influenza advisory committee to develop a plan with clearly defined roles and responsibilities.<sup>2</sup> The British Columbia Centre for Disease Control (BCCDC) was set up along with a province-wide communication system to send out communicable disease alerts to all hospital facilities, an infection control auditing system for all hospital facilities every few months, and an empowered workplace watchdog (WorkSafeBC) with communication links to infection control.<sup>2</sup> In early 2003, these systems had been monitoring the unexplained atypical pneumonia in China and the re-emergence of influenza A H5N1 in Hong Kong and were preparing for possible outbreaks: four alert bulletins had been sent out, preparations to protect healthcare professionals had been made, and inspections ensuring compliance were being implemented.<sup>2</sup> Vancouver General's emergency room had recently been audited by infection control and the front line staff was well informed of the possibility of unexplained fevers and respiratory ailments in patients returning from Asia.<sup>2</sup> They were instructed to take the utmost precautionary measures, including barrier precautions for all acute-onset respiratory infections.<sup>2</sup>

In contrast, Ontario had no pandemic plan. It had a fragmented disease control infrastructure and no province-wide communication system.<sup>2</sup> There was little collaboration between the Ministry of Health and front line workers, and the Ministry of Labour and worker safety experts were "largely sidelined."<sup>2</sup> Public health staff had been slowly depleted through the 1990's, and the Ministry had shut down laboratory facilities and laid off air sampling technicians.<sup>2</sup> Health facility inspectors were not performing infectious disease audits.<sup>2</sup> No warning was sent out to healthcare workers in the months preceding the outbreak and when disease spread, there was mass confusion over proper safety protocols, worker rights, who was in charge, and how to properly communicate to the front line.<sup>2</sup> Hospital inspections related to the SARS crisis were not instituted until June 2003, which was months after the initial outbreak.<sup>2</sup>

The independent SARS commission, established by the Ontario government and headed by Mr. Justice Archie Campbell, released its final report on January, 2007. Mr. Justice Campbell concludes:

"[Ontario's] public health and emergency infrastructures were in a sorry state of decay, starved for resources by governments of all three political parties. The health system's capacity to protect its workers was in a state of neglect: what little existed was

badly malnourished. There was no system in place to prevent SARS or to stop it in its tracks."<sup>2</sup>

### Precautionary Principle

The SARS Commission report highlights the systemic failures that were exposed during the SARS outbreak and states that:

"...if the Commission has one single take-home message, it is the precautionary principle that safety comes first, that reasonable efforts to reduce risk need not await scientific proof."<sup>2</sup>

The controversy over the use of N95 masks illustrates the importance of the precautionary principle. Despite there being no irrefutable evidence at the time that SARS – or influenza, for that matter – was spread by airborne transmission, British Columbia had mandated the use of N95 masks before the outbreak, and had properly trained and fit tested healthcare workers to ensure full protection. British Columbia's policy was to start at the highest precautionary level, and then deescalate as more details emerged.<sup>2</sup> In contrast, Ontario senior hospital officials contested the efficacy of the masks, and even denied there was a safety law that required the masks to be fit tested (a law dating back to 1993). A survey by the Ontario Nurses' Association found that "almost two-thirds [of nurses] felt their health and safety had been compromised during the SARS outbreak."<sup>2</sup>

### Learning From the Past

The SARS crisis exposed failures that had also manifested in other investigations, such as the Krever Inquiry into tainted blood and the O'Connor Inquiry into tainted water.<sup>2</sup> Mr. Justice Krever had emphasized the importance of the precautionary principle back in 1997 – some provinces evidently learned more from the past than others.<sup>2</sup> Even more alarming is that not more than two months after the initial Ontario outbreak, another Ontario outbreak occurred of similar magnitude. Again, the spread was mostly in the healthcare workplace, the place that should be most optimally prepared to identify and fend off infectious diseases. Now, not two months, but rather four years later, will we remember the lessons from SARS?

### References

1. Epidemic and Pandemic Alert and Response (EPR) [homepage on the Internet]. Switzerland: World Health Organization; c2007 [updated 2003 Dec 31; cited 2007 Mar 13]. Available from: [http://www.who.int/csr/sars/country/table2004\\_04\\_21/en/index.html](http://www.who.int/csr/sars/country/table2004_04_21/en/index.html).
2. Campbell JA. The SARS Commission Final Report. Spring of Fear. Toronto: The SARS Commission, 2007 [serial on the Internet]. 2007 Jan [cited 2007 Mar 13]. Available from: <http://www.sarscommission.ca/report/index.html>.
3. Matthews G. The public/private response to sudden disease outbreak [monograph on the Internet]. Atlanta: CDC Foundation; 2005 [cited 2007 Mar 13]. Available from: <http://www.cdcfoundation.org/sitefiles/TorontoReport.pdf>.
4. Skowronski DM, Petric M, Daly P, Parker RA, Bryce E, Doyle PW, et al. Coordinated response to SARS, Vancouver, Canada. Emerg Infect Dis [serial on the Internet]. 2006 Jan [cited 2007 Mar 13]. Available from: <http://www.cdc.gov/ncidod/EID/vol12no01/05-0327.htm>.

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# The Financial Barriers that Discourage Students from Entering Primary-Care Practice

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Pursuing a career in medicine is an extremely costly process. On average, medical doctors undergo 13.4 years of post-secondary education and training before they are licensed to practice, which means that medical students and residents are required to secure financial resources over this long period of time in order to adequately finance their education and living expenses. Recent surveys and studies have shown that financial issues are now a critical factor that influence which specialties students choose. The burden of student loans has caused an increasing preference towards higher paying specialties over lower remunerated programs, such as family medicine.<sup>1</sup>

### Cost of Tuition as a Deterrent

Since the 1997 deregulation of medical tuition in Ontario, there has been a steady increase in the cost of medical education.<sup>2</sup> A report in the *Canadian Medical Association Journal* has described this trend being a “nightmare for many medical students.”<sup>3</sup> Tuition at the University of Toronto has increased from \$3118 in 1995/1996 to \$17,000 in 2006/2007.<sup>4</sup> Even more disheartening is the fact that tuition is often not the only cost, as textbooks and living expenses add to the financial burden. Over the course of four years, the average undergraduate medical student is likely to spend approximately \$125,000 in tuition, academic, and living expenses,<sup>5</sup> and will have incurred an average debt of \$158,728 upon graduation.<sup>6</sup> This hefty sum adds additional stress to an already stressful education program. It has been proposed that rising tuition may be contributing to the shortage of primary-care physicians in Canada. The number of medical students that selected family medicine as their first career choice fell from 44% in 1992 to 25% in 2003.<sup>7</sup>

To fully understand the impact of rising tuition, it is helpful to examine the issue from a medical student’s perspective. The median age for medical graduates upon completion of their residency training is much older than the majority of university graduates.<sup>8</sup> With an increased duration of training combined with the fact that 59% of residents have family responsibilities, the result is a higher debt load compared to university graduates from other programs.<sup>6</sup>

Currently, 93% of residents report having a commercial debt, such as a line of credit, with a median amount of \$135,000.<sup>6</sup> The 2004 National Physician Survey showed that the amount of debt a medical resident incurs is inversely proportional to their family income. Taking these figures into account, the cost to service one’s debt in 10 years would be approximately \$24,000/year. Since first-year residents in Ontario currently earn \$46,017, this means that they will take

home less than one-third of their salary after deductions, such as debt repayment, training fees, association fees, medical insurances, travel expenses and examination fees.<sup>9</sup>

Furthermore, financial assistance for medical students may not be adequate to meet their needs. Only a small fraction of medical students are provided with grants and scholarships towards their education. The Ontario Student Assistance Program (OSAP) provides students with a maximum of \$13,000 in loans. According to the University of Toronto’s estimate of total annual tuition and living expenses (\$35,520), OSAP’s contribution to a student’s funding is only 37% (assuming that the student will receive the maximum loan for which they are eligible). In addition, the Millennium Scholarships provide only minimal benefit to most medical students, since most provincial governments use the scholarship to reduce the provincial contribution to the loan maximum.

The implications of the debt load are clearly demonstrated in the 2004 National Physician Survey. On average, specialists earn at least 20% more than general practitioners, and an increasing number of higher-end specialties earn more than double the primary-care physicians’ income.<sup>10,11</sup> As a result, over a quarter (28%) of residents agree that debt load has affected their choice of specialty by encouraging a preference towards higher paying specialties over programs, such as family medicine, which have a much lower earning potential.<sup>6</sup> Over half (53%) of the residents indicated that the anticipated debt load will strongly influence their future practice location.<sup>6,12</sup> With a continuous rise in tuition and in debt load, it will be interesting to see whether increasing debt loads will lead to increasing preferences towards high-paying specialties. The shortage of primary-care physicians, especially in the rural communities, continues to be a major national concern. It is conceivable that the continuous rise in tuition will only exacerbate this already precarious situation.

### Recommendations

In addressing the problem of rising tuition, the Canadian government must take an active leadership role in providing more support and funding for higher education. Thus far, the Ontario Medical Student Association (OMSA) and the Canadian Federation of Medical Students (CFMS) have taken proactive roles in organizing provincial and national lobby days that address the issue of increasing tuition. Such initiatives have called on the government to extend a medical student’s interest-free status and to defer student loan repayment until the completion of residency training. Additionally, they have advocated for the modification of the student loan

assessment policy. It is time for the government to appreciate the significant role that finances play in a medical student's decision to pursue a career in primary care.

**Reference**

1. Rosenthal, MP, Diamond, JJ, Rabinowitz, LC, Bauer, RL, Jones, GW, Kears, RB, et al. Influence of Income, Hours Worked, and Loan Repayment on Medical Students' Decision to Pursue a Primary Care Career. *Journal of the American Medical Association*, March 1994;271(12):914-7.
2. Kwong, JC, Dhalla, IA, Streiner, DL, Baddour, RE, Waddell, AE, Johnson, IL. Effects of Rising Tuition Fees on Medical Class Composition and Financial Outlook. *Canadian Medical Association Journal*, 2002;166(8):1023-8.
3. Sibbald, B. Rising Tuition Fees a Nightmare of Many Medical Students. *Canadian Medical Association Journal*, 1998;159:553.
4. Dhalla, IA, Kwong, JC, Streiner, DL, Baddour, RE, Waddell, AE, Johnson, IL. Characteristics of First-year Students in Canadian Medical Schools. *Canadian Medical Association Journal*, 2002;166(8):1029-35.
5. Budgeting Guide for Medical Students: 1999-2000. University of Western Ontario, Faculty of Medicine, Admissions/Student and Equity Affairs, 1999.
6. Canadian Institute for Health Information. Analytical Bulletin: 2004 National Physician Survey. Response Rates and Comparability of Physician Demographic Distributions with those of Physician Population. Ottawa, 2005.
7. Wright, B, Scott, I, Woloschuk, W, Brenneis, F. Career Choice of New Medical Students at Three Canadian Universities: Family Medicine versus Specialty Medicine. *Canadian Medical Association Journal*, June 2004;170(13):1920-4.
8. Allen, M, Vaillancourt, C. Class of 2000: Profile of Post-Secondary Graduates and Student Debt. Statistics Canada Catalogue 81-595. Ottawa: 2000.
9. Torgerson, C, Loblaw, A, Morra, D. *Canadian Medical Residency Guide: 4th Edition*. Toronto: RBC Financial Group; 2006.
10. Buske, L. Doctors Working Harder, Earning Less. *Canadian Medical Association Journal*, March 2000;162(6):851.
11. Wang, S. Is There a Doctor in the House: A Look at the Family Doctor Shortage in North America. *MedHunters*; 2007 [cited April 9, 2007]. Available from: <http://www.medhunters.com/articles/familyDoctorShortage.html>.
12. Rosser, WW. The Decline of Family Medicine as a Career Choice. *Canadian Medical Association Journal*, 2002;166(11):1419.

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A 76-year-old Greek male presented to the Emergency Department with a two-month history of increasing abdominal girth and fatigue. He was seen by his family physician one week prior, but presented to the hospital when he had difficulty breathing due to his abdominal distension. The patient described a weight gain of about 10 lbs over the past year but a noticeable increase in his waist size. His fatigue progressively worsened; he has gone from being able to walk several blocks to only a half a block, and has recently been bed-ridden for the past two days. He endorsed having dark urine, pale stools with occasional melena, decreased appetite, and early satiety. He denied nausea, vomiting, diarrhea, or constipation. The patient did not have any constitutional symptoms, confusion, or pruritus.

The patient's past medical history included chronic hepatitis B infection, sciatica, bilateral cataract surgery, and mild osteoarthritis. His medications included spironolactone (initiated one week prior to presentation) and oxycodone plus acetaminophen (Percocet). He had no known drug or food allergies. The patient had a 60-pack year history of smoking (he quit in February 2006) and described a binge-drinking alcohol history of approximately 5-6 drinks of Metaxa (Greek brandy) per night. The patient denied any history of intravenous drug use. The patient's family history was unremarkable. The patient is a retired barber.

On examination, the patient was alert, cooperative and not in respiratory distress. His heart rate was 82 bpm and regular, his respiratory rate was 20 breaths/min, his oral temperature was 36.9°C, and his oxygen saturation was 97% on room air. The patient had jaundice, temporal wasting, scleral icterus, palmar erythema, ecchymosis on his abdomen, multiple spider angiomas on his chest, and petechiae on his back. A grossly distended abdomen with bulging flanks and mild peripheral edema was present. There were bowel sounds present with a positive fluid wave test and shifting dullness.

Laboratory investigations revealed a decreased hemoglobin level of 104, a normal leukocyte count of  $6.6 \times 10^9/L$ , an increased INR of 1.40, a decreased albumin of 30, and a total bilirubin of 108. His liver enzymes were elevated: his AST level was 201 units/L, his ALT level was 61 units/L, his ALP level was 116 units/L, and his LDH level was 442 units/L. The alpha-fetoprotein (AFP) level was 3000 ng/ml. The chest x-ray demonstrated a small right pleural effusion. An abdominal ultrasound and portal venous doppler revealed a cirrhotic liver with moderate ascites and a portal vein thrombus. A triphasic contrast CT demonstrated two masses (one 5.5 x 5.7 cm, the other 3.1 cm in diameter) in the right liver lobe and a tumor thrombus within the portal vein (Figure 1). An oesophagogastroduodenoscopy revealed grade 2-3 esophageal varices. A diagnostic and therapeutic paracentesis produced 1.2 L of straw-

coloured fluid with negligible leukocytes or erythrocytes, an albumin of 6.0 g/dL, a protein of 6.0 g/dL, which was negative for cytology and with no bacterial growth.

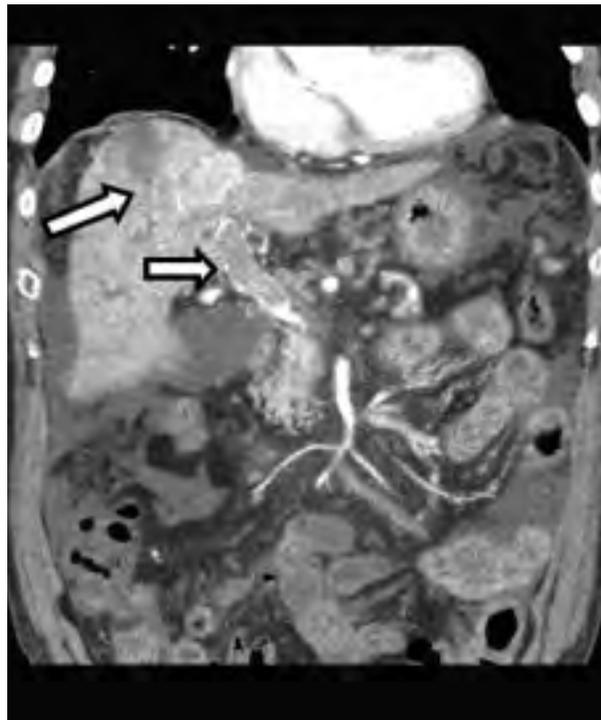


Figure 1. Contrast CT arterial coronal image of abdomen.

**What is the diagnosis?**

## And the diagnosis is . . .

### Case 1

#### Diagnosis: Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver that is currently one of the most common causes of cancer mortality worldwide. The prevalence of HCC is predominant in regions of Asia and sub-Saharan Africa in comparison to North America or Europe.<sup>1</sup> This difference in incidence worldwide reflects the varying prevalence of viral hepatitis. Asia and sub-Saharan Africa have high rates of infectious hepatitis B and C.<sup>1</sup> These infections lead to liver cirrhosis, a major risk factor in the development of HCC. In fact, 80% of patients presenting with HCC have preexisting cirrhosis at first presentation.<sup>1</sup>

The most common causes of cirrhosis include alcohol, hepatitis B virus (HBV) infection, and hepatitis C virus (HCV) infection. Approximately 30% of HCC cases are related to excessive alcohol use.<sup>2</sup> It requires chronic alcohol use of greater than 6-7 drinks per day for greater than 10 years to increase the risk of HCC 5-fold.<sup>2</sup> Chronic HBV infection is the most common cause of HCC worldwide, increasing the risk of HCC 1000-fold.<sup>3</sup> Although not as prevalent, HCV infection has a higher rate of chronic infection than HBV and contributes a lifetime risk for HCC of 5%, sometimes appearing 30 years after the initial infection.<sup>4</sup> In combination, alcohol use with chronic HCV doubles the risk of HCC compared to HCV alone.<sup>1</sup> Recent studies demonstrated that immunization for HBV or treatment of HCV may play a role in the prevention of HCC.<sup>3</sup>

Other uncommon causes of cirrhosis predisposing to HCC development are: hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, alpha-1 antitrypsin deficiency, tyrosinemia, non-alcoholic fatty liver disease, and aflatoxin toxicity.<sup>1</sup> It has been postulated that chronic low-grade hepatocyte damage due to inflammation predisposes to genetic alteration of hepatocyte DNA.<sup>1</sup> The latency period from hepatic damage to HCC development can be quite long, on the order of years to decades.<sup>1</sup> As a result, this disease often afflicts an older population. In North America or Europe, patients present at a median age of 65. However, in Africa and Asia, patients present in the fourth and fifth decade of life, respectively. HCC occurs more frequently in men than in women.

Patients with HCC usually present with symptoms of cirrhosis, including: pruritus, jaundice, splenomegaly, variceal bleeding, cachexia, increasing abdominal girth, hepatic encephalopathy, and uncommonly, right upper quadrant pain.<sup>1</sup> Physical findings are consistent with stigmata of liver disease: jaundice, ascites, hepatomegaly, alcohol stigmata, asterixis, pedal edema, and varices.<sup>1</sup> Laboratory values reflect changes due to cirrhosis:

increased bilirubin, liver enzymes, INR, and decreased albumin. Alpha-fetoprotein is a marker that is commonly elevated in HCC.<sup>5</sup> In fact it is often correlated inversely with prognosis.

The prognosis of HCC is quite poor. There is a cure rate of <5% in all patients, usually through surgical intervention.<sup>5</sup> The length of survival is dependent upon the extent of cirrhosis, as well as the presence of portal vein occlusion.<sup>5</sup> HCC frequently invades locally to the portal vein, but may also metastasize to periportal nodes, lung, bone, or brain. Some complications of HCC are hepatic failure, variceal bleeding, cachexia, and rarely, tumour rupture and bleeding into the peritoneum.<sup>1</sup>

Imaging investigations include ultrasonography, triphasic CT scanning, and MRI. Ultrasound is the least expensive modality, but is very operator-dependent.<sup>6</sup> Although it requires further imaging for diagnosis and staging, its main advantage is the use of the Doppler to determine patency of the portal vein. A triphasic CT scans the patient first without contrast, then with early (arterial) and late (portal) contrast imaging. This method increases the number of tumor nodules detected, and is able to detect extra-hepatic disease and lymphadenopathy. It has, however, a lower sensitivity in nodular cirrhotic livers compared to MRI.

A liver biopsy for diagnosis is a controversial issue. There is a potential risk of tumour seeding along the needle tract, and is contraindicated in the clinical setting of a growing mass (>2 cm) in a cirrhotic liver. In fact, a clinical diagnosis of HCC can be made with the detection of an enlarging mass in a cirrhotic liver using one imaging modality and a serum AFP level of greater than 500-1000 ng/ml.<sup>6</sup> Staging the tumour is only useful in patients who are candidates for surgical resection, usually a small minority of patients. When unresectable, the prognosis largely depends on clinical features of liver disease, such as ascites, portal vein involvement, and liver function. The Cancer of the Liver Italian Program (CLIP), is a prognostic indicator which integrates: Child-Pugh scores (stage A=0, B=1, C=2), tumor morphology (uninodular and extension <50% =0; multinodular and extension <50%=1; massive and extension >50% =2), AFP (<400 ng/ml = 0, >400 ng/ml=1), and portal vein thrombosis (absent=0, present=1). The estimated survival according to the CLIP score is: score of 0 = 31 months; score of 1 = 27 months; score of 2 = 13 months; score of 3=8 months; and score of 4= 2 months.<sup>5</sup>

The treatment for HCC can be divided into surgical or non-surgical modalities. Surgical resection and liver transplant have the potential to cure, but have limited applicability.<sup>3</sup> Supportive treatment for symptoms of cirrhosis include: large-volume paracentesis, diuretics, lactulose for treatment and prevention of encephalopathy, ursodiol for pruritus, variceal banding or sclerosis, and antibiotic treatment for spontaneous bacterial peritonitis.<sup>5</sup> Other thera-

pies for HCC include: chemoembolization, ethanol ablation, radiofrequency ablation, cryoablation, radiotherapy, and systemic treatment with chemotherapy.<sup>6</sup> Unfortunately HCC is a relatively chemotherapy-resistant tumour, with response rates of around 10%.<sup>6</sup> In addition, chemotherapy is not well tolerated and less efficacious in patients with underlying liver disease, such as cirrhosis. Doxorubicin, cisplatin, and fluorouracil are chemotherapeutic agents which have been used as single or combination therapies with no clear impact on overall survival.<sup>5</sup> Chemoembolization is contraindicated in patients with portal vein thrombosis, encephalopathy, or biliary obstruction.<sup>5</sup>

### Back to the Case

The patient's symptoms improved after a repeat therapeutic paracentesis which yielded 1000 cc of straw-coloured

fluid. He was discharged home with weekly home care and follow-up with a hepatologist in three weeks. Unfortunately, he was not deemed a suitable candidate for therapy, and was therefore managed palliatively at home.

### References

1. Dienstag JL, Isselbacher KJ. Tumors of the Liver and Biliary Tract. In: Kasper DL, et al, editors. Harrison's principles of internal medicine. New York: McGraw-Hill; 2005. p.533-536.
2. Di Bisceglie AM, Carithers RL, Gores GJ. Hepatocellular carcinoma. *Hepatology*.1998;28: 1161-5.
3. Forner A, Hessheimer AJ, Isabel Real M, and Bruix J. Treatment of hepatocellular carcinoma. *J Crit Rev Oncol Hematol*. 2006 Nov; 60(2):89-98.
4. Marrero JA, Pelletier S. Hepatocellular carcinoma. *Clin Liver Dis*. 2006 May;10(2):339-51.
5. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival. *Cancer*.1996;77:2217-22.
6. Llovet JM. Updated treatment approach to hepatocellular carcinoma. *J Gastroenterol*. 2005 March;40(3):225-35.

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### Sudden Cardiac Death: Small Plaques, Big Problems

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#### Case Presentation

**M**rs. C., a 62 year-old Caucasian woman, was transferred to the Toronto General Hospital for definitive management of an ascending aortic aneurysm and aortic valve regurgitation.

Relevant past medical history includes a silent inferior wall myocardial infarction and a 30 pack-year smoking history with emphysema.

Her workup consisted of an angiogram, which revealed massive dilation of the aortic root associated with severe aortic regurgitation. The coronary arteries were normal. Transthoracic echocardiography confirmed an aneurysm of 2.5 cm at the proximal root and 7.1 cm at maximal diameter in the proximal ascending aorta. Akinesis of the basal inferior and posterior walls and a grade 3-4 left ventricle were reported. Grades [1-4/4] are based on left ventricular ejection fraction %: grade 1, 60%; grade 2, 40%-60%; grade 3, 20%-40%; and grade 4, 20%.

Surgical replacement of the ascending aorta, remodeling of the sinotubular junction and aortic valve repair were performed. Post-operatively, the patient developed episodes of atrial fibrillation (that were treated with amiodarone and later, diltiazem), as well as bilateral pleural effusions and atelectasis. She remained afebrile, her cardiovascular status was stable, and her course in hospital was otherwise uneventful.

On post-operative day 8, amiodarone was stopped and the patient was started on metoprolol. She developed upper back, shoulder, and anterior chest pain controlled with morphine and Gravol (dimenhydrinate). The following day, her pain recurred at 6:30 AM and an inferior wall myocardial infarction with possible lateral wall ischemia was detected by ECG. At 7:00 AM, the patient was found pulseless and unresponsive. Code blue was called. The initial rhythm was bradycardia with pulseless electrical activity, which became ventricular fibrillation and asystole. The patient was pronounced dead at 8:30 AM.

#### What is her differential diagnosis?

In the case presented, a 62 year-old female, who had risk factors for coronary artery disease (CAD), died suddenly and unexpectedly on the 9th day after aortic replacement and aortic valve repair. The differential diagnoses are post-surgical complications, such as severe hemorrhage, ventricular arrhythmias, severe bleeding, cerebrovascular accident, and acute respiratory distress syndrome, as well as sudden cardiac death (SCD).

#### What is sudden cardiac death?

Sudden cardiac death (SCD) is best described as natural, non-violent, but unexpected death resulting from an abrupt

loss of heart function occurring within one hour of the onset of symptoms.<sup>1</sup> As many as 40% of cases are not witnessed, and typically occur out-of-hospital or in emergency rooms; this reflects the unexpected nature of this disease. A common phenomenon, SCD accounts for approximately 325,000 deaths per year in the United States and tens of thousands in Canada. In fact, of deaths from cardiac causes, approximately 50% are defined as SCD.

The peak incidences of SCD are at 0-6 months of age, known as sudden infant death syndrome, and at 45-75 years of age. The Framingham study reported that the proportion of coronary artery disease deaths that were attributed to SCD was 62% in men between 45-54 years, but that this percentage fell to 58% between 55-64 years and to 42% between 65-74 years.<sup>2</sup> In adulthood, the declining incidence with age is likely due to the susceptibility of elderly to complications of heart failure. The incidence was 3.8-fold higher in men than in pre-menopausal women, who are relatively protected against coronary artery disease. In this case, the patient was post-menopausal and as such, was not afforded the same cardio-protective effects.

#### What is the clinical presentation of SCD?

The presentation of SCD is extremely variable and ranges from sudden death to arrhythmia and congestive heart failure. Patients often experience vague prodromes of chest pain, fatigue, palpitations, and other non-specific complaints. Hours prior to collapse, our patient developed acute back, shoulder, and chest pain.

#### What is the pathophysiology of SCD?

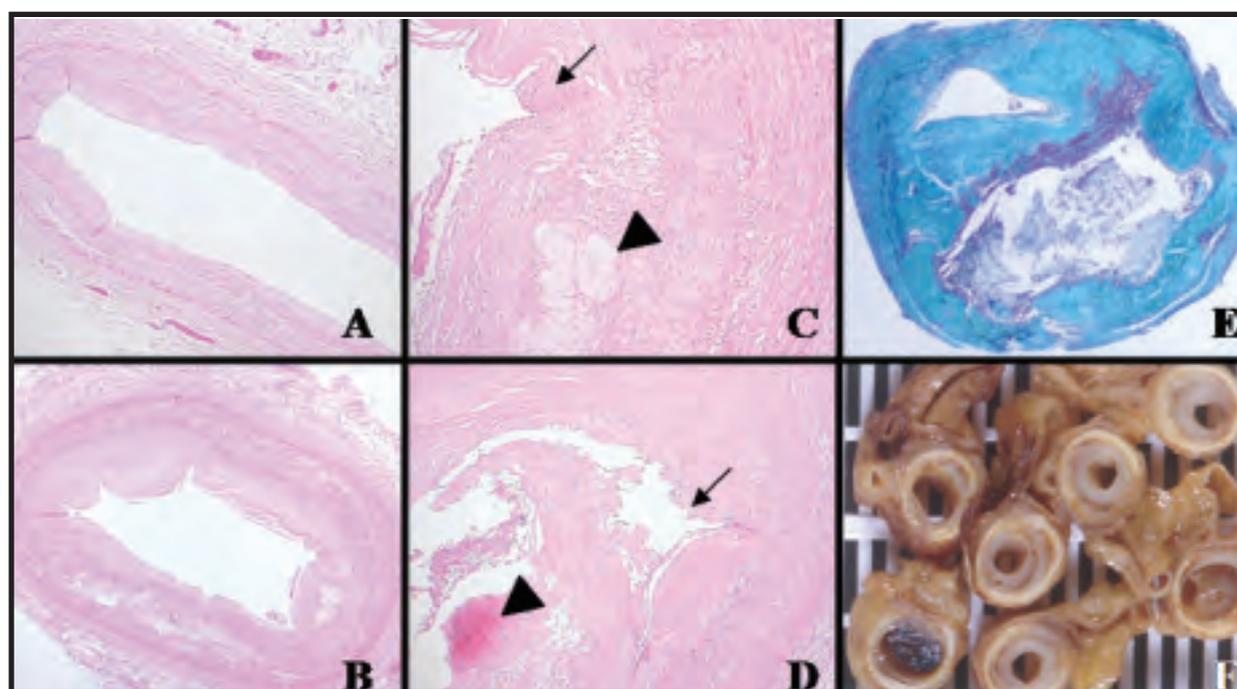
Postmortem studies demonstrate that coronary atherosclerosis and subsequent thrombosis accounts for approximately 90% of SCD cases, particularly within the first 6-24 months after a myocardial infarction. Risk factors for adults with SCD thus tend to parallel those for coronary artery disease and include male sex, smoking, obesity, diabetes, and previous history of major cardiovascular events or arrhythmias. The next most common risk factor is dilated cardiomyopathy, particularly from prior ischemic episodes ("ischemic cardiomyopathy"), and hypertrophic cardiomyopathy, found in young patients and athletes. A summary of common causes and mechanisms of SCD is presented in Table 1.

The most common mechanisms of death in SCD are arrhythmias. Of these, ventricular tachyarrhythmias account for roughly 80%, whereas bradyarrhythmias account for roughly 20%. This highlights the importance of tachycardiac interference using an automatic external defibrillator or implantable cardioverter defibrillator. Since most events occur out of hospital, it follows that publicly accessible

## Sudden Cardiac Death

Immediate Cause	Underlying Cause	Mechanism
Acute Ischemia	CAD, Aortic Stenosis	Ventricular Fibrillation, Bradycardia
Cardiac Hypertrophy	Hypertrophic Cardiomyopathy, Systemic Hypertension, Aortic Stenosis	Ventricular Fibrillation
Cardiac Dilation	Dilated Cardiomyopathy, Ischemic Cardiomyopathy, Systemic Hypertension, Mitral Insufficiency	Ventricular Fibrillation
Cardiac Tamponade	Ruptured Myocardial Infarction	Electromechanical Dissociation
Acute Heart Failure	Massive Myocardial Infarction, Ruptured Papillary Muscle	Ventricular Fibrillation, Electromechanical Dissociation
Disruption of Cardiac Output	Pulmonary Embolism, Mitral Stenosis, Atrial Myxoma	Ventricular Fibrillation, Electromechanical Dissociation

**Table 1.** Common causes and mechanisms of sudden cardiac death.<sup>1</sup>



**Figure 1.** Histological sections and gross images of coronary arteries. (a) Healthy and (b) mildly diseased coronary arteries. (c) Higher magnification view of a plaque shoulder with increased cellularity (arrow) and a lipid rich core (arrowhead). (d) Ruptured plaque (arrow) and intraplaque hemorrhage (arrowhead). (e) Masson's trichrome stain of a stable intracoronary plaque with a large lipid core and small lumen (collagen stains green; muscle stains red). (f) Serial gross coronary sections illustrating thrombosis in a mild (bottom left) but not in a severe plaque (top right). Images a-d were taken from the case patient.

external defibrillators, if used in a timely and appropriate manner, could have a significant impact on survival.

In our patient, the index of suspicion for SCD was elevated based on her age, smoking history, cardiomyopathy, post-operative arrhythmia, and silent myocardial infarction. The mechanism of death was bradycardia with pulseless electrical activity, also referred to as electromechanical dissociation

### Back to the Case

At autopsy, the heart showed features of status post-aortic root replacement and aortic valve repair, and was enlarged at 600 g with pronounced biventricular hypertrophy and some dilatation. The heart also showed multiple areas of ischemic change. An old, large, healing transmural infarct was found in the lateral left ventricle, posterior wall, and posterior septum. Most significantly, the right coronary artery showed a segment with 30-40% luminal stenosis,

plaque inflammation, plaque disruption, and intraplaque hemorrhage, leading to luminal occlusion. Death was attributed to coronary atherosclerosis with acute plaque disruption, acute right coronary artery occlusion, and myocardial infarction.

### What is atherosclerosis?

Atherosclerosis is a disease of small and medium sized arteries, characterized by thickening of the intima and development of an atherosclerotic plaque. Such plaques are composed of a lipid-rich core containing a heterogeneous mixture of fibrous tissue, smooth muscle cells and inflammatory cells, and an overlying fibrous cap. Healthy and mildly atherosclerotic coronary arteries from the case patient are presented in Figure 1a-c. For comparison, Figure 1e demonstrates severe coronary artery disease. Russell Ross first proposed, and later revised, the response-to-injury hypothesis for the etiology of atherosclerosis, which galvanized our current understanding of the disease process.<sup>3</sup>

In essence, the current paradigm reflects the appreciation of atherosclerosis as an inflammatory disease, and not as a straightforward lipid deposition process. The inciting event is endothelial dysfunction. The possible causes are many and include elevated and modified low-density lipoprotein (LDL), hypertension, free radicals, and infection. Such injury induces endothelial adhesion and, over time, the infiltration of macrophages and T-cells resulting in a proinflammatory cytokine milieu. Circulating LDL particles are trapped in the lesion and modified by macrophages into a pernicious oxidative form. These early lesions are known as fatty streaks. Smooth muscle cells then migrate from vessel wall media into the developing lesion and deposit a connective tissue matrix.

Plaque growth may eventually continue unabated, causing occlusion and symptomatic angina pectoris. Alternatively, previously stable plaques may degenerate in a rapid and unpredictable manner to become unstable. Clinically, thrombosis of unstable plaques results in acute coronary syndrome (ACS) in the form of (1) unstable angina, (2) myocardial infarction, or (3) SCD.

### Are all plaques the same?

Atherosclerotic plaques can be conceptualized in terms of size, complexity, and stability. Complicated plaques are associated with increasing calcification, erosion, and ulceration. Recall that in our patient, the pre-operative coronary angiography was unremarkable. This examination tells us that the culprit lesion probably began as a non-occlusive coronary atherosclerotic plaque, likely one with no more than 30-50% luminal stenosis. Pathological assessment later confirmed the presence of thrombosis and rupture of a modest but significant right coronary plaque (Figure 1d). Rupture led to plaque hemorrhage, formation of coronary thrombosis, and clinical myocardial infarction.

In autopsy studies, the investigation of culprit lesions has revealed an interesting finding: small plaques with mild (30-40%) vessel occlusion are responsible for the majority of acute cases of ischemia.<sup>4</sup> Why is this? Advanced lesions often

have well-developed, uniformly dense fibrous caps and calcification, both of which afford plaque stability. Protracted coronary occlusion also allows for angiogenic proliferation in the form of compensatory collateral circulation to preserve downstream arterial supply. Consequently, stable plaques are much less likely to rupture and such an event is much less threatening. In contrast, complex plaques are often eccentric lesions with irregular borders and ulcerations. These are much more prone to rupture and cause coronary thrombosis.<sup>5</sup> Serial coronary artery sections post-acute myocardial infarction demonstrate evidence of culprit lesion thrombosis in a previously mild plaque, whereas adjacent severe plaques remain stable (Figure 1f).

### What causes plaque rupture?

Frank rupture is characterized by a structural gap or fissure in the fibrous cap. It was once thought that degeneration of cap thickness alone determined rupture; however, post-mortem studies, clinical and animal experiments, and long-term epidemiological evidence have revealed that there is more to this rich and complex story.<sup>6</sup> The current hypothesis of plaque rupture involves an interplay of several biological processes: (1) inflammation and thinning of the fibrous cap, (2) lipid profile changes, and (3) intraplaque hemorrhage. We will address these briefly in turn.

As alluded to earlier, atherosclerotic plaques contain a smooth muscle cell-derived connective tissue fibrous cap. Complex and metabolically-active plaques typically have thin or fragile fibrous caps. The tendency for plaque disruption is based on the integrity of the fibrous cap overlying the plaque's thrombogenic lipid core.

Immune cell infiltration is associated with plaque instability. Macrophages, lipid-laden macrophage foam cells, and T-cells predominate within these lesions. Macrophages release inflammatory mediators including cytokines and proteases; the latter can promote matrix degradation and plaque instability. Matrix metalloproteinases (MMPs), major enzymes in matrix degradation, are expressed in a harmonious manner in normal human tissues and in pathologic settings such as the lipid core of human atherosclerotic plaques. Increasing evidence supports the role of MMPs in matrix degradation and weakening of extracellular matrix, which results in susceptibility to mechanical stresses leading to plaque rupture. The co-localization of macrophages in close proximity to ruptures at the shoulder or edge of plaques supports this notion (Figure 1c, arrow).

Plaque stability is also dependent on lipid content and distribution within the lesion. Macrophages accumulate atherogenic lipoprotein cholesterol through scavenger receptors that recognize modified LDL. Oxidized LDL acts as a macrophage and T-cell chemoattractant. In fact, oxidized LDL is localized to areas of plaque rupture and elevated circulating oxidized LDL is an independent risk factor for acute cardiac events.

Complex plaques often develop a rich microvasculature, termed the vasa vasorum, which provide circulating cellular and acellular material access to the lesion. However, these thin-walled vessels are lined only by endothelial cells, without the support of smooth muscle cells. They are at signifi-

cant risk of rupture and an intrinsic, slowly growing intraplaque hemorrhage (Figure 1d, arrowhead), again compromising structural integrity and lumen patency.

A synergistic combination of the aforementioned processes may therefore work in concert to promote plaque rupture.

### Who is vulnerable to atherothrombosis?

A greater understanding of the cellular and molecular mechanisms of atherosclerosis and the need to identify people with a predilection for SCD has led to the developing concept of the vulnerable patient.<sup>7</sup> Vulnerability may come from rupture-prone atherosclerotic plaques, a prothrombotic state, ischemia-vulnerable myocardium, or a combination of such. In our patient, although her aortic aneurysm was not a focus of this report, it was significant as she died of SCD in the days after her surgery. Her surgery and significant smoking history likely contributed to a prothrombotic state. Also, any ischemic cardiovascular event increases myocardial vulnerability to arrhythmias and sudden death. In this case, our patient had a previous silent myocardial infarction.

### What is on the horizon?

An important challenge is to identify patients with vulnerable plaques and preclude the progression to future acute coronary thrombosis. As mentioned earlier, culprit lesions are difficult to detect angiographically due to the lack of coronary hemodynamic compromise. Positive remodeling by compensatory vessel dilation can lead to further underestimation of plaque size by angiography. These caveats underscore the fact that angiographic diagnosis of coronary atherosclerosis is problematic. In this regard, the development of new imaging modalities, such as intravascular ultrasonography and high-resolution magnetic resonance imaging to measure plaque size, and molecular imaging of inflammation with radionuclide tracers and thermal detection to detect so called 'hot lesions,' is an intense area of research. Several cardiac biomarkers that act as surrogates to predict major adverse atherothrombotic events have also been identified, the most promising of which are C-reactive protein and fibrinogen.<sup>8</sup>

The development of effective cholesterol reducing agents and lifestyle modification initiatives has only modestly decreased rates of coronary atherosclerosis and its clinical sequelae, acute coronary syndrome. In light of this, a greater understanding of the regulators of inflammation and plaque rupture in atherosclerosis may lead to the identification of novel biological checkpoints to interrupt this process.

### Conclusion

Sudden cardiac death is a major source of mortality in the western world and a rapidly increasing one in the new industrial economies – the incidence of which is increasing with the pervasiveness of coronary artery disease. Importantly, human pathological studies have demonstrated that the majority of coronary thrombotic events occur in small, difficult to diagnose, unstable atherosclerotic plaques. Recent advances in the evaluation of tissue and

experimental modeling of human disease will provide new knowledge on the molecular structure and function of the cells and tissues in these lesions. Specifically, elucidation of the mechanism of rupture has led to the concept of unstable plaques and vulnerable patients. It is clear, however, that there still exists a need for new, non-invasive tools to identify and treat patients with unstable atherosclerotic plaques.

### Take Home Points

1. Atherosclerosis is an active, complex biological process.
2. The majority of coronary thrombosis occurs in small, unstable plaques.
3. Identification of vulnerable plaques and at-risk patients remains an ongoing challenge.

### References

1. Virmani R, Burke AP, Farb A. Sudden cardiac death. *Cardiovasc Pathol.* 2001; 10(5):211-8.
2. Schatzkin A, Cupples LA, Heeren T, Morelock S, Kannel WB. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. *Am J Epidemiol.* 1984; 120(6):888-99.
3. Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med.* 1999;340(2):115-26.
4. Maseri A, Fuster V. Is there a vulnerable plaque? *Circulation.* 2003;107(16):2068-71.
5. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med.* 2000;343(13):915-22.
6. Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, Chesebro JH. Atherosclerotic plaque rupture and thrombosis. Evolving concepts. *Circulation.* 1990;82(3 Suppl):II47-59.
7. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation.* 2003;108(14):1664-72.
8. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* 2002 Nov 14;347(20):1557-65.

### Multimodality Image-Guided Cardiovascular Intervention

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#### Abstract

Percutaneous cardiovascular interventions (PCI) that require insertion of a catheter into the vasculature are among the leading treatment options for a variety of cardiovascular diseases. High-resolution imaging modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and cardiac magnetic resonance imaging (CMRI) are emerging as important complimentary tools to traditional x-ray angiography, as they provide inherent soft tissue contrast and improved spatial resolution at the region of interest. The use of multiple imaging modalities is safer for the patient due to improved image-guidance, and the lack of ionizing radiation and nephrotoxic contrast agents. IVUS provides a detailed cross-sectional view of the vascular lumen and layers of the arterial wall, ideal for imaging coronary artery pathology. OCT is capable of distinguishing tissue composition with detail similar to histological examination (axial resolution of 3-15  $\mu\text{m}$ ) for a limited depth. MRI can provide image contrast based on soft tissue, functional and molecular characteristics, which is useful for both vascular and myocardial interventions. Applications of multimodality image-guidance discussed in this article include traversing chronic total occlusions (CTO), regeneration of infarcted myocardium, catheter-based ablation procedures and various pediatric cardiovascular interventions.

#### Introduction

The use of multiple imaging modalities (x-ray, ultrasound, optical, magnetic resonance, nuclear) in the diagnosis and treatment of cardiovascular disease (CVD) has grown in popularity in recent years.<sup>1-4</sup> The rationale for a combined approach is to draw upon the strengths of each imaging modality in order to improve visualization and characterization of CVD. Multimodality approaches are useful for both early detection of CVD and guiding percutaneous cardiovascular interventions (PCI) that require insertion of a catheter into the vasculature. During PCI, x-ray flu-



**Figure 1.** XMR interventional unit at IRCCI. X-ray fluoroscopy unit (left) can be connected via a moving patient table (center) to the GE 1.5 Tesla MRI scanner (top-right).

oroscopy is almost exclusively used to guide catheters through the vasculature to the target tissue; however ultrasound, optical, electrophysiological and magnetic resonance (MR) methods are useful for soft tissue assessment when necessary.

In November 2006, the Schulich Heart Centre at Sunnybrook Health Sciences Centre in Toronto announced the opening of the Imaging Research Centre for Cardiac Intervention (IRCCI). The new state-of-the-art research centre will use a combined approach of x-ray, ultrasound, optical and MR methods for diagnosis and treatment of CVD. The facility features a combined X-ray / MR imaging (XMR) unit which consists of an x-ray fluoroscopy unit attached via a moving patient table to a GE™ 1.5 Tesla MRI scanner in the adjacent room (Figure 1). The XMR interventional unit represents a significant advancement in multimodality image-guided therapy. X-ray fluoroscopy offers high spatial and temporal resolution of the vascular lumen, while MR imaging allows visualization of the surrounding soft tissue anatomy during



**Figure 2.** (a) X-ray fluoroscopy visualizes blood vessels which are opacified with iodinated contrast agent; (b) IVUS distinguishes between cell wall layers using reflected sound waves; (c) OCT provides histological detail of the vessel wall.

catheter guidance. Combined with ultrasound and optical imaging techniques, it will provide the potential for greater safety, speed and efficacy during difficult cardiovascular interventions. In this article, we review the standard and emerging imaging modalities under investigation at IRCCI and explore several novel applications in cardiovascular intervention.

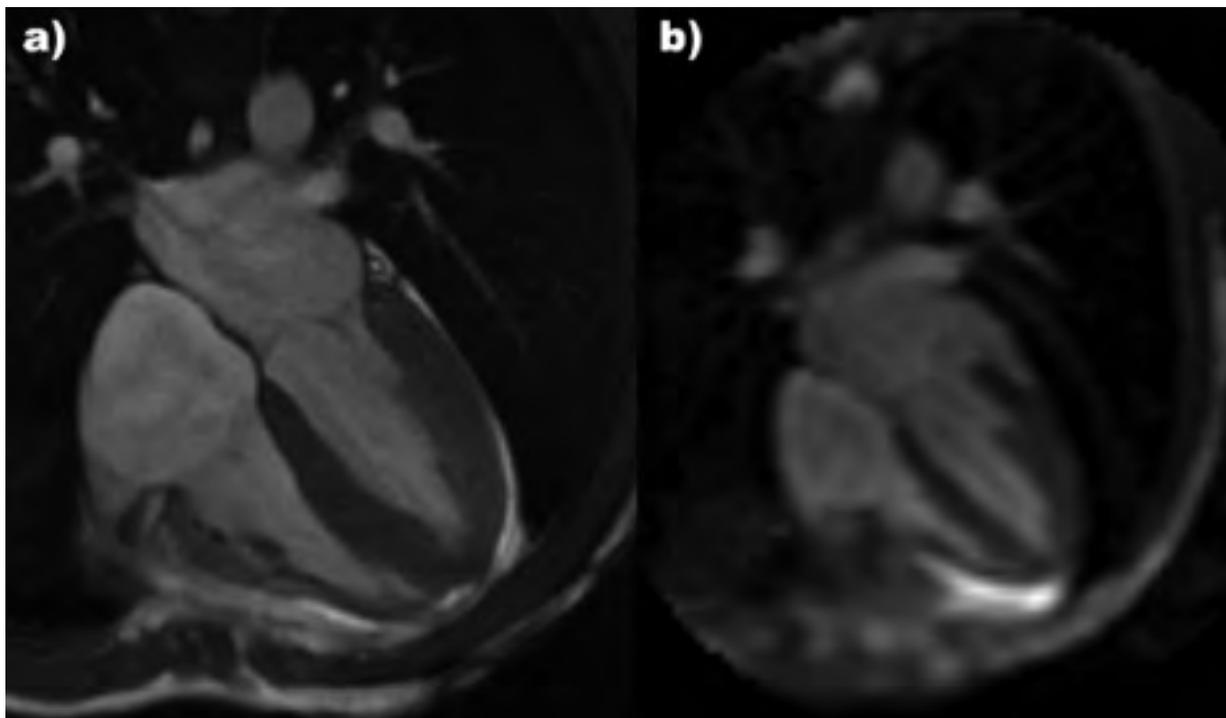
## CARDIOVASCULAR IMAGING

### X-Ray Fluoroscopy: Advantages and Limitations

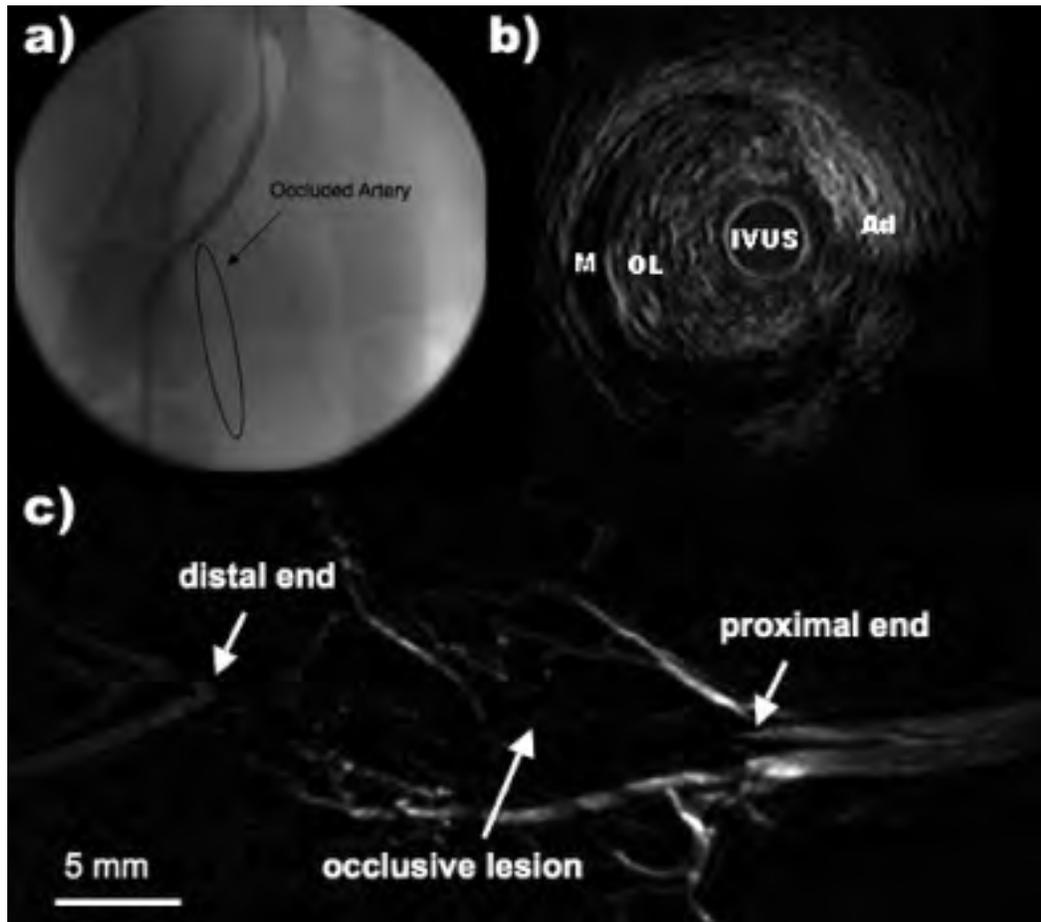
Invasive x-ray angiography remains the current gold standard for image-guided cardiovascular intervention. The use of angiography has been described as “lumenology” since the

image represents a two-dimensional planar projection of the vascular lumen that has been injected with radiopaque dye (Figure 2a). The operator gains a three-dimensional understanding of the anatomy by repeatedly injecting contrast agent and visualizing the arteries at different oblique angles. The spatial resolution (less than 0.2 mm) and temporal resolution (less than 0.1 s) represent the greatest strengths of x-ray angiography.<sup>5</sup> These are essential for imaging moving structures such as the coronary arteries in-vivo in order to avoid motion-induced image artifacts and for receiving immediate feedback regarding the position of the interventional device.

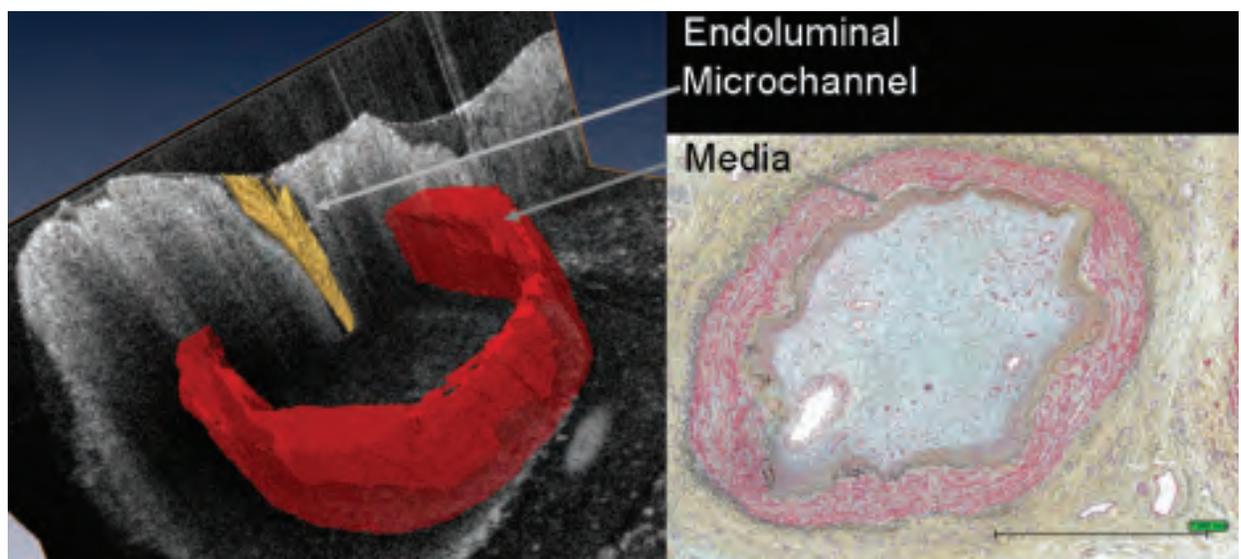
Since x-ray angiography only provides a view of the patent



**Figure 3.** Comparison of General Electric (GE) FIESTA (static) MR image (a) and GE RealCARD (real-time) MR image (b) of the four cardiac chambers during ventricular systole.



**Figure 4.** (a) Three imaging modalities visualizing a CTO. X-ray fluoroscopy often cannot visualize past the occlusion; (b) IVUS image of a CTO, including the IVUS catheter (IVUS), occluded lumen (OL) and media (M) and adventitia (Ad) layers of the vessel wall; (c) MRI angiogram of a CTO imaging the proximal and distal end of the occlusion as well as collateral circulation.



**Figure 5.** A volumetric OCT image of an occluded anterior tibial artery is shown on the left. Image segmentation was used to isolate the media wall (red) and the endoluminal microchannel (yellow). Corresponding histology (Movat) is shown on the right.

vascular lumen, lack of soft tissue contrast is a clear disadvantage.<sup>6,7</sup> This includes the inability to characterize atherosclerotic plaques, vascular wall pathology and myocardial disease. Soft tissue contrast is also useful for orienting the operator anatomically with respect to the location of the catheter tip during an intervention.

Safety concerns regarding x-ray angiography include the patient exposure to ionizing radiation and the potential nephrotoxicity of contrast agents.<sup>8-11</sup> For example, the UK National Radiation Protection Board has estimated that the average risk of developing a solid tumor from a single cardiac catheterization procedure is approximately 1 in 2,500.<sup>9</sup> The radiation concern is especially important in younger children, as their lifetime risk for malignancy is much higher and procedures for congenital heart disease often require longer x-ray exposure.<sup>10</sup> Contrast-medium induced nephrotoxicity is a dose-related phenomenon whose rate is substantially increased in patients with pre-existing renal impairment, especially in those with diabetes mellitus. The risk for nephrotoxicity could be reduced by the use of alternative imaging techniques that do not require injection of iodinated contrast medium.<sup>11</sup>

### Ultrasound: Outside-In and Inside-Out

Ultrasound techniques such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and intra-vascular ultrasound (IVUS) are important complementary tools for visualizing soft tissue during cardiovascular interventions. TTE represents the standard approach for echocardiography where the imaging transducer is placed on the chest wall over an intercostal space. TTE transducers normally operate between 2.0 and 5.0 MHz, depending on the depth of the region of interest. Higher transducer frequencies provide greater spatial resolution, yet reduce the effective imaging depth.<sup>12</sup> TTE is used as a non-invasive first-line approach for visualizing valvular disease, myocardial pathology, and obtaining estimates of blood flow patterns. Assessment of the left ventricle represents one of the greatest strengths of echocardiography.<sup>13</sup>

In TEE, the ultrasound transducer is inserted into the esophagus and images of the heart are acquired through the esophageal wall. TEE operates using a higher transducer frequency range (3.5–7.0 MHz) than TTE and thus it is capable of acquiring higher resolution images.<sup>14</sup> The transducer can operate at these higher frequencies since the imaging device is closer to the cardiac structures and the air-filled lungs do not obstruct the view from this vantage point. TEE is a more invasive ultrasound modality than TTE and it usually requires the use of local anaesthesia and intravenous sedation. TEE is often used during percutaneous mitral valvuloplasty and pediatric interventions such as atrial or ventricular septal defect (ASD, VSD) closure.<sup>15</sup>

IVUS represents a new standard technique for examining atherosclerotic plaques and vascular wall pathology during cardiovascular intervention. In IVUS, the ultrasound transducer is mounted on a catheter tip and inserted into the vasculature. IVUS displays a 360 degree cross-sectional view of the arterial wall (intima, media and adventitia) and the vascular lumen typically up to a depth of 10 mm (Figure 2b). The transducer operates at frequencies between 15-50 MHz,

which provides much higher axial resolution (100  $\mu\text{m}$ ) than TTE or TEE at the cost of imaging depth.<sup>16,17</sup> Applications of IVUS include the evaluation of coronary artery stent deployment in order to prevent restenosis, visualizing atherosclerotic changes in the vessel wall and assessing changes in plaque volume and composition.

### Optical Imaging Methods

Optical coherence tomography (OCT) is a relatively new microscopic imaging technique with tremendous potential in the field of image-guided procedures. OCT acquires cross-sectional images by examining the interference of light backscattered from tissue. OCT is often considered to be the optical equivalent of ultrasound. OCT's high axial resolution (3-15  $\mu\text{m}$ ) is ideal for evaluating the thickness of arterial layers and the fibrous cap of plaques.<sup>18,19</sup> Images are acquired through an optical fiber in a catheter. The catheter is inserted into the vasculature and then guided to the region of interest. The fiber is rotated at high speeds (<30 Hz) and pulled back to allow for volumetric imaging at microscopic resolution over several centimeters.<sup>20</sup> Current frequency-domain OCT systems based on wavelength tunable lasers are able to acquire such pull-backs in less than 15 seconds. OCT can also differentiate between tissue types and identify specific tissue composition with detail similar to histological examination (Figure 2c). Groups have also reported being able to quantify macrophage content within the arterial wall using OCT; thus giving a potential imaging modality to assess arterial inflammation *in vivo*. Functional extensions of OCT such as Doppler OCT<sup>21</sup> and polarization-sensitive OCT may also provide further insight into the progression of vessel wall disease.

### Cardiovascular MRI: Thinking "Outside the Lumen"

Magnetic resonance imaging (MRI) represents a powerful technology for imaging cardiovascular morphology and function. Over the past decade, significant advances in MRI have included developments in real-time MR imaging, MR angiography and assessment of hemodynamics and myocardial function. Several advantages of MRI include the inherent soft tissue contrast, high-quality four-dimensional (three spatial dimensions over the dimension of time) imaging, lack of ionizing radiation and the dynamic nature of MR pulse sequences (Figure 3a). For example, MR pulse sequences can provide image contrast based on anatomical structures, tissue perfusion, rates of intracardiac and intravascular blood flow, molecular features and cardiac wall mechanics. The limitations of MR technology include the cost, lack of portability and contraindication to certain implanted devices (especially vascular clips and pacemakers).

With the emergence of MR fluoroscopy techniques, MRI now includes the potential to guide a variety of cardiovascular interventions. In interventional MR, high-resolution (>500  $\mu\text{m}$ ) static MR images are merged with real-time data and catheter tracking to produce accurate soft tissue visualization. Real-time MRI is capable of updating one or two imaging planes at a rate of 15-30 frames per second (Figure 3b). Local imaging coil techniques, where the MR signal is received from a small ( $\leq 2$  mm) solenoid coil on the distal tip of the catheter, are used to increase the signal quality during

intravascular imaging to obtain high resolution images over a small field of view. For instance, when working at high-field (3 Tesla scanner) with local imaging coils, MR can reasonably achieve a spatial resolution of 100-200  $\mu\text{m}$  in-plane and about 1 mm through-plane.<sup>22</sup> The image quality obtained with local imaging coils is crucial in imaging small structures such as occluded coronary arteries in-vivo.

## APPLICATIONS IN IMAGE-GUIDED CARDIOVASCULAR INTERVENTION

### Chronic Total Occlusions: A Shot in the Dark

Chronic total occlusion (CTO) represents a major problem facing traditional image-guided intervention. A CTO, defined as a complete vascular occlusion for a period greater than 3 months,<sup>23</sup> is one of the most common reasons for referral for coronary artery bypass graft, as opposed to PCI.<sup>24</sup> The main difficulties arising from CTO are both the inability to image beyond the proximal end of the lesion using x-ray contrast and the inability to cross the CTO using a standard guidewire.<sup>22</sup> X-ray fluoroscopy provides almost no information regarding the geometry of CTOs since the vessel must first be opacified with contrast medium for visualization to occur (Figure 4a). CTO crossing with an interventional guidewire is believed to be impeded by collagen-rich extracellular matrix deposition within the CTO. Several promising studies have identified the presence of microchannels (generally 100-200  $\mu\text{m}$ ) throughout CTOs which may provide an alternative route for crossing them.<sup>18,22,25</sup>

In recent years, MRI, IVUS and OCT have been investigated for the potential to safely guide the recanalization of CTOs. MRI provides a detailed view of the regional anatomy, including the composition of the occlusion and the distal portion of the vessel (Figure 4c). Elements of the atherosclerotic plaque such as thrombus, lipid, fibrous tissue and calcium can be differentiated based on T1-, T2- and proton-density weighted images.<sup>22</sup> IVUS and OCT provide a detailed intravascular view of the atherosclerotic plaque by placing the transducer directly proximal to the CTO. The images are acquired millimeters ahead of the probe in cross-section by using a "forward-looking" imaging technique. IVUS is capable of differentiating between lipid, necrosis and thrombi (low echogenicity) and fibrous plaque (intermediate echogenicity) in the CTO (Figure 4b). Calcified plaque poses a problem for IVUS imaging due to the acoustic shadow beyond the calcified portion.<sup>26</sup> OCT provides detailed images of the composition in the CTO, similar to histological examination, up to a depth of 2-3 mm.<sup>18</sup> Volumetric imaging of microchannels is easily identified on OCT, which is an exciting prospect for safely crossing CTOs (Figure 5).

### Myocardial Interventions: Potential for Stem Cell, Drug and Biological Therapy

Myocardial regeneration is currently under investigation for patients who have suffered ischemic damage from infarction. Some proposed regeneration techniques include injection of mesenchymal stem cells (MSCs),<sup>27</sup> local drug delivery<sup>28</sup> and biological therapies such as cell products, plasmids and viral vectors.<sup>29</sup> X-ray fluoroscopy is a limited technology with respect to these procedures since they require an imag-

ing modality that can differentiate between infarcted and viable tissue. MRI is considered the leading technology in guiding myocardial regeneration since it provides excellent soft tissue contrast and physiological information, even without the use of contrast agent.<sup>27-29</sup> For instance, successful injection of MSCs into the myocardium post-infarction requires visualization of the border between normal and infarcted tissue. This landmark is important since MSCs assume fibroblast-like characteristics in infarcted tissue and cardiomyocyte-like characteristics at the border of infarction.<sup>30</sup> MRI has been successful in the past in visualizing and injecting MSCs in the infarct border, thus potentially providing a suitable medium for regeneration of functional myocardium.<sup>27</sup> Ultrasound and electrophysiological methods have been used for similar injection systems with less spatial precision.<sup>31,32</sup>

### Electrophysiology

Prior to recent advances in image-guided technology, defective electrical tissue causing cardiac arrhythmia was managed either medically using long-term drug therapy or surgically via cryoablation (freezing) or radiofrequency ablation. Surgical ablation therapy has been traditionally performed with a full thoracic opening; however more recently, percutaneous cardiac catheter ablation has become the gold standard in the management of arrhythmias. For instance, catheter ablation has been successful in 91-99% of cases of paroxysmal atrial fibrillation – thus eliminating the need for open-heart surgeries or long-term drug therapies.<sup>33,34,35</sup>

Catheter-based ablation techniques, however, possess critical limitations. Image guided cardiac catheter ablation often depends on a three-dimensional electroanatomical mapping (EAM) system to aid in defining the geometry of the atrial or ventricular chambers. The use of the EAMs is problematic, however, due to technical difficulties and the amount of time required to obtain sufficient mapping information.<sup>36</sup> The addition of MRI in cardiac ablation is a relatively novel concept and has proven to be quite successful in clinical research trials for the treatment of arrhythmias. High spatial resolution obtained in MR imaging will provide tremendous assistance in visualizing atrial or ventricular anatomy. Furthermore, it is capable of distinguishing normal cardiac tissue from chronically infarcted tissue with sub-millimeter spatial resolution which is particularly valuable in treating arrhythmias in post-myocardial infarction patients.<sup>37,38</sup> Combined MR imaging, x-ray guidance and electrophysiological data for cardiac catheter ablation is a prime example of the utility of multi-modal technology.

### Pediatric Cardiovascular Interventions

In spring 2007, the Hospital for Sick Children in Toronto is scheduled to open the Cardiac Diagnostic and Interventional Unit (CDIU), a new \$23 million clinical cardiovascular centre. The centre will feature two cardiac catheterization labs and an integrated Siemens MR unit, which are dedicated for the purpose of diagnosis and treatment of congenital heart disease. Congenital cardiovascular malformations (CCVMs) affect 3-12 per 1000 live births, representing the most common form of birth defect.<sup>39</sup> In the field of pediatric cardiology, cardiac catheterization is a defin-

itive diagnostic modality, providing anatomic, hemodynamic and electrophysiological data crucial to patient care.<sup>40</sup> It is important to note that imaging cardiovascular structures in a fetus, infant, or child is especially challenging when compared with adults due to the smaller anatomic structures, increased heart rate, restless patients and a wide spectrum of congenital anomalies. As such, pediatric interventional procedures are often longer and more complicated than adult procedures. Imaging modalities that provide high-resolution anatomic information without prolonged exposure to ionizing radiation, such as TEE and more recently real-time MR, are therefore more desirable for pediatric patients than traditional x-ray fluoroscopy.<sup>10</sup>

TEE has been used for many years as a standard imaging modality for pediatric cardiovascular interventions such as the treatment of atrial and ventricular septal defects (ASD, VSD), and percutaneous valvuloplasty, angioplasty and other stenting procedures.<sup>41,42</sup> TEE is suitable for cardiovascular intervention since it offers high resolution soft tissue contrast; however it must be used in combination with x-ray fluoroscopy for successful image-guidance. Furthermore, TEE is subject to imperfect imaging windows, device-related shadow artifacts and tissue trauma.<sup>42-44</sup> Recent developments in real-time MR now include the potential to guide pediatric cardiovascular interventions. In comparison to TEE, MRI offers superior soft tissue and blood contrast imaging in any arbitrary plane and does not require nephrotoxic contrast agent or ionizing radiation. Applications of MR guidance in pediatric interventions include: ASD closure, percutaneous vascular angioplasty, electrophysiological mapping, myocardial regeneration, portosystemic shunts, abdominal aortic endograft and inferior vena cava filter devices.<sup>44-46</sup>

## Conclusion

The use of multiple imaging modalities provides more information regarding anatomy, physiology and pathology during cardiovascular intervention than x-ray angiography alone. The advances in ultrasound, optical and magnetic resonance techniques discussed in this article will provide the framework for safer and more effective percutaneous treatments for cardiovascular disease. Reducing x-ray exposure and improving soft tissue contrast are integral for performing more complex procedures such as traversing CTOs, catheter-based electrophysiological ablation, myocardial regeneration and CCVM interventions. As more imaging modalities become routinely used in clinical practice, there will be a reduction in morbidity and mortality related to cardiovascular procedures and the possibility for novel image-guided interventions will continue to expand.

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## References

1. Worthley SG, Omar Farouque HM, Helft G, Meredith IT. Coronary artery imaging in the new millennium. *Heart, Lung and Circulation*. 2002;11(1):19-25.
2. Escolar E, Weigold G, Fuisz A, Weissman NJ. New imaging techniques for diagnosing coronary artery disease. *CMAJ*. 2006;174(4):487-495.
3. Sauer F. Image registration: enabling technology for image guided surgery and therapy. *Conf Proc IEEE Eng Med Biol Soc*. 2005;7:7242-5.
4. Sra J, Narayan G, Krum D, Akhtar M. Registration of 3D computed tomographic images with interventional systems: Implications for catheter ablation of atrial fibrillation. *J Interv Card Electrophysiol*. 2006;16(3):141-148.
5. Spahn M. Flat detectors and their clinical applications. *Eur Radiol*. 2005;15(9):1934-47.
6. Ellis SG, Guetta V, Miller D, et al. Relation between lesion characteristics and risk with percutaneous intervention in the stent and glycoprotein IIb/IIIa era: an analysis of results from 10,907 lesions and proposal for new classification scheme. *Circulation*. 1999;100:1971-1976.
7. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation*. 1990;82:1193-1202.
8. Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet*. 2004;363(9406):345-351.
9. NRPB. Guidelines on patient dose to promote the optimization of protection for diagnostic medical exposures. National Radiation Protection Board. 1999. 10(1).
10. Modan B, Keinan L, Blumstein T, Sadetzki S. Cancer following cardiac catheterization in childhood. *Int J Epidemiol*. 2000;29(3):424-8.
11. Morcos SK. Prevention of contrast media-induced nephrotoxicity after angiographic procedures. HYPERLINK "javascript:AL\_get(this,%20'jour',%20'J'%20Vasc%20Interv%20Radiol.);" J Vasc Interv Radiol. 2005 Jan;16(1):13-23.
12. Picard MH. M-Mode echocardiography: Principles and examination techniques. In Weyman AE: Principles and Practice of Echocardiography. Philadelphia: Lea & Febiger. 1994. 282-301.
13. Pizzuto F, Voci P, Romeo F. Value of echocardiography in predicting future cardiac events after acute myocardial infarction. *Curr Opin Cardiol*. 2003;18(5):378-84.
14. Rice MJ, McDonald RW, Li X, et al. New technology and methodologies for intraoperative, perioperative, and intraprocedural monitoring of surgical and catheter interventions for congenital heart disease. *Echocardiography*. 2002; 19(8):725-34.
15. Daniel WG, Mugge A. Transesophageal echocardiography. *N Engl J Med*. 1995; 332(19):1268-79.
16. Kawase Y, Suzuki Y, Ikeno F, et al. Comparison of nonuniform rotational distortion between mechanical IVUS and OCT using a phantom model. *Ultrasound Med Biol*. 2007;33(1):67-73.
17. Goertz DE, Frijlink ME, de Jong N, van der Steen AFW. Nonlinear intravascular ultrasound contrast imaging. *Ultrasound in Medicine & Biology*. 2006;32(4):491-502.
18. Munce NR, Yang VX, Standish BA, et al. Ex vivo imaging of chronic total occlusions using forward-looking optical coherence tomography. *Lasers Surg Med*. 2007;39(1):28-35.
19. Tearney GJ, Jang IK, Bouma BE. Optical coherence tomography for imaging the vulnerable plaque. *J Biomed Opt*. 2006;11(2):021002.
20. Yun SH, Tearney GJ, Vakoc BJ, et al. Comprehensive volumetric optical microscopy in vivo. *Nat Med*. 2006;12(12):1429-33.
21. Yang VX, Gordon ML, Qi B, et al. High speed, wide velocity dynamic range Doppler optical coherence tomography (Part I): System design, signal processing, and performance. *Opt Express* 2003;11:794-809.
22. Strauss BH, Segev A, Wright GA, et al. Microvessels in chronic total occlusions: pathways for successful guidewire crossing? *J Interv Cardiol*. 2005;18(6):425-36.
23. Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: A consensus document: Part I. *Circulation* 2005;112:2364-2372.
24. King SB 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med*. 1994;331(16):1044-50.
25. Srivatsa SS, Edwards WD, Boos CM, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol*. 1997;29(5):955-63.

26. Fujii K, Ochiai M, Mintz GS, et al. Procedural implications of intravascular ultrasound morphologic features of chronic total coronary occlusions. *Am J Cardiol.* 2006;97(10):1455-62.
27. Dick AJ, Guttman MA, Raman VK, et al. Magnetic resonance fluoroscopy allows targeted delivery of mesenchymal stem cells to infarct borders in Swine. *Circulation.* 2003;108(23):2899-904.
28. Lederman RJ, Guttman MA, Peters DC, et al. Catheter-based endomyocardial injection with real-time magnetic resonance imaging. *Circulation.* 2002;105(11):1282-4.
29. de Silva R, Gutierrez LF, Raval AN, et al. X-ray fused with magnetic resonance imaging (XFM) to target endomyocardial injections: validation in a swine model of myocardial infarction. *Circulation.* 2006;114(22):2342-50.
30. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature.* 2001;410(6829):701-5.
31. Park SW, Gwon HC, Jeong JO, et al. Intracardiac echocardiographic guidance and monitoring during percutaneous endomyocardial gene injection in porcine heart. *Hum Gene Ther.* 2001;12(8):893-903.
32. Oron U, Halevy O, Yaakobi T, et al. Technical delivery of myogenic cells through an endocardial injection catheter for myocardial cell implantation. *Int J Cardiovasc Intervent.* 2000;3(4):227-230.
33. Scherlag BJ, Patterson E, Po SS. The neural basis of atrial fibrillation. *J Electrocardiol.* 2006;39(4):180-3.
34. Grant AO. Recent advances in the treatment of arrhythmias. *Circ J.* 2003;67(8):651-5.
35. Gaita F, Riccardi R, Gallotti R. Surgical approaches to atrial fibrillation. *Card Electrophysiol Rev.* 2002;6(4):401-5.
36. Burke MC, Roberts MJ, Knight BP. Integration of cardiac imaging and electrophysiology during catheter ablation procedures for atrial fibrillation. *J Electrocardiol.* 2006;39(4):188-92.
37. Malchano ZJ, Neuzil P, Cury RC, et al. Integration of cardiac CT/MR imaging with three-dimensional electroanatomical mapping to guide catheter manipulation in the left atrium: implications for catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* 2006;17(11):1221-9.
38. Reddy VY, Malchano ZJ, Holmvang G, et al. Integration of cardiac magnetic resonance imaging with three-dimensional electroanatomic mapping to guide left ventricular catheter manipulation. *J Am Coll Cardiol.* 2004;44:2202-2213.
39. Hoffman JL. *Pediatr Cardiol.* Incidence of congenital heart disease: I. Postnatal incidence. 1995;16(3):103-13.
40. Kanter JP, Hellenbrand WE. Recent advances in non-interventional pediatric cardiac catheterization. *Curr Opin Cardiol.* 2005;20(2):75-9.
41. Holzer R, Hijazi ZM. Interventional approach to congenital heart disease. *Curr Opin Cardiol.* 2004;19(2):84-90.
42. Piaw CS, Kiam OT, Rapae A, et al. Use of non-invasive phase contrast magnetic resonance imaging for estimation of atrial septal defect size and morphology: a comparison with transesophageal echo. *Cardiovasc Intervent Radiol.* 2006;29(2):230-4.
43. Magni G, Hijazi ZM, Pandian NG, et al. Two- and Three-Dimensional Transesophageal Echocardiography in Patient Selection and Assessment of Atrial Septal Defect Closure by the New DAS-Angel Wings Device. *Circulation.* 1997;96:1722-1728.
44. Raval AN, Lederman RJ. Real-time magnetic resonance imaging to guide pediatric endovascular procedures. *Pediatr Cardiol.* 2005;26(3):251-9.
45. Kellenberger CJ, Yoo SJ, Buchel ER. Cardiovascular MR imaging in neonates and infants with congenital heart disease. *Radiographics.* 2007;27(1):5-18.
46. Rickers C, Kraitchman D, Fischer G, et al. Cardiovascular interventional MR imaging: a new road for therapy and repair in the heart. *Magn Reson Imaging Clin N Am.* 2005;13(3):465-79.

## The Uterus and Female Illness: Western Uterine Medicine from the Classical Period to the Renaissance

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### Abstract

From the Classical period through to the Renaissance, Western medicine blamed a woman's uterus for causing a variety of symptoms, many of which came to be grouped under an illness known as hysteria. Hysteria, an illness specific to women, manifested in a wide variety of symptoms, ranging from fainting to severe pain to madness. Common themes included the womb as an entity that wandered in a woman's body when it was sexually unsatisfied (thereby causing illness), or the womb as a passive "field" into which a man sowed his seed to create a new life. Treatments often included marriage and sexual intercourse. As anatomical dissection became more prevalent and other aspects of medical science became more sophisticated in the 1700s, scientists began to move towards linking hysteria to the mind. Nevertheless, Western uterine medicine from the Classical period to the Renaissance provided "scientific" encouragement for women to conform to roles as wives and mothers.

### Background

For many centuries, a woman's uterus was a mysterious symbol of her sex. It bled at regular intervals; it could house and then expel a new life. Its workings were unclear, hidden away as it was inside the body – unlike the male organs that were involved in intercourse. Throughout the history of Western medicine, the uterus would come to be blamed (usually unfairly) for a variety of illnesses from which women suffered. A common classical belief was that the womb would wander around a woman's body, causing a variety of symptoms. Out of this wandering womb theory sprang the condition known as hysteria, and its place in the medical canon as an illness from which women were prone to suffer by virtue of their sex.

The concept of the wandering uterus dates at least as far back as the Ancient Egyptians. Two of their medical texts to which we still have access today are the Kahun and Ebers papyri, in which they blame a woman's wandering womb for causing disease. The Kahun papyrus is a gynaecological and veterinary text that blamed symptoms as varied as pain in the neck to pain in the feet on the "falling of the womb."<sup>1</sup> The Ebers papyrus also addressed some gynaecological matters.

Notable among its remedies for a wandering womb was the use of male excrement. The text directed that the excrement be placed on frankincense and burned, and the resulting fumes held to the patient's vulva.<sup>2</sup> The belief that a substance from the male sex might lure the uterus was perhaps the precursor of later ideas that would personify the disease-causing uterus as sexually unsatisfied. James Ricci postulated that it is precisely from the Ebers papyrus that the ancient Greeks derived their belief in the wandering womb, since the papyrus listed treatments to "enable the uterus of a woman to return to its proper region."<sup>1</sup>

The womb and its link to hysteria is an idea that would persist in Western medicine well into the modern age, until scientific advances in the 1700s paved the way for the realization that hysteria was related to the mind and not the womb.

### The Uterus in the Classical Period (ca. 1200 BCE – 476 CE)

Some of the earliest classical representations of the uterus compared the organ to a pot or vessel.<sup>3-7</sup> In order for the womb to perform its proper functions during menses, intercourse, pregnancy, and delivery, the mouth of the pot needed to open and close at the right times. Other common representations included animals, namely, the frog<sup>8</sup> and the octopus. Véronique Dasen discussed the octopus imagery on classical amulets, and noted that the octopi depicted had seven tentacles, not eight. She postulated that it arose out of earlier imagery of the uterus as a pot whose mouth was sealed by a key with seven teeth.<sup>8</sup>

This comparison of the uterus to an animal was not confined to amulets and other aspects of medical folklore. The idea that it was an entity capable of movement was also espoused by some classical medical writers. There are many examples in the Hippocratic Corpus of the womb's tendency to wander, which caused an illness that would come to be known as hysteria, after the Greek word for the uterus, *hysteria*.<sup>2</sup> Hippocrates did not say explicitly that the uterus was an animal, but instead attempted to rationally explain its wanderings based on natural laws. Various Hippocratic works referred to the humoral theory, stating that when the womb was deprived of moisture, it travelled about the body to seek it out. In *On the Diseases of Women*, for example:

If one of these situations exists, that the woman does not have sexual intercourse and that the abdomen is emptied more than it should be due to some stomach illness, the uterus undergoes a displacement; for it is not moist in and of itself, since it has not had intercourse, and it has room above it, since the stomach is empty, and so it moves about because it is drier and lighter than normal.<sup>9</sup>

As to the suffering that an ascending womb could cause:

When [the uterus] has climbed onto the liver, it causes a sudden suffocation, intercepting the breath in the chest [...] When the uterus has reached the liver and the hypochondrium and causes suffocation, the whites of the eyes roll up, the woman becomes cold, and even sometimes livid. She grinds her teeth; saliva drips from her mouth, and she appears to be having an epileptic fit. If the uterus stays on the liver and hypochondrium for a long time, the woman will suffocate to death.<sup>9</sup>

Sufferers of a wandering womb could also exhibit fever, shivering, and pain in the lower regions of the body; eventually this could turn into more widespread pain, loss of the voice, and swelling of the legs and feet.<sup>9</sup> Because the ascending uterus could also supposedly crush the heart and lungs, the term *uterine suffocation* would also be used interchangeably with *hysteria*.

Some writers went so far as to say that the uterus was in fact an autonomous entity within a woman's body. Aretaeus called the uterus an "animal within an animal."<sup>10</sup> Being an animal, it had its own needs and desires, and in its quest to fulfill these, it would wander throughout a woman's body. Plato says, in *Timaeus*, "Whenever the matrix or womb, as it is called, – which is an indwelling creature desirous of child-bearing – remains without fruit long beyond the due season, it is vexed and takes it ill; and by straying all ways through the body [...] causes, moreover, all kinds of maladies."<sup>11</sup> Aretaeus summed it up thus: "In a word, [the womb] is altogether erratic."<sup>10</sup>

Some later classical writers agreed that the uterus caused feminine illnesses, but disagreed that it did so by virtue of its wandering. Soranus was one of these,<sup>5</sup> as was Galen. Galen's explanation for uterine-caused diseases was the retention of menses, which strained the ligaments connected to the uterus, "If one side pulls more strongly, the womb is attracted by the part which exerts the greater strength. Therefore, the human uterus does not move from one place to another like a wandering animal but is pulled up by the tension [of the ligaments]."<sup>12</sup>

Prescribed treatments for hysteria varied according to the etiological theory to which writers subscribed. For those who believed that the uterus could travel around the body, one of the most important treatment methods was to use odours to drive the uterus back to its proper location. For a womb that travelled upwards, for example, Aretaeus advised, "[the womb] delights, also, in fragrant smells, and advances towards them; and it has an aversion to fetid smells, and flees from them."<sup>2,10</sup> Thus, the treatment was to put noxious smells to a woman's nose, while fragrant vapours were placed under her vagina. Those who believed that the uterus could not wander criticized this approach. Soranus prescribed a variety of therapies, including the use of warm compresses, massage with olive oil, and only "gruel-like food" in the initial stages of the illness.<sup>5</sup> He also suggested that exercise, baths, and a varied diet were useful should the woman be subject to recurrent hysteria.<sup>5</sup>

Everyone was generally agreed, however, that there existed a female illness that was called, variously, *hysteria*, *uterine*

*suffocation*, or *uterine stoppage of respiration*.<sup>12</sup> Aretaeus said that, although symptoms similar to those of hysteria could occur in males, hysterical suffocation occurred only in females.<sup>10</sup> As to which women were most prone to hysteria, again there are varying ideas. Aretaeus claimed that younger women were more prone to hysteria, "For those in whom the age, mode of life, and understanding is more mobile, the uterus also is of a wandering nature; but in those more advanced in life, the age, mode of living, understanding, and the uterus are of a steady character."<sup>2,10</sup> His belief was not widely shared. Older writers argued that the hysteria-prone were more likely to be older women and widows – that is, those who did not have intercourse because they were unmarried, or those who were used to having intercourse but no longer had a husband with whom to perform it. In Hippocrates' *On the Diseases of Women*, he wrote, "Sudden uterine suffocation: this affection is found most often in women who do not have sexual intercourse, and in women of a certain age rather than in young women."<sup>9</sup> The recurring theme in most writings, however, is that sexual abstinence provoked uterine illness, and so women were counselled to seek marriage and intercourse.<sup>13</sup> "If [women] have intercourse with men their health is better than if they do not. For in the first place, the womb is moistened by intercourse [...] In the second place, intercourse by heating the blood and rendering it more fluid gives an easier passage to the menses,"<sup>14</sup> wrote Hippocrates in *The Seed*. Young girls suffering from retained menses at the time of menarche were counselled to find a husband; widows were urged to remarry. It was not the union itself that cured, but rather the sexual intercourse that occurred between husband and wife.

Another facet of classical uterine medicine was the belief that the female was a less perfect version of the male,<sup>5</sup> a belief that was extrapolated to the results of intercourse, namely, conception and embryogenesis. Hippocrates believed that men and women both produced weak and strong sperms, and their relative amounts in the uterus determined the sex of the embryo: male if there were more strong sperms, and female if there were more weak sperms.<sup>14</sup> Furthermore, Aristotle espoused the idea that, in the act of regeneration, the woman simply provided the physical matter, while the man supplied the formative substance that imbued the resulting embryo with a human soul. "Thus, if the male is the active partner, the one which originates the movement, and the female *qua* female is the passive one, surely what the female contributes to the semen of the male will be not semen but material."<sup>15</sup> This idea that the role of women in procreation was to receive the sexual offering of the man would persist in subsequent centuries.

### The Uterus in the Middle Ages (ca. 400 CE – 1450 CE)

It was the idea of the wandering womb, and not its counterargument, that was transmitted to physicians in the Middle Ages. Galen's objections to a wandering uterus did not influence subsequent physicians, although his assertion that hysterical suffocation was caused by retention of menses persisted. Likewise, despite Soranus' influence in this era, due to the translations of Oribasius and Mustio, his objections to a wandering uterus were presumably not included in those texts, and so had no influence on subsequent uterine medicine. In fact, in his sixth-century text based on Soranus, Mustio wrote

of a womb that could “[rise] upwards to the chest.”<sup>16</sup>

The earlier period of the Middle Ages, sometimes known as the Dark Ages, marked the time after the collapse of the Roman Empire. A major trend in uterine medicine during this time reflected the different attitude of Christianity towards sex. Chastity was paramount, and the Church could not condone the prescription of intercourse as the treatment for a wandering womb. What they *could* prescribe was marriage, an acceptable male-female relationship within whose bounds the act of intercourse could take place. St. Augustine cautioned, however, that there should be no pleasure in the sexual act. It was for the sole purpose of procreation, and to indulge in it for pleasure was a sin. “Who does not know what passes between husband and wife that children may be born? Is it not for this purpose that wives are married with such ceremony?” he asked, in *City of God*.<sup>17</sup> A thirteenth-century text, Ricardus Anglicus’ *Anatomia Vivorum*, echoed this idea of divine purpose, “God created the uterus to be the instrument and the place of generation in women.”<sup>18</sup>

In the same work, St. Augustine also wrote, “...when sexual intercourse is spoken of now, it suggests to men’s thoughts not such a placid obedience to the will as is conceivable in our first parents [i.e. Adam and Eve], but such violent acting of lust as they themselves have experienced.”<sup>17</sup> Thus, because lust was sinful, the element of control over the sexual desires of the body was important. An early medieval text, *Anatomia Magistri Nicolai Physici*, attempted to explain rationally why, once aroused, women took longer to quench their sexual desires. For, “women, on account of their own complexion (cold and wet compared to men) as well as the complexion and solidity of the uterus, are not easily aroused, but once inflamed their desire does not quickly subside.”<sup>18</sup>

A twelfth-century medieval manual on porcine anatomy, *Anatomia Porci*, attributed to Copho, described the perceived function of the uterus as a “field”:

“...whatever superfluities are generated during the course of the month may be sent to the organ as if to form the bilge-water of the whole body; this is the nature of the menses which women have. This organ is also nature’s field, which is cultivated that it may bear fruit.”<sup>18</sup>

It is interesting to note, in passing, the comparison of the menses to bilge-water. Historically, and across cultures, this stigma of uncleanness was often attached to menstruation, which may help to explain why medical writers, ranging from Galen to Ambroise Paré in the Renaissance, believed that retention of menses in the body caused illness.

The *Anatomia Porci* described the uterus as having “seven cells.”<sup>18</sup> It was echoed by the *Anatomia Magistri Nicolai Physici*, which expanded on the subject by describing where foetuses are formed, according to gender.

“The uterus is divided into seven cavities [...] [Some] say that both males and females are generated on the right side and also on the left; but they also say that a male generated on the left side will be a weak and effeminate man, and conversely a female generated on the right will be mannish and rough.”<sup>18</sup>

Note that males who formed on what is usually the female side were thought to emerge “weak”. *The Anatomia Vivorum* agreed that males formed on the right, and females on the left.<sup>18</sup> It also agreed with Aristotle about the male and female contributions to generation, “The male sperm acts upon the female, for the male sperm naturally tends to impress the form of that from which it comes, and the female sperm tends to receive form.”<sup>18</sup>

A discussion of uterine medicine in the Middle Ages would not be complete without a consideration of Trotula, whose obstetrical and gynaecological works were some of the most important texts that have been passed down to us from that era. Although Trotula described the womb as capable of displacement, she was sensitive to women who did not want to have intercourse, even going so far as to suggest remedies to dampen a husband’s sexual urges, which include the testis of a cock, lettuce seed, and topaz.<sup>19</sup> However, despite not only this sensitivity, but also her intention to “write of how to help [women’s] secret maladies so that one woman may aid another in her illness,”<sup>19</sup> and her assertion that men “fail to realize how much sickness women have before they bring them into this world,”<sup>19</sup> she agreed that women were the frailer sex.

The stronger qualities, that is the heat and the dryness, should rule the man, who is the stronger and more worthy person, while the weaker ones, that is to say the coldness and humidity, should rule the weaker [person], that is the woman. And [God did this] so that by his stronger quality the man might pour out his duty in the woman just as seed is sown in its designated field...Therefore, because women are by nature weaker than men and because they are most frequently afflicted in childbirth, diseases very often abound in them especially around the organs devoted to the work of Nature.<sup>20</sup>

It is notable that Trotula referred to the uterus as a “field”, as did the author of the *Anatomia Porci*, and that its purpose is to be “sown” with male seed, which echoed the reference in Plato’s *Timaeus* (given previously) to “fruit” growing within the womb. This analogy, combined with the belief that it was the male seed that actively formed the foetus, implies that a passive female role in generation was expected.

Trotula continued on the theme of female illness and wrote, “And many of the sicknesses that women have come from the ailments of this “mother” that we call the marice [uterus].”<sup>19</sup> She attributed hysteria to evil fumes from the uterus, due to retention of menses or corrupt humours. Sufferers fainted and experienced great pain. For treatment, she advised the purging of the blood or humours, and also reverted to the classical use of fumigation:

And let the patient smell stinking things that are exceptionally odorous, such as burnt felt, dog’s hair, goat’s hair, or a horse’s bone set alight and then extinguished, or hartshorn, old shoes, burnt feathers, a wick, moistened in oil, ignited and then extinguished, a woollen rag, or a live smoking coal [...] and make a fumigation underneath of pleasant, sweet-smelling things and draw the matter down from the heart.<sup>19</sup>

Trotula's texts also showed a clear link between uterine illnesses and sex. Suffocation of the womb occurred in women, she wrote,

"[...] because corrupt semen abounds in them excessively, and it is converted into a poisonous nature. This happens to those women who do not use men, especially to widows who were accustomed to carnal commerce. It regularly comes upon virgins, too, when they reach the age of marriage and are not able to use men and when the semen abounds in them a lot, which Nature wishes to draw out by means of the male."<sup>20</sup>

Here, we have again the theme of marriage (the only social institution in the context of which sexual intercourse was acceptable) as a preventive measure against uterine suffocation.

### The Uterus in the Renaissance (ca. 1450 CE – 1650 CE)

The Renaissance marked a period in European history when scholars looked back upon the classical period with admiration. The French author and cleric, François Rabelais (1483-1553), although not strictly a medical writer, was well-read and familiar with classical medical texts. The persistence of the idea of the wandering womb and its link to hysteria is evident in his satire, *Pantagruel*, where Rabelais commented dryly on women and their tendency to hysteria as a result of the uterus. This was done through the character Rondibilis, a physician, who referred to the uterus as an animal-like organ.<sup>21</sup> Rabelais also cited classical authors, "Let it not here be thought strange that I should call [the uterus] an *animal*, seeing therein I do no otherwise than follow and adhere to the doctrine of the Academic and Peripatetic philosophers."<sup>21</sup> Two of these "academic and peripatetic philosophers" were Aristotle and Plato. Rondibilis then concluded that what would satisfy the uterus was intercourse with a man, "the said animal (i.e. the uterus) being once satiated [...] by that aliment which nature hath provided for it out of the epididymal storehouse of man (i.e. sperm), all its former and irregular and disordered motions are at an end."<sup>21</sup>

The English doctor, Edward Jorden (1578-1632), also continued in the tradition of ascribing uterine causes to feminine hysteria. His work, *A Disease Called the Suffocation of the Mother*, was notable because it rejected supernatural causes of the hysterical symptoms that were often taken, at this point in history, to indicate witchcraft or demonic possession.<sup>22</sup> "The passive condition of womankind is subject unto more disease and of other sortes and natures than men are"<sup>23</sup> because of the uterus, and so the causes of this feminine disease must have been natural. With regard to uterine suffocation:

In English the Mother, or the Suffocation of the Mother, because most commonly it takes them with choaking in the throat: and it is an affect of the Mother or wombe wherein the principal parts of the bodie by consent do suffer diversly according to the diversitie of the causes and diseases wherewith the matrix is offended.<sup>23</sup>

In his last chapter, Jorden wrote of treatments that friends and attendants of the patient might perform. In keeping with

his insistence on natural causes of disease, he did not have much patience for "those superstitious remedies which have crept into our profession,"<sup>23</sup> including charms, amulets, and incense.

Ambroise Paré (1517-1590) also rejected supernatural explanations for the symptoms associated with hysteria. He did, however, persist in the belief that women were erratic because of their wombs and were, in addition, a less perfect version of men, with generative organs analogous to the male ones, but inverted.<sup>22</sup> Interestingly, he believed that, in some cases, hysteria generated a form of madness, a *furor uterimus*<sup>2</sup> in the woman, anticipating the time when hysteria would be seen as a condition of the mind. However, his is reliance on Galenic and Hippocratic theory was evident in his insistence that sexual abstinence caused retention of the menses, which in turn caused uterine suffocation.<sup>2</sup>

In general, the Renaissance would see the beginnings of a shift, as the female body came to be portrayed more and more realistically. This was in large part due to the increasing acceptance of female cadavers being displayed in medical classes for the purpose of education through dissection.<sup>22</sup> Some physicians began to postulate that the symptoms associated with hysteria did not in fact have their origin in the womb.<sup>2</sup> The 1700s would then usher in another new scientific era. As anatomical illustration and dissection became more sophisticated, and new technologies included microscopy, hysteria gradually became less associated with the uterus, and instead became associated with the mind.<sup>22</sup>

### Conclusion

In Western medicine, from the Classical period through to the Renaissance, the uterus was believed to be the cause of feminine illness. The prevailing theme was one where the uterus, whether by migrating through the female body or by acting through some other natural mechanism, caused symptoms that were brought together under the general heading of *hysteria* or *uterine suffocation*. This was deemed an illness specific to the female sex.

There are several aspects to this theme. One is that women were believed to be not only the frailer sex, but also the passive partner in intercourse and conception, with a recurring image – from the classical period through to the Renaissance – of the female womb as a "field" in which the male seed was "sown". This implied that the female only supplied the environment in which the embryo would grow, while it was the male who supplied the vital component that would create a new life.

As to why the uterus was believed to cause illness, we must look to the perceived function of the uterus, which is to bear children. This is a theme that was covered by writers ranging from Plato in the classical age, to the medieval author of *Anatomia Porci*, to Rabelais in the Renaissance. It was believed that if the uterus could not fulfill its function, as a result of sexual abstinence, then it would be the source of disease, although the mechanism of this causation differed from writer to writer. Plato's depiction of the uterus as an entity that *desired* to bear fruit – that is, a child – was echoed as late as the Renaissance, by such writers as Rabelais. Women were therefore instructed to marry and engage in intercourse with their husbands, and this course

of treatment was justified by the aforementioned medical explanations of uterine illness. Although the social context of intercourse changed in the early part of the Middle Ages, when Christian morality dictated that sex was not for pleasure but for procreation, uterine illness continued to be explained as the result of abstinence, and so marriage continued to be urged upon women as beneficial to their health.

Thus, Western uterine medicine, from the Classical era to the Renaissance, provided a means of rationalizing social attitudes towards the female sex, which could then be used to justify prescribed treatments (i.e. marriage) that encouraged women to conform to their roles as wives and mothers.

### References

- Ricci JV. The genealogy of gynaecology; history of the development of gynaecology throughout the ages, 2000 B.C.-1800 A.D., with excerpts from the many authors who have contributed to the various phases of the subject. Philadelphia: The Blakiston Company; 1943.
- Veith I. Hysteria: The history of a disease. Chicago: University Press; 1965.
- Hippocrates. De Antiqua Medicina [monograph on the Internet]. Cambridge, MA: Massachusetts Institute of Technology, Internet Classics Archive; 22 Nov 2004. Available from: <http://classics.mit.edu/Hippocrates/ancimed.html>
- Persaud TVN. Early history of human anatomy: from antiquity to the beginning of the modern era. Springfield (IL): Thomas; 1984.
- Soranus, of Ephesus. Soranus' Gynecology. Temkin O, translator. Baltimore: Johns Hopkins Press; 1956.
- Singer CJ. A short history of anatomy from the Greeks to Harvey. 2nd ed. New York: Dover Publications; 1957.
- Hanson AE. Uterine amulets and Greek uterine medicine. *Med Secoli*. 1995;7(2):281-99.
- Dasen V. Métamorphoses de l'utérus d'Hippocrate à Ambroise Paré. *Gesnerus*. 2002;59(3-4): 167-86.
- Hippocrates. Oeuvres complètes d'Hippocrate: traduction nouvelle avec le texte grec en regard, collectionné sur les manuscrits et toutes les éditions: accompagnée d'une introduction de commentaires médicaux, de variantes et de notes philologiques: suivie d'une table générale des matières. Vol. 8. Littré E, translator. Paris: J.B. Baillière; 1839-61.
- Aretaeus, of Cappadocia. Des causes et des signes des maladies aiguës et chroniques. Grmek MD, editor. Laennec RTH, translator. Genève: Droz; 2000.
- Plato. Timaeus, Critias, Cleitophon, Menexenus, Epistles. Bury RG, translator. London: Heinemann; 1929.
- Galen. Galen on the affected parts: translation from the Greek text with explanatory notes. Siegel RE. New York: S. Karger; 1976.
- Allison DB, Roberts MS. On constructing the disorder of hysteria. *J Med Philos*. 1994 Jun;19(3):239-59.
- Hippocrates. Hippocratic Writings. Lloyd GER, editor. Chadwick J, Mann WN, translators. Harmondsworth (NY): Penguin; 1978.
- Aristotle. Generation of animals. Peck AL, translator. Cambridge: Harvard University Press; 1963.
- Soranus, of Ephesus. Gynaecia Mustionis: the midwives' catechism of Mustio (englisch und lateinisch); & Eucharius Rösslin's Rosegarden. Medert H, translator. Frankfurt am Main: Haag + Herchen; 1998.
- Augustine, Saint, Bishop of Hippo. The city of God by Saint Augustine. Dods M, translator. New York: Modern Library; 1950.
- Corner GW. Anatomical texts of the earlier Middle Ages: a study in the transmission of culture, with a revised Latin text of Anatomia Cophonis and translations of four texts. New York: AMS Press; 1977.
- Rowland B. Medieval woman's guide to health: the first English gynecological handbook. Kent (OH): Kent State University Press; 1981.
- Green MH. The Trotula: a medieval compendium of women's medicine. Philadelphia: University of Pennsylvania Press; 2001.
- Rabelais F. The works of Rabelais, faithfully translated from the French with variorum notes, and numerous illustrations by Gustave Doré. Doré G, translator. Nottingham: Printed for private circulation; 1800.
- Thompson L. The wandering womb: a cultural history of outrageous beliefs about women. Amherst (NY): Prometheus Books; 1999.
- Jorden E. A disease called the suffocation of the mother. Amsterdam: Theatrum Orbis Terrarum; 1971.

## Maternal Care Practices and Perceptions of Birth Defects in Central India

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### Abstract

With a multicultural patient base, it is important to remember that every society has its own ideas of health and illness. In the cases of birth defects and developmental disabilities in children, it is vital for healthcare providers to act with sensitivity in response to ethnocultural variations in belief systems. This study employed structured interviews investigating the maternal care beliefs and perceptions of birth defects in 37 patients at a rural health post in central India. This study elucidated a range of widely held culturally- and superstitiously-based beliefs regarding what characteristics make a child "healthy", how a pregnant woman can ensure a healthy child, and common beliefs about birth defects in this rural Indian population.

### Introduction

The iconography of ancient Indian deities has revolved for centuries around an omniscient, benevolent Mother Goddess (*Mata*) who rewards good, punishes evil, and provides equally for all her children. This image has carried through the ages and has become the accepted model for motherhood in many cultures. For many of India's disabled children, however, this image remains an unlikely mythological ideal.

India is a country with more than a billion citizens, 35.6% of whom are under the age of 15.<sup>1</sup> Although the nation's total literacy rate is 65.8%, half the population is not immunized by their first birthday, 14% of children are engaged in active labour, 54% of children are betrothed in child marriages, and only 60% of students entering primary school actually reach grade five. The prevalence of underweight children is 47%.<sup>2</sup>

In impoverished areas of India, many children are born with abnormalities or malformations. Due to persisting belief systems, children from families who cannot afford to raise a child or those born out of wedlock may be left to grow up in orphanages or on the streets with few resources available to ensure healthy development. In 2003, UNICEF recorded 35 000 new orphans in India.<sup>3</sup> Upon visiting orphanages in Gwalior, Madhya Pradesh, it is clear that most of the residents inhabiting these institutions are disabled, often with congenital abnormalities. With conditions ranging from Down Syndrome to cerebral palsy, these children are unable to function at the level of their healthier peers and are rarely adopted.

Research indicates that India's children have a 20/1000

rate of both major and minor birth defects.<sup>3</sup> Studies confirm that the fetus is susceptible to injury during fertilization and implantation, the embryonic period, and the fetal period.<sup>4</sup> Although genetics play a significant role, it is noted that up to two-thirds of fetal anomalies may occur due to non-genetic causes.<sup>5</sup> In 2003, 30% of Indian newborns were recorded with a birthweight of less than 2500 g, mostly attributed to maternal malnutrition and illness.<sup>2</sup> Further statistics suggest that during labour and delivery only 43% of females receive obstetric care from a skilled birth attendant. This may increase the possibility of trauma endured by infants during partum, thus increasing the chances of neurological and developmental deficits in the long-term. It is conjectured that one of the primary factors keeping pregnant women from accessing antenatal and antepartum care is the cost of care.

Of all the Indian states, Madhya Pradesh ranks highest in terms of poverty with 42.5% of citizens living below the poverty line and a poor rating on the human development index.<sup>6</sup> The rural literacy rate is 37.9%, with most education being passed informally through oral traditions and folklore. Madhya Pradesh also ranks among the highest rates of child marriage in the country, with 65% of brides under the age of 18.<sup>7</sup> As such, many Madhya Pradeshi women bear children at a young age and learn about maternal care practices through traditional beliefs and customs.

This study investigated the beliefs of individuals in Gwalior and surrounding areas with regards to maternal care practices and birth defects.

### MATERIALS AND METHODS

#### Participants

Forty patients receiving care at the Gwalior Children's Hospital in Madhya Pradesh, India, were approached for a structured interview during the summer of 2005. The patients were requested to be interviewed immediately after their physician encounter, either at the main hospital site or at a rural health post served by the hospital's mobile unit. Participation in the study was voluntary, and responses were recorded on paper with a random identification number assigned to each respondent in order to maintain anonymity. Participants had to be greater than sixteen years of age and had to have lived for at least five years in Gwalior or the surrounding area.

#### Interviews

Participants were first asked questions concerning demographic data. Respondents were then asked a series of questions about their experiences and opinions regarding birth abnormalities and pregnancy (Table 1).

Interviews were conducted in Hindi by a Canadian medical student, who was volunteering at the hospital and mobile health unit. Due to occasional disparities between the interviewer's Hindi and the local dialect, hospital staff helped to translate when necessary. All interviews were conducted by the same interviewer to minimize inter-rater bias.

Some patients expressed concern toward having their responses audiotaped, so all responses were translated into English and recorded in writing during the process of interviewing.

Identifying data	Age Level of education attained, occupation Marital status, age of first marriage Area of residency, population of resident village or city
Social history	Number of pregnancies (female respondents only) Number of children, ages of children Please describe the health of your children. Do they attend school?
Understanding of developmental disabilities	What are the characteristics of a healthy baby? What do you think a mother can do during her pregnancy to have a healthy baby? Some children are born with abnormalities, why do you think this occurs? Do you know any families with children who have abnormalities? If so, how have they coped?

**Table 1.** Structured Interview Questions

## RESULTS

Forty individuals were approached and 37 agreed to participate in the study, with the remaining three reporting lack of time as the reason they declined to participate. Of these 37 respondents, 32 were individuals seeking medical advice from the Gwalior Children's Hospital or rural health post for themselves or a family member. Of the remaining five respondents, three were nurses while two were caregivers in the orphanages.

Of the participants, 20 were female (54%). The respondents' ages ranged from 18 to 78 years, with a mean age at marriage of 16.4 for females and 18.2 for males. Eighty-nine percent of those interviewed lived in small agricultural villages surrounding the Gwalior area, with populations ranging from 1300 to 4000. Ninety-five percent of respondents had children of their own. The mean number of children per family was 4.2 and 65% of respondents' families delivered their infants without a physician, nurse or midwife present. Six of the female respondents (30%) admitted to having either a miscarriage or still-birth delivery. All but one respondent claimed that their children were attending school. All respondents described their children as being "healthy" and none were currently caring for any children with significant birth defects or developmental anomalies.

### Perceptions of healthy infants

In order to assess individuals' perspectives on birth defects and children's health, they were first questioned about what characteristics they considered hallmarks of good health in children. Eighty-nine percent of respondents described good health as the absence of symptoms of illness, such as cough, runny nose, fever, and vomiting. Physical characteristics considered important were steady growth in comparison to peers

(both height and weight) (65%), full cheeks (54%), rosy complexion (54%), and smooth skin (49%). Personality behaviours described as being important characteristics of health were alertness and awareness of surroundings (65%), early age of speaking and walking independently (89%), performing well academically (89%), and absence of fatigue (65%). Conversely, unhealthy children were described as those with visible signs of illness (cough (95%), fatigue (78%), stunted growth (89%)) or physical abnormalities (cleft lip (59%), cerebral palsy (73%)).

### Maternal care beliefs

Overwhelmingly, respondents expressed that the best care for a woman during pregnancy was proper nutrition. Ninety-five percent of interviewees claimed that milk, yogurt, and other dairy products were the most important staple foods required for a healthy pregnancy. Eighty-one percent listed the importance of vegetables and fruits in a mother's diet.

Other factors listed as important were prayer and meditation (49%), rest during pregnancy (49%), abstaining from the use of farm equipment and sewing needles (14%), and taking multivitamin supplements (8%). There was no significant difference between the responses of male and female participants.

### Perceptions of birth abnormalities

Study participants were asked about why they thought birth defects were likely to occur. Again, 95% of interviewees described an insufficient diet as being the chief cause of infant abnormalities. Sixty eight percent recognized the importance of up-to-date vaccinations for pregnant women.

Notably, 32% of respondents listed supernatural causes of birth abnormalities in children. All of these respondents suggested that a woman should avoid directly viewing an eclipse during her pregnancy to avoid harming her fetus. Also, 14% claimed that, during pregnancy, women should refrain from the use of sewing needles, scissors, and knives during a full moon. Some respondents claimed that pregnant women should fast during certain times of the lunar cycle and also wake at dawn each morning to pray.

Somewhat related, 22% of respondents mentioned the possible effects of karmic forces and witchcraft. It was suggested that repercussions of sins committed in a past life could be manifested in a current life in the form of a sick child. Although some suggested that "serving" a disabled child could be seen as an opportunity to receive karmic exoneration, it was mentioned by 19% of respondents that most people would find raising a disabled child embarrassing because of social stigma. These respondents were further probed about how these karmic forces could be counteracted. In order to avoid later onset of supernaturally-caused disabilities, all 22% of respondents described at least one of: the application of dark kohl around the eyes and on the forehead, symbolic tattoos, or wearing coloured bangles and amulets that had been blessed by a priest.

Most interviewees were unable to describe specific methods of caring for disabled children, often claiming they had had no such experience. The 7% who did respond simply claimed that the children should be raised with affection and their medical needs met, as scientifically and economically possible.

Overall, 22% expressed that parents of disabled children could be socially marginalized because of widely held beliefs that they had committed a mistake during pregnancy or in a past life. Notably, only the healthcare providers at the hospital

mentioned the possibility of uncontrollable genetic or hereditary factors affecting fetal development.

### Discussion and Conclusion

Low levels of health education and social stigma may be contributing factors to the declining care of India's disabled children. Due to the negative attitudes towards foreigners and researchers, it is difficult to fully assess the presence of these barriers and the extent of prejudice towards the disabled.

This qualitative study attempted to elicit data from patients, families, and healthcare workers to develop a basic comprehension of perceptions of birth defects and related maternal care practices. Hopefully, information from this study will allow for a better understanding of maternal care practices and how disabled infants are perceived in the community.

It is evident from this study that many young mothers may be ill-equipped to make informed nutritional and lifestyle choices during pregnancy. Although folk knowledge is certainly not to be discounted, research studies have proven the significant effects that diet modification and vitamin supplementation can have on an infant's wellbeing.<sup>8</sup> In countries where nutritionally fortified foods are not widely available or are too expensive, achieving sufficient levels of nutrients for a healthy fetus may be difficult. This is also true in remote or rural communities, where most dairy products (a staple in north Indian diets) are consumed without processing or fortification. What is considered a nutritionally complete diet during pregnancy in the western world may be difficult to administer when relying solely on farm-grown products in these areas.

Despite the fact that 89% of interviewees lived or worked in agricultural settings, none mentioned the possible effects of exposure to farm chemicals on the developing fetus. Chemicals, such as dioxins, which are widely distributed in agricultural settings can have significant teratogenic effects.<sup>9,10</sup> This could be particularly detrimental to women in these areas due to ongoing exposure and bioaccumulation. Although guidelines attempt to regulate the nature of chemicals used in farm settings, infrastructural gaps often make these regulations difficult to enforce and therefore exposure to these chemicals continues.

From an anthropological perspective, perhaps one of the most interesting aspects of this study was the elucidation of many superstitious and religious customs that govern behaviour during pregnancy. The fact that families will go to great lengths to avoid delivering infants with disabilities clearly indicates that children with disabilities are undesired.

Further, anecdotes from seven separate interviewees identified acquaintances who had delivered a child perceived as "abnormal" and had chosen not to keep the child. Oftentimes, this was the case among financially unstable families, whose resources would be further stretched if a parent were to stay at home and care for a child, who would never be able to earn money. Currently, supports available to parents of disabled infants are few in rural areas. It was suggested that families had decided to give up their disabled child because they feared social ostracism. According to four interviewees, they believed that if they kept the child, their family would be shunned by society and considered to be sinners who were being punished by a divine entity.

A criticism of the study was the effect of the participants' perceptions of the interviewers on the information gathered.

Local hospital workers explained that it was generally believed that non-Indians frown upon traditional or superstitious beliefs. As such, respondents could be apprehensive about giving this information to a recognizably foreign interviewer, as in this study. Local residents and healthcare staff suggested that interviewees were more likely to give what they thought would be acceptable answers, instead of telling the truth. Interestingly, patients who claimed to have no superstitious beliefs with regards to their children's health often still adorned their children with kohl, black string and anklets – all traditional signs of warding off the "evil eye". Upon questioning by Canadian researchers, interviewees seemed to reveal their superstitions with some hesitation. When local hospital workers questioned individuals with the same list of questions, however, participants seemed more willing to discuss religious or superstitious issues without requiring further probing.

The pieces of the puzzle are numerous and diverse. It is incredibly important that we recognize and comprehend that superstition and religious beliefs play a huge part in maternal care and parenting. In societies that have strong roots in traditional customs, it may be worthwhile to complement the traditional knowledge passed between generations with research-based knowledge in order to increase the health of developing fetuses and expectant mothers.

With increasingly multicultural patient populations across North America, it is important for health care practitioners to be informed of variations in values and belief systems. A heightened awareness of these cross-cultural variations may allow practitioners to provide more appropriate counseling to patients in obstetric and pediatric settings and to allow for more culturally sensitive responses to their concerns.

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### References

1. Census of India, 2001 [database on the Internet]. New Delhi: Census India. [cited 2007 February 27]. Available from: <http://www.censusindia.net>
2. United Nations Children's Fund. Unicef – India – Statistics [homepage on the Internet]. New York: UNICEF [cited 2007 February 27]. Available from: [http://www.unicef.org/infobycountry/india\\_india\\_statistics.html](http://www.unicef.org/infobycountry/india_india_statistics.html)
3. Verma IC. Burden of genetic disorders in India. *Indian J Pediatr*. 2000;67:893-898.
4. Bazzoli AS, Manson J, Scott WJ, Wilson JG. The effects of thalidomide and two analogues on the regenerating forelimb of the newt. *J Embryol Exp Morphol*. 1977 Oct;41:125-35.
5. Kalter H, Warkany J. Congenital malformations: etiologic factors and their role in prevention. *N Engl J Med*. 1983;308:424-431.
6. Madhya Pradesh: Statistics [homepage on the Internet]. Madhya Pradesh: National Informatics Centre [cited 2007 February 28]. Available from: <http://www.mp.nic.in/aboutState/statistics/>
7. Public Health and Family Welfare Department. National Family Health Survey (NFHS) II. Delhi (India): Government of Madhya Pradesh;1999.
8. Gupta P, Gupta H. Neural Tube defects and folic acid. *Indian Pediatr*. 2004;41:577-586.
9. Dyke PH, Foan C, Wenborn M, Coleman PJ. A review of dioxin releases to land and water in the UK. *Sci Total Environ*. 1997;207:119-31.
10. Schulz AJ, Wiesmuller T, Appuhn H, Stehr D, Severin K, Landmann D, et al. Dioxin concentration in milk and tissues of cows and sheep related to feed and soil contamination. *J Anim Physiol Anim Nutr (Berl)*. 2005; 89:72-8.

## HIV/AIDS-Related Knowledge and Practices of Adults Following Government-Initiated Education Campaigns in Kep, Cambodia

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### Abstract

**Background:** Cambodia has the highest prevalence of HIV infection in Asia, at 1.6% of adults. Due to growing concern about this epidemic, the Cambodian government has initiated nationwide educational campaigns in an attempt to decrease the transmission of HIV. In 2004 Ho and Grewal conducted a baseline survey to determine HIV-related knowledge, attitudes, and practices of adults in one village in Kep, Cambodia. This follow-up study assessed the sustainability of knowledge following educational efforts by the Ministry of Health. **Objective:** To assess HIV/AIDS-related knowledge and practices of adults in rural Cambodia following the initiation of government-aided education programs. **Design:** Cross-sectional interview survey. **Setting:** Kep District of Cambodia. **Participants:** Adults between the ages of 18 and 58 living in ten different villages across the Kep District. **Measurements:** One hundred and twelve semi-structured interviews to assess knowledge regarding the transmission, prevention, management, and mother-to-child transmission of HIV. **Results:** The majority of respondents had an accurate knowledge of the modes of transmission and methods of prevention of HIV. Shortfalls in understanding included knowledge of mother-to-child transmission (MTCT). **Conclusion:** The findings of this study will be used by the Ministry of Health in Cambodia, in conjunction with the Centre for International Health at the University of Toronto, to focus community-based educational efforts and interventions in the fight against HIV/AIDS.

Cambodia has the highest prevalence rate of HIV infection in Asia, at 1.6% of the adult population. The Ministry of Health has established nationwide education campaigns to prevent the spread of HIV infection. In 2004, Ho and Grewal conducted a baseline study looking at the knowledge, attitudes, and practices of adults living in Okrasa Village in the Kep region. At that time, 56 participants were interviewed in Okrasa Village. It was found that educational efforts were largely successful at communicating the modes of transmission of HIV, though there was a lack of knowledge about the availability of anti-retroviral therapy and treatment for persons living with HIV/AIDS (PLWHA). This current study served as an extension of the work completed by Ho and Grewal for the Centre for International Health to assess the long-term effectiveness of government-initiated education campaigns in rural areas of Cambodia. Semi-structured interviews were conducted with adults in ten villages in the Kep district. Several main objectives were identified: 1) to assess the knowledge of HIV/AIDS in adults, including definition, transmission, and prevention; 2) to examine the practices of adults regarding prevention of HIV infections and voluntary HIV testing; and 3) to determine the sustainability of knowledge following the initiation of educational programs, by comparison with baseline data.



Figure 1. Author and translator conducting an interview in Kep, Cambodia.

### Introduction

With a population of 14.1 million, Cambodia is a country recovering from a tragic history of civil unrest and political brutality culminating in the Pol Pot Regime of the 1970s. Despite the political and economic improvement of the last thirty years, the health status of Cambodia is still among the poorest in the world, with a life expectancy at birth of only 51 years. Some of the current health problems include malnutrition, malaria, tuberculosis (TB), preventable infectious diseases, Human Immunodeficiency Virus, and Acquired Immune Deficiency Syndrome (HIV/AIDS).<sup>2</sup>

### MATERIALS AND METHODS

#### Study Population

This study was conducted in June and July of 2006 through individual semi-structured interviews with inhabitants (Figure 1) of the Kep municipality in Cambodia (Figure 2) under the guidance of the Centre for International Health at the

University of Toronto. In 2005 the estimated number of residents in this area was 34,000 people in 6,800 families. The study population consisted of adults between the ages of 18 and 58 years in ten of the sixteen villages and three health centers in Kep. The researcher was accompanied by a local translator to households in the various villages where interviews were conducted in the Khmer language. Each interview lasted approximately 45 minutes. One hundred and twelve adults, both men and women, were interviewed over the course of two months. Households were randomly selected based on geographical location to approximate representation across the municipality. Confidentiality was assured for every participant and oral consent was obtained.



**Figure 2.** Village in Kep district, Kingdom of Cambodia.

### Questionnaire

The interviews were structured around a questionnaire containing 48 closed and open-ended questions. The interview opened with 7 demographic questions followed by 21 questions directly assessing the knowledge, clinical

symptoms/signs, transmission, and prevention of HIV/AIDS. Next, there were 10 questions pertaining to attitudes towards people living with HIV/AIDS and awareness of HIV testing, and, finally, there were 8 questions regarding sexual practices and high-risk behaviours associated with sexually transmitted infections. Further questioning around relationships with neighbours or family members who were HIV-positive was pursued if participants were open to the discussion.

## RESULTS

### Demographic Data

One hundred and twelve interviews were conducted with 52 men and 60 women. The mean age of all participants was 34 years. Literacy rates were 38% for women and 54% for men. The mean age of those who had completed high school (grade 12) was 24.5 years, while the mean age of those with no education was 39.1 years. Participants were asked whether they had ever heard of the educational outreach events hosted by the Operational District (OD). The main topics of presentation attended were: HIV/AIDS, malaria, TB, and Avian Flu.

### HIV/AIDS-Related Knowledge and Practices

Participants were asked questions to directly assess their knowledge of HIV and AIDS (Table 1). Eighty-three respondents (74%) indicated that they had knowledge of HIV. When asked more specifically to give a definition of HIV, the majority of respondents (76%) stated that "HIV is a transmissible and fatal disease"; however, some respondents (8%) believed that "HIV is a disease due to poor hygiene" and others (16%) did not know what HIV was. Respondents identified the following risk factors for acquiring HIV: sex workers, "people who go out at night" (presumably those with high-risk sexual behaviours), business people, and people who travel for work. With regard to transmission, all participants knew that HIV was transmitted through sexual contact. Misconceptions regarding transmission via mosquitoes and saliva remained. Condoms were indi-

	Yes (%)	No (%)
<b>Ministry of Health Educational Outreach</b>		
1. Are you aware of the Educational Outreach programs conducted by the Operational District (OD)?	52	48
2. Have you ever attended a session conducted by the OD?	31	69
<b>Definition</b>		
3. Do you know what HIV/AIDS is?	74	26
4. Do you know what a virus is?	25	75
5. Can a person die from HIV/AIDS?	100	0
<b>Transmission</b>		
6. Do you know how HIV/AIDS can be transmitted?	94	6
7. Can HIV/AIDS be transmitted from mother to child?	86	14
<b>Testing and Treatment</b>		
8. Have you heard of a blood test to determine if a person has HIV/AIDS?	89	11
9. Have you been tested for HIV/AIDS?	17	83
10. Has your partner ever been tested for HIV/AIDS?	21	79
11. Do you know anyone with HIV/AIDS?	80	20
12. Do you know of any treatment for HIV/AIDS?	71	29

**Table 1.** Participants' responses to HIV/AIDS-related knowledge questions.

cated as the primary method of preventing HIV transmission. Some respondents (<5%) indicated that sleeping with a bed net could reduce the risk of acquiring HIV, which is consistent with the belief that HIV can be acquired from mosquitoes. Study participants were asked about mother-to-child transmission of HIV. Nearly all respondents knew that the virus could be transmitted from mother to child; most believed that this occurred in utero and could not be prevented. The majority of respondents also indicated that an HIV positive mother should not breastfeed her baby.

General knowledge of the common signs and symptoms of HIV was accurate and included weight loss, fever/chills, diarrhea, headache, and dark spots on the skin (Kaposi's sarcoma). The majority of respondents (82%) also understood that HIV could not be diagnosed by appearance alone and that many people with HIV appear healthy. Most respondents (70%) were aware of a treatment for HIV though could not specifically name antiretroviral therapy. Furthermore, nearly all respondents stated that an HIV positive person should be treated at a hospital, as opposed to a traditional healer or private clinic. The two hospitals in the surrounding districts that provide treatment for HIV positive patients (Kampong Trach and Takeo Hospital) were named in a minority of interviews. The main sources of HIV/AIDS-related information are illustrated in Figure 3.

Study participants were questioned on their knowledge of HIV testing and testing centers. Nearly all respondents (94%) were aware of a test for HIV and stated that HIV testing was available at any hospital. The main reasons given for seeking voluntary, confidential counseling and testing (VCCT) included the patient's partner having had multiple sex partners, the patient's being chronically ill, the patient's having lost a lot of weight, or the patient's being about to get married and the spouse-to-be requesting an HIV test. However, only 22% of respondents had personally been tested for HIV.

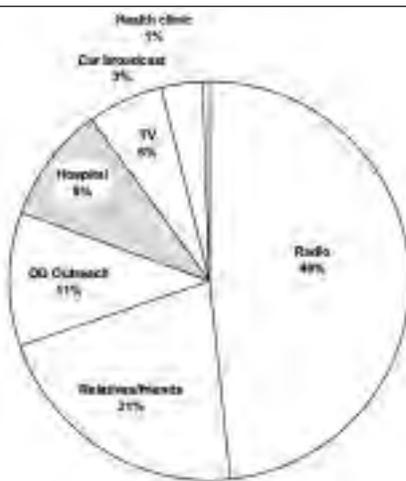


Figure 3. Sources of HIV/AIDS-related information.

## DISCUSSION

The general understanding of HIV/AIDS in adults in the Kep region was reasonably accurate with regards to the definition, risk factors, modes of transmission, and methods of pre-

vention. Though misconceptions regarding transmission via mosquitoes remain, this increased motivation to use mosquito nets could provide additional benefits by protecting against malaria. Many of the risk factors for acquiring HIV reflected cultural practices common in developing countries. Sex workers were correctly identified as a high-risk population, although data has shown that in fact sex work-related transmission has decreased dramatically since 1995 as a result of education campaigns and condom usage programs.<sup>4</sup> Businessmen and men who travel far from home were identified as being at higher risk for HIV infection. In Cambodia, men are often forced to seek employment outside their native community, often near the Thai-Cambodian border. Similar data from China has shown that men who work away from home are likely to engage in high-risk sexual activities and are therefore active players in the propagation of HIV when they return home to their wives. The common signs and symptoms of HIV/AIDS recognized by respondents were accurate. Interestingly, only 11% of respondents identified the Ministry of Health Outreach programs as a source of HIV knowledge. The main source of information was radio broadcasts sponsored by the Federal government.

## Mother-to-Child Transmission (MTCT) of HIV

In Cambodia, 25% of new HIV cases are due to MTCT of the virus, compared to 5% in the early 1990s. Several factors contribute to the problem of MTCT: 1) stigma associated with being HIV positive prevents many women from being tested; 2) lack of targeted education means that many pregnant women who are HIV positive are not aware of the methods to reduce the risk of viral transmission; 3) access to healthcare is often a barrier to receiving antiretroviral therapy (ART) and the appropriate support. Estimated rates of HIV transmission from mother to child range from 25 to 48% in developing countries. With proper therapy, transmission rates can be reduced to less than 2%. While many of the methods for preventing MTCT used in developed countries are impractical or unfeasible in developing countries, appropriate methods include the use of ART and counseling mothers regarding breastfeeding. The World Health Organization currently recommends that all HIV-positive mothers in developing countries should breastfeed exclusively for at least six weeks, as studies have found that where there is a lack of resources (clean water, sterile containers, and appropriate infant formula), the benefits of breastfeeding an infant outweigh the risks of transmission of HIV through breastfeeding. This policy has been formally adopted by the Ministry of Health in Cambodia, however, the practice had not been implemented by the participants of this study. Most respondents believed that breastfeeding should be discouraged in HIV-positive women, a misunderstanding that could potentially increase the health risks of babies born to HIV-positive mothers, where breastmilk substitutes are not readily available. Educational efforts toward communicating effective methods for preventing MTCT of HIV need to be in place to oppose the increasing incidence of HIV among newborns.

## Voluntary, Confidential Counseling and Testing for HIV (VCCT)

Cambodia initiated voluntary counseling and testing for HIV in 1995. Ten years later, in 2005, there were 95 registered

Ministry of Health VCCT sites, with at least one in every province.<sup>16</sup> Though the rate of VCCT is increasing, several barriers remain: 1) the fear of social stigma and discrimination prevent many people from seeking VCCT; 2) due to a lack of education regarding available treatment, many Cambodians do not perceive a benefit to knowing their HIV status.<sup>16</sup> HIV testing is currently available at several hospitals in neighbouring districts but is as yet unavailable at the Kep Hospital. Only 22% of respondents in this study had gone for VCCT; this suggests a need to encourage testing to help ensure timely and effective treatment for HIV-positive adults and children in the Kep region.

### Comparison to Baseline Data

The results of this study were comparable to those of Ho and Grewal in 2004, suggesting that education efforts have been effective in conferring sustainable HIV/AIDS-related knowledge. At that time, the authors stated that study participants had an adequate knowledge of HIV/AIDS, modes of transmission, signs and symptoms, and HIV testing. MTCT of HIV/AIDS was not assessed in the baseline study. In this follow-up project, respondents once again demonstrated a simple understanding of HIV/AIDS as a sexually-transmitted infection, of modes of transmission, and of methods of prevention. In contrast to baseline data, the current study found that only 89% of participants were aware of how and where to get tested for HIV, and only 17% of participants had personally been tested. This could reflect the fact that the village where Ho and Grewal conducted their study (Okrassa) is one of the more affluent and centrally-located villages in Kep with easier access to HIV testing facilities. While baseline data indicated a lack of knowledge regarding available treatment for HIV/AIDS, 71% of respondents in this study were aware of medical treatment, and a minority were able to name hospitals where treatment was available. In 2004, ART was only available at Takeo Hospital, but since that time Kampong Trach Hospital has also initiated a treatment program for PLWHA. These encouraging findings suggest that government-sponsored education have resulted in sustainable knowledge about the basic facts regarding HIV/AIDS, transmission, and prevention. Areas in need of development include knowledge and prevention of MTCT and availability of VCCT. Further studies to accurately gauge the current prevalence of HIV infection are needed to assess whether increased knowledge of HIV/AIDS translates into a reduction in HIV infection rates.

It is hoped that the findings in this research project will be used by the Ministry of Health in Cambodia, in conjunction with the Centre for International Health (CIH) at the University of Toronto, to improve education campaigns and HIV-related prevention strategies and, thus, play a role in the global fight against HIV/AIDS.

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### References

- 2006 World Population Reference Sheet. [database on the Internet]. Population Reference Bureau. [cited 2007 Mar 2]. Available from: <http://www.prb.org/pdf06/06WorldDataSheet.pdf>.
- Country Profiles. Cambodia Country Profile. [database on the Internet]. World Health Organization. [cited 2006 Jun 2]. Available from: <http://www.who.int/countries/khm/en/>.
- Pisani E, Garnett GP, Brown T, Stover J, Grassly NC, Hankins C, et al. Back to Basics in HIV Prevention: Focus on Exposure. *BMJ*. 2003 Jun 21;326(7403):1384-7.
- Fact Sheet: Asia 2006 [database on the Internet]. United Nations Program on HIV/AIDS. [cited 2007 Mar 2]. Available from: [http://data.unaids.org/pub/GlobalReport/2006/200605-FS\\_Asia\\_en.pdf](http://data.unaids.org/pub/GlobalReport/2006/200605-FS_Asia_en.pdf).
- Ho EY, Grewal S. HIV/AIDS-Related Knowledge, Attitudes, and Practices of a Rural Community in Kep, Kingdom of Cambodia. *UTMJ*. 2005 Mar;82(2):82-7.
- Kep Malaria Program; Number of VHV in Kep Municipality. Kep (Kingdom of Cambodia): Health Department; 2005 May 20.
- Leng HB, Wantha SS, Sun LP, Sopheap S, Natpratan C, Stuer F, et al. Low prevalence of sexually transmitted infections in Cambodia supports recent behavioral and HIV seroprevalence trends: 2001 Cambodia STI prevalence survey final report. Phnom Penh (Cambodia): National Center for HIV/AIDS, Dermatology and STDs, Ministry of Health; 2002.
- He N, Detels R, Chen Z, Jiang Q, Zhu J, Dai Y, et al. Sexual behaviour among employed male rural migrants in Shanghai, China. *AIDS Educ Prev*. 2006 Apr;18(2):176-86.
- Liu H, Li X, Stanton B, Liu H, Liang G, Chen X, et al. Risk factors for sexually transmitted disease in rural-to-urban migrants in China: implications for HIV/sexually transmitted disease prevention. *AIDS Patient Care STDS*. 2005 Jan;19(1):49-57.
- Khmer HIV/AIDS NGO Alliance (KHANA). Improving Access to Antiretroviral Treatment in Cambodia [monograph on the Internet]. Phnom Penh (Cambodia); 2003 Sept [cited on 2007 Feb 26]. Available from: <http://www.aidsalliance.org/sw7405.asp>.
- Dabis F, Msellati P, Dunn D, Lepage P, Newell ML, Peckham C, et al. Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues Ghent (Belgium), 1992 Feb 17-20. The Working Group on Mother-to-Child Transmission of HIV. *AIDS*. 1993 Aug;7(8):1139-48.
- Kind C, Rudin C, Siegrist CA, Wyler CA, Biedermann K, Lauper U, et al. Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. *Swiss Neonatal HIV Study Group*. *AIDS*. 1998 Jan;12(2):205-10.
- Consensus Statement: WHO HIV and Infant Feeding Technical Consultation. [monograph on the Internet]. World Health Organization; 2006 Oct; [cited 2007 April]. Available from: <http://www.who.int/hiv/mediacentre/Infantfeedingconsensusstatement.pdf>.
- Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS*. 2005 Apr 29;19(7):699-708.
- National Center for HIV/AIDS, STD and Dermatology (NCHADS). Voluntary, Confidential Counselling and Testing: An Overview. *Health Messenger*. 2005 Sept;24:2-7.

## Dr. Kevin Chan: Conflicts and Synergies between Environmentalism and International Development Initiatives

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**Figure 1.** Dr. Kevin Chan (left) with a community health care worker in Malawi.

### Introduction

Environmentalism and international health efforts are not commonly perceived to be associated with one another. However, according to physician and distinguished global health scholar Dr. Kevin Chan (Figure 1), it is important to acknowledge the intimate connection between these two concepts. Dr. Chan has a long history of global health scholarship and advocacy, including past roles as consultant to WHO, UNICEF, the World Bank, and the Canadian government on issues of global health and development. We sat down with Dr. Chan to discuss the importance of placing environmental issues at the forefront of the global health agenda.

Dr. Chan is a paediatric emergency physician at the Hospital for Sick Children in Toronto, Assistant Professor of Paediatrics at the University of Toronto, a fellow of the Munk Centre for International Studies at the University of Toronto, and a doctoral candidate in Population and International Health at the Harvard School of Public Health. He earned his undergraduate degree at the University of Toronto and his medical degree at the University of Ottawa. During his paediatrics residency training at the University of British Columbia, he concurrently pursued a Masters degree in Public Health at Harvard University. Dr. Chan currently holds a Knox Fellowship at Harvard University and the Pierre Elliott Trudeau Scholarship, a prestigious Canadian social science scholarship.

### Can you tell us about your upbringing and academic background and which experiences contributed to your interest in international health?

When I was a teenager, I was lucky enough to go with a group of Médecins Sans Frontières (MSF) doctors to a

refugee camp in Ethiopia. Originally, I was supposed to be there for 5 weeks but after only three-and-a-half weeks, they sent me home because they said I wasn't coping well. When you're young and a situation such as this one arises, it makes you do one of two things: either give up, go home, and never do it again, or try to make a difference. I took the latter path. Shortly after coming back home, I started noticing many of the inequities here, and that's how I started working with street kids in Toronto. I saw the inequities here reflected by the inequities abroad, so I started working a lot more with street kids internationally. When I got to medical school in Ottawa, I started working a lot with communities in northern Malawi, where I continue to do a lot of my work today.

### What were you planning on doing before you decided on medicine and international health?

I was always interested...in international development, specifically, in issues affecting unfortunate and disadvantaged populations in the world, whether at home or abroad. Medicine was a pathway that actually wasn't my original plan. I was really thinking along the lines of doing international development through [a doctorate in] economics. During the second year of my undergraduate studies, though, I got in touch with people who were doing international development from a medical perspective, and they swayed my thinking to at least consider medicine as an option. Later on, I applied to study in three different areas: medicine, law from a human rights perspective, and economics. When I got acceptance letters along all three lines, I debated what I wanted to do, and I figured that medicine was a safer choice in that it gave you more options to do things. In a very circuitous route, I went back, so my present doctorate degree is in international health economics.

### You are a clinician as a paediatrician but also a researcher. Can you share with us your work in both of these roles and what they specifically entail?

As a clinician, I do paediatric emergency at Sick Kids. The vast majority of my time is spent doing research: some in emergency medicine – more to do with public policy, and a great deal in global health. Overall, a considerable amount of my work is done abroad: a lot of my research now is abroad, and when we go abroad, we do a lot of clinical work. For example, last summer when I was in Uganda, I was seeing one hundred patients every day in addition to keeping up on the research aspects of my project, going to communities and teaching, and so forth. So I have those clinical opportunities while abroad, in addition to my research.

The clinical paediatric emergency is confined to Toronto, while a lot of my global health research is elsewhere, but

there are certainly emergency medicine aspects that I take to my global health research. For example, I'm now in the process of setting up emergency medical services in Nairobi. That is putting some of my clinical practice very much into my global health research... I think it's always nice if you can combine the two and synthesize them in a certain fashion.

**From this wide spectrum of activities you are involved in, you have a new project on your plate now that deals with environmental issues. What led you to aim your focus at environmental concerns?**

I think I'm a person who's extremely cognizant of the dilemma and discrepancy between the two worlds of environmentalism and developmental issues. As alluded to earlier, I'm a Trudeau scholar, and one of the areas of focus of the Trudeau Foundation is the environment. During dinner one day, I was talking to a fellow Trudeau Scholar [David Boyd] about my work in Africa, and he simply asked me, "As an ordinary citizen who has no knowledge of Africa, what can I do to help?" This led to an incredibly wonderful discussion about the demands of environmentalism and the issues of trying to put environmental issues along global development, at the forefront, especially in the most impoverished areas of the world.

**Is it right for us to tell China or India, "stop firing up the coal firing plants" when [these countries] have only one-sixth the wealth of Canada or the United States?**

About ten years ago, I wrote a paper about global climate change, its being one of the top ten things that we need to address as developmental experts. My work in northern Malawi has been going on for 15 years now, and I've knocked 'under 5 malnutrition' by about 90%, and 'under 5 mortality' by about 50%. But I sat down and thought about it – all the things that I've done so far to improve the communities in northern Malawi go for naught if global climate change comes to fruition. So if the world gets 2, 3, 4 degrees warmer, and if there's desertification of land in Malawi, if crops start withering, if Lake Malawi starts to recede, and so on, all the developmental work I've spent 15 years trying to accomplish will fail because global climate change hasn't been addressed. I can't imagine not addressing some of the determinants behind what the issue really is. And that's why I got interested in the environment... if I don't address some of the issues here at home, it's going to affect all of my development work abroad.

**Related to this, can you explain the concept of poverty reduction through climate change?**

I think climate change disproportionately affects the poor. They don't have the same coping mechanisms that you and I have for climate change. This is especially true of a lot of societies that are agrarian by origin. How do you expect poverty reduction to occur when you destroy the bases of these societies? In tropical areas, the average temperature is about 20 degrees. With global warming, this will increase by anything between 2 and 10 degrees, on average, by 4 degrees... It destroys the survival bases of these societies. You can't reduce poverty, therefore, without addressing climate change.

When you think about it, western countries have enormous wealth and are the ones that are spewing out greenhouse gasses. Canada, for example, spews out 16.8 tons of carbon dioxide per person per year; in Uganda, the average is 0.6 tons of carbon dioxide per person per year. We're talking about a 25 fold difference between Canada and Uganda. And so, when we drive our SUVs, fly around the world, or indiscriminately use water and have carbon dioxide released from the tar sands, our thought process is to our own individual convenience. The ethical consideration isn't about global warming leading to water loss and famine on the other side of the world, but if you think about it, it would be fascinating to trace our impacts, to see if we're causing harm by our actions here. Are we actually killing people on the other side of the world? Is our development and well being actually causing death? These are enormously tough ethical questions, but just because there isn't direct causation doesn't mean that we aren't implicit in our harm.

**What are your opinions on Canada's efforts in addressing environmental issues?**

I think we're doing very little. Let's be honest here. We're anywhere from the worst to the top 5 OECD countries (the richest countries in the world) in polluting per capita. In reality, we're among the top 5 polluters per capita around the world in major greenhouse gas emissions. So I think there are issues in Canada surrounding truly addressing pollution from an individual basis, from a business basis, and from a governmental basis. If anything, things are going to get worse if we leave things as they are. With the increase in digging the Alberta tar sands, there are going to be significant increases in carbon dioxide emissions, if the harvesting isn't done properly.

**What can students do to get involved in international health and development work?**

I think things are changing, and there are many more opportunities available nowadays, especially in the States and Canada, for students to do international health. There's increasing interest too. The universities are getting involved and there's significantly more funding at the national level for global health issues. Faculties are getting involved... from high school to graduate and medical programs to post-graduate schools, there are about 35,000 students in North America who go abroad to do international development work. The key is to find good opportunities and good mentorship. I think that's really the best pathway to go forward in global health.

We would like to thank Dr. Chan for sharing his insights with us and providing us with an approach to recognizing the conflicts and synergies of environmental and development initiatives. Although the connection between environmental issues and international development efforts is frequently unacknowledged, it deserves greater attention as our generation searches for solutions to global health inequities.

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## Regulation of Acupuncture and Traditional Chinese Medicine In Ontario

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### Abstract

Acupuncture, a therapy in traditional Chinese medicine (TCM), is a popular modality of complementary and alternative medicine that has, until recently, been unregulated in the province of Ontario. The Government of Ontario has recently passed Bill 50, the *Traditional Chinese Medicine Act, 2006* to regulate the practice of TCM and acupuncture. This paper discusses the Act and its implications on the practice of acupuncture and TCM in Ontario, focusing on issues of safety.

### Background

Acupuncture is the technique of using metallic, hair-thin needles to insert through the skin at specific points on the body for the purpose of promoting, maintaining, and improving health. Acupuncture, under the system of traditional Chinese medicine (TCM), aims to correct imbalances in yin and yang forces and to release blockages of qi (energy). Other therapy modalities used in TCM include herbal therapy, moxibustion (the burning of herbs near the body), massage therapy, and therapeutic exercises. Techniques used in TCM for diagnosis include history taking, observation of the patient's appearance and demeanor, and palpation (for pulse characteristics and for tenderness and temperature).

### The Traditional Chinese Medicine Act

On December 20 2006, the Government of Ontario passed Bill 50, the *Traditional Chinese Medicine Act, 2006*, making Ontario the second province in Canada, after British Columbia in 1999, to regulate the practice of TCM and acupuncture.<sup>1</sup> This legislation will lead to the creation of a self-governing, regulatory college for the practice of TCM, entitled the *College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario*. The Act amends the *Regulated Health Professions Act, 1991* to include the practice of TCM alongside a large number of other health professions including medicine, dentistry, occupational therapy, nursing, chiropractic, pharmacy, dietetics, midwifery, and massage therapy.

The *College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario*, which is expected to begin operation in two to three years,<sup>2</sup> will set standards of entry and practice for TCM and acupuncture. Currently, there is no uniformly

accepted standard of practice for acupuncture in Ontario. Practicing acupuncturists may have received their training from other countries or from local institutions, such as the Toronto School of Traditional Chinese Medicine, the Canadian College of Naturopathic Medicine, or the Canadian Memorial Chiropractic College (CMCC).

Although there are currently no formally accepted standards of practice, acupuncturists with recognized training may become members of the Acupuncture Council of Ontario (ACO). Eligible ACO members can be compensated for acupuncture treatments through the Workplace Safety and Insurance Board (WSIB) or Veterans Affairs, as acupuncture is not covered by the Ontario Health Insurance Plan (OHIP).<sup>3</sup> An example of training recognized by the ACO is the CCMC 220-hour clinical acupuncture training program offered to chiropractors, physicians, dentists and physiotherapists.<sup>4</sup>

With the advent of *The College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario*, current practitioners who do not meet the standards to be set by the College will have to undergo further training. The College will outline the scope of practice of its members, and only its members, some of whom will be given the title "doctor", will be able to use the titles "traditional Chinese medicine practitioner" or "acupuncturist" in Ontario. The regulation of TCM will purportedly ensure a certain level of competency of practitioners and promote effective and safe practice.<sup>5</sup>

### Safety of Acupuncture in Ontario

The *Ontario Traditional Chinese Medicine Act, 2006* will place the responsibility of enforcing safety standards for all acupuncture clinics in Ontario on the new *College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario*. Minor adverse events associated with acupuncture include bleeding, bruising, excessive pain, fainting, nausea and vomiting, and aggravation of existing symptoms.<sup>6,7</sup> Two studies reported minor adverse event rates of 13 and 14 per 10,000 acupuncture consultations and no serious adverse events among 34,407 and 31,822 treatments, respectively.<sup>6,7</sup> Several rare cases of serious injuries such as pneumothorax and spinal cord injury have, however, been previously recorded.<sup>6</sup>

As acupuncture involves the use of skin-penetrating needles, infection control practices are required to prevent the transmission of disease. Several outbreaks of acupuncture-associated hepatitis B and cutaneous *Mycobacterium abscessus* infections have been previously reported.<sup>8-13</sup> The *Ontario Ministry of Health* in 1998, under the statutory basis of the *Health Protection and Promotion Act, 1990*, created the Infection

Control in Personal Services Settings Protocol that governs settings in which there is a risk of exposure to blood or other body fluids, including tattoo parlors, hair salons and barbers, body piercing studios, and, although not specifically mentioned, acupuncture clinics.<sup>14</sup> Public health units under the *Ontario Ministry of Health's Mandatory Health Programs and Services Guidelines* are then required to perform inspections to enforce infection control standards with a primary goal of reducing the risk of transmission of diseases, such as Hepatitis B and HIV.<sup>15</sup> The following is an example of a set of criteria that inspectors may examine for:<sup>16</sup>

### General requirements:

- Work areas must be clean and well-lit
- There must be a sink with hot and cold water, soap, and single-use towels for hand washing and cleaning equipment
- Work contact surfaces such as patient chairs and worktables must be adequately cleaned after each client
- Used needles must be placed in a sharps container

### Infection control/prevention requirements:

- Hand washing must be performed between clients, before and after wearing gloves, and before breaks
- Single-use gloves must be changed between clients
- Needles should be single-use and disposed of immediately after use
- Reusable handles that attach needles must be properly sterilized after each use
- All other equipment, such as tweezers and forceps, that are in contact with needles, cupping equipment, and electric stimulation clips/hoops must be adequately sterilized after each use
- There must be proper sterile handling of needles as they are removed from packaging prior to use
- Adequate patient records and records of any accidental blood/body fluid exposure must be kept
- Hepatitis B vaccination is recommended for all practitioners

Without regulation requiring the systematic registration of acupuncture practices, however, public health inspectors are limited to examining known clinics (e.g. through registration of business licenses) while other health professionals (physicians, chiropractors, etc.) who practice acupuncture are subject to standards set by their own self-regulating bodies. It is conceivable that, with the support of public health, uniform infection control requirements will be adopted and enforced by the College as part of the new regulations governing all acupuncture clinics in Ontario.

The reaction to the passing of the *Traditional Chinese Medicine Act, 2006*, has been mixed. Some argue that it validates this long-standing profession, and will lead to better standards of effective and safe practice. Others argue that there is a limited amount of evidence supporting TCM and that the Act may give undue support to a profession that has not been widely validated.<sup>2</sup>

The body of evidence on TCM has been primarily focused on acupuncture, and continues to grow. Acupuncture is used to treat a variety of diseases, but is used in North America pri-

marily to relieve pain and improve function in conditions such as headaches, migraines, addiction, osteoarthritis, back-pain, myofascial pain, and dental pain. It has also been used for nausea, vomiting, anxiety, depression, and weight control. Evidence on the efficacy of acupuncture has been mixed, with some promising evidence for the treatment of nausea and vomiting and for the relief of pain.<sup>17</sup> A recent review of the literature indicated that acupuncture may be effective in providing long-term relief of persistent, non-specific low back pain and for the symptoms of fibromyalgia, while showing no benefit in the treatment of migraines.<sup>18</sup> In contrast, the evidence on the efficacy of other components of TCM has been limited.

While the use of TCM and acupuncture may be popular in certain population subgroups in North America,<sup>19</sup> the growth of evidence for the different modalities of TCM, along with the creation of further legislation and regulating bodies, will be important factors that will affect the level of acceptance for the practice of TCM throughout the population.

### References

1. Government of Ontario. Traditional Chinese Medicine Act, 2006. [monograph on the Internet]. Ottawa: MOAG; 2006 [cited 2007 Mar 7]. Available from: [http://www.e-laws.gov.on.ca/DBLaws/Source/Statutes/English/2006/S06027\\_e.htm](http://www.e-laws.gov.on.ca/DBLaws/Source/Statutes/English/2006/S06027_e.htm).
2. Mackay B. New Ontario college for traditional Chinese medicine. *CMAJ*. 2007;176:435-6.
3. Acupuncturists of Ontario. Who we are. [homepage on the Internet]. Toronto: AOC; 2007; [cited 2007 Mar 7]. Available from: <http://www.aocweb.com/home.html>.
4. Canadian Memorial Chiropractic College. Graduate Studies – Certificate Programs. [monograph on the Internet]. Toronto: CMCC; 2007 [cited 2007 Mar 7]. Available from: [http://www.cmcc.ca/grad\\_studies/div\\_contuing\\_education.htm#aCertificateProgrammes](http://www.cmcc.ca/grad_studies/div_contuing_education.htm#aCertificateProgrammes).
5. Ministry of Health and Long-Term Care. McGuinty government regulating traditional Chinese medicine. [monograph on the Internet]. Toronto: MOHLTC; 2006 [cited 2007 Mar 8]. Available from: <http://ogov.newswire.ca/ontario/GPOE/2006/12/20/c9530.html?match=&lang=e.html>.
6. White A, Hayhoe S, Hart A, Ernst E. Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists. *BMJ*. 2001;323:485-6.
7. MacPherson H, Thomas K, Walters S, Fitter M. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ*. 2001;323:486-7.
8. Vincent C. The safety of acupuncture. *BMJ*. 2001;323:467-8.
9. Stryker WS, Gunn RA, Francis DP. Outbreak of hepatitis B associated with acupuncture. *J Fam Pract*. 1986;22:155-8.
10. Slater PE, Ben-Ishai P, Leventhal A, Zaher D, Bashary A, Moses A, et al. An acupuncture-associated outbreak of hepatitis B in Jerusalem. *Eur J Epidemiol*. 1988;4:322-5.
11. Kent GP, Brondum J, Keenlyside RA, LaFazia LM, Scott HD. A large outbreak of acupuncture-associated hepatitis B. *Am J Epidemiol*. 1988;127:591-8.
12. Song JY, Sohn JW, Jeong HW, Cheong HJ, Kim WJ, Kim MJ. An outbreak of post-acupuncture cutaneous infection due to *Mycobacterium abscessus*. *BMC Infect Dis*. 2006;6:6.
13. Tang P, Walsh S, Murray C, Alterman C, Varia M, Broukhanski G, et al. Outbreak of acupuncture-associated cutaneous *Mycobacterium abscessus* infections. *J Cutan Med Surg*. 2006;10:166-9.
14. Ontario Ministry of Health. Ministry of Health Infection Control in Personal Services Settings Protocol. January 2008.
15. Ontario Ministry of Health. Mandatory Health Programs and Services Guidelines. Toronto, Ontario: Queen's Printer for Ontario, 1997.
16. Region of Waterloo Public Health. Acupuncture. Patient information sheet/internal documents.
17. National Centre for Complementary and Alternative Medicine [homepage on the Internet]. Bethesda: National Institute for Health; [updated 2006 Mar 14, cited 2007 Mar 19]. Acupuncture; [1 screen]. Available from: <http://nccam.nih.gov/health/acupuncture/>
18. Tanuseputro P, Yip G, Kwong E. Acupuncture: A synopsis and highlights of recent evidence of efficacy in the literature. *UTMJ*. 2006;84:424.
19. Wu AP, Burke A, Lebaron S. Use of traditional medicine by immigrant Chinese patients. *Fam Med*. 2007;39:95-200.

## Commercial Surrogacy: Commodification or Choice?

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### Introduction

The advent of new reproductive technologies has brought unprecedented opportunities to infertile individuals wishing to have children. Among these opportunities is commercial surrogacy, whereby a woman is commissioned and paid a fee (above and beyond compensation) to carry the fetus of another individual. After giving birth, the child is delivered to the commissioning parent(s), who raise the child as their own and hold all parental rights.<sup>1,2</sup> Commercial surrogacy is further subdivided into partial and full surrogacy. In partial surrogacy, the surrogate is the genetic mother and provides the egg from which the child develops. Full surrogacy refers to arrangements in which the gametes are provided by the commissioning parent(s) and the surrogate acts solely as a “gestational host”.<sup>2,3</sup> The practice of commercial surrogacy does bring with it several ethical concerns, however. Some have criticized the practice, comparing it to the commodification, the transformation of a non-commodity into a commodity, not only of children, but also of the reproductive capacities of women.<sup>4</sup> Others have likened it to “new-wave prostitution”.<sup>5</sup> On the other hand, advocates of the practice have defended it on the grounds that it is no different than sperm donation.<sup>6</sup>

This review will analyze the controversy surrounding commercial surrogacy under the guidance of several ethical frameworks. It should be noted that commercial surrogacy is not the same as non-commercial or “altruistic” surrogacy. In the latter, “the surrogate is not paid for her services and is motivated mainly by a desire to help an infertile couple have a child of their own.”<sup>7</sup>

### Case

To help navigate the ethical analysis of commercial surrogacy, the following is a prototypical clinical case based loosely on the results of a study analyzing the characteristics of 44 surrogate pregnancies:<sup>8</sup>

Mary, a 25-year-old female, is seeking to become a partial commercial surrogate. She is unmarried, with a two-year-old son. She has a high school education and a 10 pack-year smoking history, but quit smoking one year ago. Presently, her only source of income is welfare. Her annual household income is approximately \$23,000. She has consulted a surrogacy agency and met with Frank and Emma, the commissioning parents. Frank and Emma have an average household income of \$400,000. Emma is unable to have children as a result of a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) to treat Stage III ovarian cancer. They have agreed to pay Mary \$10,000 in addition to any medical fees to be inseminated by Frank’s

sperm and carry the child to term. Mary hopes that the monetary compensation from the surrogacy will help improve her financial situation. It offers an effective means of income given her minimal education. Is it ethical for Mary to carry through with commercial surrogacy?

### Deontological Argument

The commodification argument against surrogacy is deontological in principle. As outlined by Anderson, a commodity is defined as a good or service that is governed by market norms that regulate its “production, exchange, and enjoyment.” However, market norms may be objectionable if the production and distribution of a given good or service “fail[s] to value it in the appropriate way.”<sup>4</sup> Deontology, the ethical theory concerned with duties and rights, proposes a similar logic, stating that it is unethical to treat beings worthy of respect merely as means to satisfy one’s own interests or ends. Ultimately, commercial surrogacy commodifies both the reproductive capacity of the surrogate and the rights of the newborn child. As such, this practice fails to acknowledge these intrinsically valuable human beings and thus violates the deontological tenet of respect for persons. Van Niekerk & van Zyl further explore the nature of reproductive labour by stating:

“What distinguishes women’s reproductive labour from other forms of labour, [is] that the product...is not something but someone...[A] person’s relationship with material things is instrumentalist; things are means to an end, but not ends in themselves. People’s relationships to other people, and mothers’ relationships to their infants in particular, are manifestly different. Children are not means, but [rather] ends in the relationships with their mothers...[and] mothers regard the relationship as a meaningful end in itself, and not...as means to some other end.”<sup>3</sup>

As such, in the case of Mary, the use of an unborn child as a means to subsequent financial gain, rather than accepting it as an end in itself, is in clear conflict with deontological interpretation.

Deontology’s second tenet requires the need for ethical principles to be universalizable in asking an individual to “act only on that maxim through which [he/she] can at the same time will that it should become a universal law.”<sup>9</sup> To investigate the universalizability of commercial surrogacy, we may consider two hypothetical additions to Mary’s case:

Consider the scenario where Mary has an annual household income of \$100,000. Given her new financial circumstances, it is highly improbable that she would seek commercial surrogacy as a means of further financial gain. Returning to

universalizability, Mary's contradictory actions are dependent on her financial situations, and are at odds with the ideal that one should act by a universal standard, independent of circumstance.

Consider a situation in which all children are born via commercial surrogacy, as would be the case if it were a universal law. This construction is typical of most "slippery slope" arguments, which contend that the loosening of ethical standards may lead to social chaos.<sup>10</sup> In a world of commercial surrogacy, it is feasible to envision a distinct separation of classes in which the poor bear children for the rich. Such a society is remarkably similar to the fictional dystopia presented by Margaret Atwood in her novel, *The Handmaid's Tale*, in which Handmaids are fertile women whose social function is to bear children for the social elite.<sup>11</sup>

Both of the above scenarios suggest that commercial surrogacy is in conflict with the deontological principle of universalizability.

### The Role of Autonomy

To refute the ethical merit of commercial surrogacy, one must show reason to overrule a voluntary transaction between competent adults. Indeed, several advocates of the practice have raised the issue that a surrogate's decision to carry a child is entirely voluntary, and thus overruling it would be a breach of her autonomy. Epstein explains that "the basic...presumption should be set therefore in favour of voluntary exchange."<sup>12</sup> However, it should be noted that valid informed consent—required for any medical procedure under the principle of autonomy—is far more rigorous than "mere voluntariness"<sup>12</sup> Consent can be given despite underlying covert duress or coercion, thus rendering the consent involuntary.<sup>13</sup> In a well-developed argument, Wilkinson introduces the concept of omissive coercion to question the validity of consent in commercial surrogacy agreements. The theoretical framework is as follows: "A omissively coerces B to do X if and only if: (1) A has a duty to do Y for B; and (2) A proposes/threatens not to do Y for B unless B does X."<sup>14</sup> Applying this rubric to the practice of commercial surrogacy, with a largely egalitarian outlook on distributive justice, a "paid surrogate may be the victim of omissive coercion" if:

"The commissioning parents have a duty to help her [on charitable grounds] without demanding surrogacy services..., but propose (threaten) not to act in accordance with this duty unless she provides surrogacy services.

Society in general...has a duty to ensure that she has a certain level of welfare, but makes it the case that she can only reach this level of welfare by selling surrogacy services."<sup>15</sup>

The latter of these premises is founded on the ideal of the welfarist assumption, wherein "society has an obligation to ensure that the prospective surrogate...obtains a certain level of welfare [or well-being]."<sup>16</sup> Reflecting on the case of Mary, the argument that she may be a victim of omissive coercion is as follows:

Based on the welfarist assumption, society is obliged to provide Mary with a certain level of well-being (ie. greater than

\$23,000/year). Alternatively, given their financial prosperity (\$400,000/year), Frank and Emma have a duty to help Mary attain a higher level of welfare through charitable means. Either society or Frank and Emma threaten not to provide Mary with the necessary level of welfare unless she acts as a commercial surrogate. Given the existence of such omissive coercion, Mary's consent to perform the commercial surrogacy is invalid.

Thus, the absence of valid informed consent in Mary's decision to undertake the surrogacy arrangement invalidates the principle of respect for autonomy. As such, commercial surrogacy appears to contradict the assertions set forth by the ethical framework of principlism.

### Utilitarian View

The case in support of commercial surrogacy has often been defended on utilitarian grounds. Under the greatest happiness principle, which is synonymous with the principle of utility, ethical decision making should be based on attaining "the greatest happiness of the greatest number."<sup>17</sup> Accordingly, it is apparent how a successful commercial surrogacy agreement offers benefits, i.e. happiness, to those involved. The following are some potential benefits in the case of Mary: (1) Mary will benefit financially by receiving \$10,000 to help improve her quality of life; (2) Frank and Emma will benefit physically, psychologically, and emotionally, having overcome the obstacles of infertility and acquiring a child genetically related to Frank; and (3) the unborn child will benefit by entering a loving home and being raised by parents who can provide him/her with a high standard of life. However, these benefits must be viewed in light of several unconscionable and unquantifiable human costs. As presented by Anderson, "most surrogate mothers experience grief upon giving up their children—in 10 percent of the cases, seriously enough to require therapy." Such grief is justifiable, considering that "her labour is alienated, because she must divert it from the end which the social practices of pregnancy rightly promote—an emotional bond with her child."<sup>18</sup> Inevitably, the strong emotional connections experienced by some surrogate mothers and the children to whom they give birth have led to numerous legal disputes over the children's custody.<sup>15</sup> These events have prompted some individuals, such as Prokopijevic, to suggest that:

"the surrogate mother might be allotted a certain period of time in which she could change her mind and keep the newly-born child, with corresponding compensation being paid to the [commissioning parents], including the expenses arising as a result of hospital care and the breaking of the contract."<sup>16</sup>

However, such a resolution undermines the legitimacy of the pregnancy with respect to the commissioning parent(s). According to Van Niekerk and van Zyl, "although the [commissioning] female partner was not physically pregnant, [both the surrogate and the commissioning parent(s) were]... 'pregnant' in the social and psychological sense of 'expecting a child'."<sup>19</sup> To deny the commissioning parent(s) of their child would cause the same alienation Prokopijevic was trying to remedy. Lastly, it should be noted that commercial surrogacy may have long-term implications for the children born from

these surrogacy agreements. In particular, Anderson argues that, given the nature of their birth, "Would it be any wonder if a child born of a surrogacy agreement feared resale by parents...?" or that, "...children of some surrogate mothers [those born without surrogacy agreements]...express a sense of loss at being deprived of a sibling."<sup>4</sup> Given these socially complex consequences, the utilitarian argument in favour of commercial surrogacy requires a broader analysis of utility prior to determining the correct course of action. In the case of Mary, the following are some potential consequences: (1) Mary may, against her will, be forced to give up the child with whom she shares an emotional and genetic bond; (2) Frank and Emma may experience tremendous grief for the loss of the child should Mary choose not to honour the surrogacy agreement; and (3) the unborn child may experience distress towards the parental guardians, be it Mary or Frank and Emma, due to a fear of being resold. Comparing these negative consequences to the aforementioned benefits of commercial surrogacy requires one to perform the unimaginable task of quantifying emotional agony. Given that such quantification cannot be made on any universally agreed-upon grounds, the case for commercial surrogacy based on utilitarian principles is questionable.

### Law and Legislation

Having considered the ethical implications of commercial surrogacy, it is worthwhile to examine the need for any necessary legal and legislative interventions. At the present time, Canadian laws concerning commercial surrogacy greatly reflect the recommendations proposed by the Royal Commission on the New Reproductive Technologies. As part of their review, the commission issued "recommendation 199, which makes surrogacy a criminal offence, [and] directed the federal government to legislate against it in the strongest possible way...".<sup>17</sup>

"to prohibit advertising for or acting as an intermediary to bring about a preconception (i.e. surrogacy) agreement, and to prohibit receiving payment or any financial or commercial benefit for acting as an intermediary, under threat of criminal sanction. It should also legislate to prohibit making payment for a preconception arrangement, under threat of criminal sanction."<sup>18</sup>

The commission further recommended that provincial bodies, particularly the Colleges of Physicians and Surgeons, "adopt strict codes of conduct, disciplinary measures and severe penalties...against members involved in brokering or performing assisted insemination...to facilitate a preconception (surrogacy) arrangement."<sup>18</sup> However, despite being well-intentioned in protecting against surrogate exploitation and condemning the unethical practice of commercial surrogacy, the commission's recommendations may have unforeseen implication; chiefly, the legal prohibition of commercial surrogacy may undermine the welfare of prospective surrogates.<sup>2</sup> This idea is based on the assumption that much of the motivation to pursue commercial surrogacy comes as a result of financial hardship. As such, the prohibition of commercial surrogacy in the absence of alternative mechanisms to help ensure the welfare of prospective surrogates, may encourage practices that are more dangerous, exploitative, and morally objectionable than the practice of commercial surrogacy.<sup>2</sup> For this reason, members of government should consider alternative methods

to improve the welfare of individuals who resort to commercial surrogacy, prior to strictly forbidding it.

### Conclusion

The ethical implications of commercial surrogacy are questionable on several grounds. (1) From a deontological perspective, the use of an unborn child as a means to some other end is unethical, as is the absence of universalizability in the practice of commercial surrogacy. (2) Employing the welfarist assumption, commercial surrogates are ommissively coerced into participating in surrogacy agreements, thus rendering their consent invalid and their autonomy violated. (3) Furthermore, the negative emotional consequences that may arise from a surrogacy arrangement challenge the prevailing justification of commercial surrogacy on utilitarian grounds. However, despite the unethical nature of commercial surrogacy, consideration should be given to the existing laws prohibiting it, in order to ensure the welfare of prospective surrogates.

Returning to Mary's case within the context of the above discussion, she should not proceed with the commercial surrogacy agreement, for it cannot be sanctioned by ethical theories.

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### References

1. Arneson RJ. Commodification and commercial surrogacy. *Philos Public Aff.* 1992 Spring;21(2):132-64.
2. Wilkinson S. The exploitation argument against commercial surrogacy. *Bioethics.* 2003 Apr;17(2):169-87.
3. van Niekerk A, van Zyl L. The ethics of surrogacy: women's reproductive labour. *J Med Ethics.* 1995 Dec;21(6):345-9.
4. Anderson ES. Is women's labor a commodity? *Philos Public Aff.* 1990 Winter;19(1):71-92.
5. Dworkin A. Right-wing women: the politics of domesticated females. London: Women's Press; 1983.
6. Shalev C. Birth power: the case for surrogacy. New Haven: Yale University Press; 1989.
7. Baker B. A case for permitting altruistic surrogacy. *Hypatia.* 1996 Spring;11(2):34-48.
8. Reame NE, Parker PJ. Surrogate pregnancy: clinical features of forty-four cases. *Am J Obstet Gynecol.* 1990 May;162(5):1220-5.
9. Singer P. *Practical ethics.* 2nd ed. New York: Cambridge University Press; 1993.
10. Herzog HA. Book review: The slippery slope to moral chaos: Line drawing and animal rights. *Ethics & Behavior.* 2005;15(2):191-4.
11. Atwood ME. *The handmaid's tale.* Toronto: McClelland & Stewart; 1985.
12. Epstein RA. Surrogacy: the case for full contractual enforcement. *Va Law Rev.* 1995 Nov;81(8):2305-41.
13. Freedman B. A moral theory of informed consent. *Hastings Cent Rep.* 1975 Aug;5(4):32-9.
14. Bentham J. *An introduction to the principles of morals and legislation [microform].* London: Printed for T. Payne, and son, at the Mews gate; 1789.
15. Faulkner E. The case of 'Baby M'. *Can J Women Law.* 1989;3(1):239-45.
16. Prokopijevic M. Surrogate motherhood. *J Appl Philos.* 1990;7(2):169-81.
17. McCormack T. *Reproductive technologies: Rights, choice, and coercion.* In: Brodie J, editor. *Women and Canadian Public Policy.* Toronto: Harcourt Brace & Company; 1996. p. 199-221.
18. Canada. *Royal Commission on New Reproductive Technologies. Proceed with care: final report of the Royal Commission on New Reproductive Technologies: summary and highlights.* Ottawa: The Commission; 1993.

### Dr. Natasha Leighl, B.Sc., M.Sc., MD, FRCPC: Leading Clinician, Scientist, and Educator

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**D**r. Leighl first became interested in Medical Oncology by a stroke of luck. While in high school, she saw a poster about the research being conducted at the Ontario Cancer Institute (OCI) at Princess Margaret Hospital. After working with Dr. Dick Hill for several summers at the OCI, she then entered medical school at the University of Toronto, later matching to Internal Medicine at the

University of Calgary and returning to Toronto to study Medical Oncology. Now, on staff at Princess Margaret Hospital, she balances the roles of clinician, educator, and research scientist. In her interview, Dr. Leighl reflects upon research, mentorship, career choices, and how to find balance as a physician.

**UTMJ: What influenced your career decision to become a Medical Oncologist?**

**NL:** It was actually luck. When I was in high school, we had to do an independent study project and I saw a poster about Biophysics research at the Ontario Cancer Institute (OCI). I thought that it sounded interesting, and I called the number and got through to Dr. Dick Hill, who is a senior scientist here at OCI. I worked as a summer student with him for about three summers. I really enjoyed my summer work at the OCI with Dr. Hill and met many of the oncologists at Princess Margaret Hospital. So I would say that my interests stemmed from there. While in medical school at the University of Toronto (9T4), I did some electives in Medical Oncology. Oncologists have good quality of life, good interaction with patients, and a great patient population to work with. Once I entered my residency in Internal Medicine, I narrowed my interests down to Cardiology, Gastroenterology, and Medical Oncology, but I just kept coming back to Medical Oncology.

**UTMJ: What made you decide to do postgraduate training?**

**NL:** Initially, I was interested in doing clinical medicine. When I was a summer student during my undergraduate studies at the University of Toronto, I didn't think that I was smart enough to do research. In medical school and Internal Medicine, I just didn't

have the time for a research project; I was never one of those people who seem to be able to do everything. When I came to Princess Margaret Hospital to do my residency training in Medical Oncology, there was no formal research program in place, but I spent some time with the clinical fellows who were great mentors. They could sense my interest in research and suggested I work with one of their colleagues in Sydney, Australia. I did a three-month elective in Sydney and afterwards, wrote a paper and published it in the *Journal of Clinical Oncology*. Then I came back and did a research fellowship with Dr. Frances Shepherd in the area of lung cancer. This really helped me realize that I was actually very interested in a research career. To further my research, I obtained my Masters Degree in Clinical Epidemiology from the University of Newcastle in Australia.

**UTMJ: Who were your mentors?**

**NL:** Dr. Hill was my first mentor; he got me involved in research and helped develop my interest in the OCI. I was also privileged to have many clinical mentors throughout my training. In fact, you will find that as you go through your training, pretty much everyone inspires you in different ways. I find that there is a focus on the staff person for mentorship, but I also learned a lot from fellows, other trainees, and my fellow medical students. The fellows I worked with in Australia were also important mentors for me. My other key mentors were Dr. Shepherd, here at PMH in lung cancer, and my supervisor in Australia, Professor Tattersall.

**UTMJ: What was the best advice you received from a mentor?**

**NL:** The first time I went to Australia, I remember that one of the hardest problems was trying to determine good research questions. It was a real challenge to write to my mentors in Australia, throw my hat in the ring and say, "these are the five research questions that I have and think are interesting". They said, "those are great ideas and here are ours". So there is a lot of benefit in discussing and sharing your research questions with knowledgeable mentors. The best advice I received was that my ideas were interesting, and to follow through on studies to test my hypotheses. The advice that I would give regarding mentors would be to give yourself a

Dr. Natasha Leighl

chance and try to develop a worthwhile mentor/mentee relationship. You need to find a mentor with a good track record, who is interested in mentoring, and has mentored other people. Sometimes, the busiest people can be the best mentors, but you need to ensure that your mentor has enough time to spend with you.

**UTMJ:** **What career would you have chosen if not medicine or research?**

**NL:** I would have liked to work for the diplomatic corps or be attached to a consulate in foreign countries – perhaps in the Far East or South America, something like Doctors without Borders or the World Health Organization.

**UTMJ:** **If you were a medical student now, how would the current state of medicine affect your choice?**

**NL:** Since I was a medical student, there have been so many technological advances and advances in therapies in all the various fields of medicine. For instance, surgery is much more technologically advanced than it used to be. Also, your generation is a little bit different from mine. Although a generalization, it seems that your generation of medical students has priorities that include having a life outside of medicine. My generation is still figuring that out. You also need to choose what you want to do having had much less experience and exposure than us. I think, however, that I would still choose Medical Oncology.

**UTMJ:** **Describe a typical day for you.**

**NL:** Working here at Princess Margaret Hospital (PMH), my job description is a little different than it would be in the community. There is a mix of clinic, research, and education. Some of my research concerns new drugs, doctor-patient communication, end-of-life care, and palliative therapy. A lot of my patients participate in clinical trials at PMH. I design or run some of these. I am also involved in education, including lectures at the medical school, and teaching residents and fellows. With my clinical work, I see patients for one-and-a-half days per week; however, the work generated by that time is about 4 days. So, a typical day for me is busy. For example, on Mondays I see patients from 8 am until about 7 pm. I also see patients from 1 pm to about 6 or 7 pm on Wednesday. The rest of the week, I may not see patients unless it is an emergency or a consult, so I lecture, give talks, and try to write papers and research grants.

**UTMJ:** **How do you manage to balance work and personal life?**

**NL:** I think you just have to make time for your personal life. Don't give up your hobbies. Don't forget that you have a social life. You are going to be busier

than a lot of your friends in other professions, but Medical Oncology is a great teacher. In oncology, you learn that we all have a limited time here. I meet a lot of young people who are not going to be here for much longer, and you look at what they have been able to achieve so far and what they want to still accomplish. I also see people who are 65 and want to travel the world, but now only have months to live. It is a very good lesson for me, and a daily reminder to maintain that balance between work and life. In my spare time I like to watch movies, go hiking with my husband, and socialize.

**UTMJ:** **What do you like about working in Toronto?**

**NL:** During medical school, I was lucky enough to be part of the Canadian Federation of Medical Students. I saw a lot of different schools across the country. Toronto is great from a lifestyle perspective – it is very cosmopolitan, and there is no city quite like it. Also, with the hospital conglomerate in Toronto, we have world expertise in everything. For example, there is a leading cardiac valve surgeon, a cancer of the pancreas expert, and so on. There is so much expertise and research in Toronto that there are numerous opportunities. I think that Toronto's great strength is in the opportunities for collaboration. The downsides are that it does get very busy, and I think that you do get very subspecialized, but that is also a strength.

**UTMJ:** **What advice do you have for medical students considering Medical Oncology?**

**NL:** I think the most important thing is to get exposure to the specialty. If you know that you are interested in Medical Oncology, I would suggest engaging in a research project and writing it up for publication. I would suggest that you meet some mentors, make sure that they know you are interested, and see if you can work on a project with them. It is definitely worth your while to spend some elective time in the specialty and make sure that it is something that you and find interesting.

### Yellow Fever: A Deadly Disease Poised to Kill Again



James L. Dickerson  
 Prometheus Books  
 ISBN: 978-1591023999  
 271 pp

Daria Pylypiak, H.B.M.Sc. (1T0), Faculty of Medicine, University of Toronto

While stories about impending epidemics plague the media, it is interesting to reflect on a past epidemic and its effects on society. The United States' struggle to understand and manage yellow fever lasted from the 1700's until the early 1900's. The book *Yellow Fever: A Deadly Disease Poised to Kill Again* by James L. Dickerson follows the history of the illness and shows a panoramic view of how an epidemic affects numerous components of society. The book discusses the historical impact of the disease, the science behind deciphering treatment and prevention, and current and prospective concerns.

The historical section of this book describes isolated incidents in Philadelphia and New Orleans, among others, in the 1700's and 1800's. These chapters provide examples on the effect of yellow fever in American society and also provide a great deal of contextual information. While the passages concerning yellow fever and its impact give just enough detail to engage the reader's interest, the contextual passages often seem excessive considering the focus of the book. Despite these intermittent passages, Dickerson astutely conveys the impact of yellow fever on different parts of society, writing clearly and linking the various topics with ease. In many cases, the familiarity of the concepts will cause an informed reader to compare the issues of the past to those in our present society. For example, Dickerson writes about the political agendas associated with yellow fever, as it was used to control trade, used to bolster political agendas, and was even considered as a means of population control in the not-so-distant past. With knowledge of current events, it is interesting to compare this to how current governments may view epidemics. The roles of the media and economy in an epidemic are briefly mentioned. Issues of race and religion in the context of an epidemic are also explored.

Dickerson also addresses the history of public health. It is interesting to see the rise of health promotion in the face of a threat, and the identification of environmental problems that were solved as a means of preventative medicine. Furthermore, he gives intriguing descriptions of medical treatments at individual and environmental levels, such as methods of cleaning the air and disinfecting the mail. The book also follows the history of how the disease etiology was elucidated using an experiment based on human volunteers

being bitten by mosquitoes and how a crude immunization was produced from human blood.

The ending section of the book leaves a lasting impact by discussing the potential threat of yellow fever in the present day. Although yellow fever is currently not a large concern in the United States, Dickerson brings up two very hot topics in the news and their link to a possible re-emergence of yellow fever. First is the topic of biological weapons used for terrorism. Dickerson writes that due to the relevance of symbolism in an Islamic terrorist attack, the biological weapon of choice would most likely have a link to American history, such as yellow fever. He then goes on to explain exactly how one could breed the disease, bring it into the United States and describes the benefits of releasing different forms of the disease in various places. He addresses the thought that must go through every reader's mind as they read this part of the text as he admits he has provided "a blueprint for terror"; however, he unsettlingly suggests that people interested in destruction would know all of this already. As a consolation after that sensational and fear-provoking passage, he offers fairly practical but generic ideas on how to prevent yellow fever from becoming a terrorist's weapon. It is evident that terrorism is a real and relevant concern considering world events; however, it is difficult to accept the suggestions of bioterrorism as a serious part of an otherwise very practical book. It is disappointing that the vivid descriptions of the illness and its impact earlier in the book seemed to be used to generate fear. In comparison, the concept that yellow fever emerging through the effects of global warming is written with much less melodrama. Dickerson, however, does suggest that we should be concerned, using the West Nile virus' well-publicized rapid spread as an example of the spreading power of a disease transmitted by mosquito.

Overall, the book gives an interesting overview of how yellow fever, and by extension, other epidemics affect society. The author's views on the future threat of yellow fever are interesting but should be read critically and kept in a context of practicality. The book is certainly a satisfying read for those interested in medical history and the social repercussions of diseases.

# The Palliative Care Unit: Does Room Design Matter?

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## Abstract

**Objectives:** The primary purpose of this needs assessment study, which looked at the palliative care population of Bridgepoint Hospital, Toronto, was to describe what patients and their families perceive to be important elements in the design of a hospital palliative care unit (PCU) for end-of-life care.

**Methods:** Twelve semi-structured interviews were conducted (six patients and six family members), using a set of nine standard questions. The qualitative philosophy of phenomenology was used for data analysis. Themes identified were grouped into two categories: I) External Reality and II) Internal Experience.

**Results:** In the External Reality category, participants identified eight themes: room size, noise, light, storage, temperature, colour, washrooms, and social spaces. Families identified additional factors: ventilation, furniture and hallways as social spaces. In the Internal Experience category, both groups identified privacy and autonomy. Shared rooms were mentioned in reference to companionship, social interaction, patient compatibility, visitor experiences and observing the dying process. Family members felt that room type should be based on the stage of illness, and expressed a need for spaces that promote participation in care.

**Conclusions:** Patients and their family members defined key issues related to end-of-life care and the physical environment. The preferences of both patients and their families demonstrate the need for a sensitive design approach to an environment for the terminally ill – one that provides a variety of private and social spaces.

This study looks at the palliative care population of Bridgepoint Hospital in Toronto, and evaluates patient and family preferences for room design and layout, as well as preferences for private versus shared accommodations.

## Background

Bridgepoint Health is Canada's largest integrated health care organization for specialized complex care services, including rehabilitation, long-term care and community-based care.<sup>4</sup> The Bridgepoint Hospital PCU has 41 patient beds and offers the option for short- or long-term palliation. The majority of rooms are shared by four patients (ward-rooms), several are shared by two patients, and there are currently no single or private rooms in either unit.<sup>5</sup> The World Health Organization (WHO) defines palliative care as, "the active, total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families."<sup>6</sup>

One of the health concerns facing the patient population at Bridgepoint Hospital is their physical environment, which is an important determinant of health.<sup>7</sup> The existing hospital structure, built in 1963, is semi-circular in shape, making it a challenge for many patients to navigate the hospital (Figure 1). Wheelchairs are difficult to manoeuvre in a curved hallway and patients suffering from neurological diseases can often become disoriented without proper visual cues. Rooms are small and unable to accommodate wheelchairs, which are left in the hall.<sup>5,8</sup> There are no washrooms in any of the rooms; they are instead located at the end of each unit. Bridgepoint Health is currently embarking on a major redevelopment project that will include a new hospital building and the design of a new and larger PCU.<sup>4,5,8</sup>

## Precedent Research

The literature presents us with precedent studies that have suggested single rooms have a number of benefits over shared rooms, including greater flexibility, increased privacy, ease of sleeping and less noise. However, single rooms have also been said to have disadvantages when compared with shared rooms, including mood disturbance due to isolation, and poor nursing observation.<sup>9</sup> A 2002 qualitative study conducted in the UK showed that while patients in a palliative setting may often prefer shared accommodations for the purposes of company and also for the constant reminder that another person may be experiencing similar events, family members often prefer private accommodations so that they may grieve and show emotion without others around.<sup>10</sup> This study attempts to document whether the research precedents apply to a Canadian hospital, and extends the literature beyond the preference for private ver-

## INTRODUCTION

Healthcare design is a growing field in research and clinical practice, with numerous studies demonstrating the impact of the built environment on health and health outcomes.<sup>1,2</sup> The notion of evidence-based design "borrows from work done in evidence-based medicine to carefully observe, quantify and analyze the way people use buildings," and is increasingly sought-after, since a lack of published data exists, especially in Canada.<sup>3</sup>

The primary purpose of this qualitative study is to describe what palliative care patients and their families perceive to be important elements in the design of a palliative care unit (PCU) for end-of-life care. Secondary objectives include exploring whether differences in preferences and perceptions exist between patients and family members.

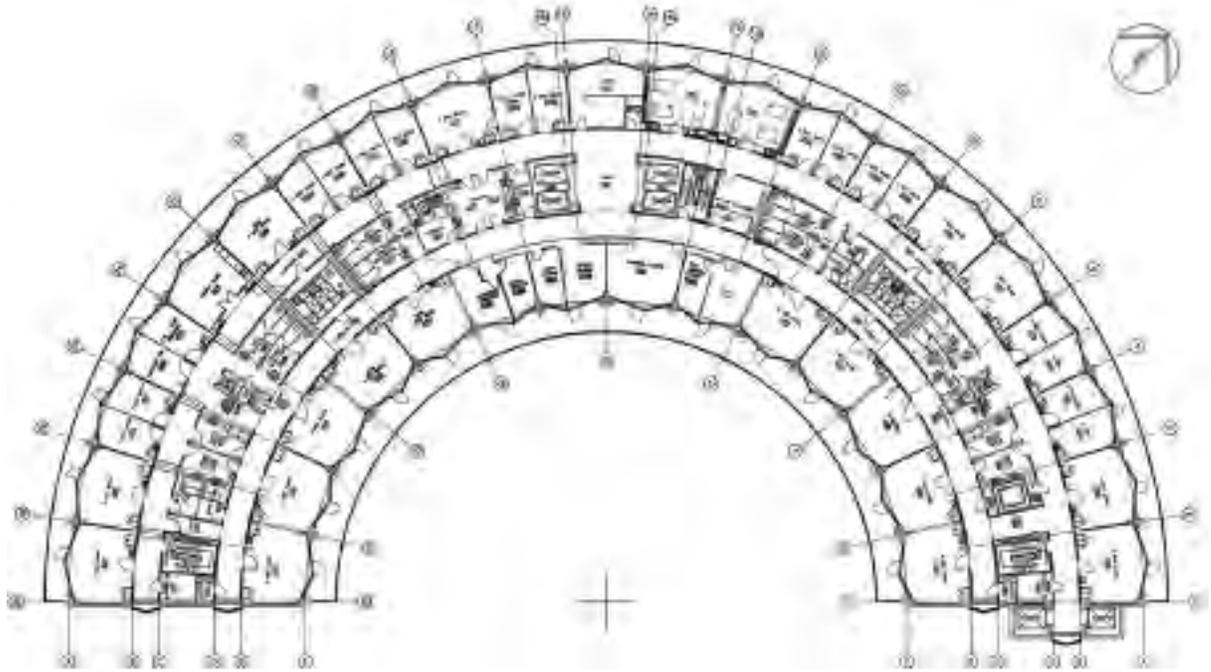


Figure 1. "Half Round" Bridgepoint Hospital Building (built 1963). Plan Courtesy of Perkins Eastman Black Architects, Toronto

sus shared rooms to include physical factors that promote comfort, layout and distribution of patient rooms.

**MATERIALS & METHODS**

Data collection was carried out during the months of February and March 2006 at the Palliative Care Unit of Bridgepoint Hospital. Both the University of Toronto Research Ethics Board and the Bridgepoint Research Ethics Board approved the study. Patients were eligible for the study if they were deemed healthy enough to participate by the medical and nursing staff on the unit. Informed written consent was obtained from all participants. Data was collected through semi-structured interviews using a set of nine open-ended questions (Table 1). Six patients and six family members were interviewed, each individually. Handwritten notes were taken during each of the sessions and were later converted into typed notes. Demographic characteristics of the participants are outlined in Table 2.

Data analysis involved five steps adapted from Nancy Diekmann, who developed a seven-step method for analysis of qualitative research based on phenomenological methodology.<sup>11</sup> The first step involved careful reading of interview notes, with the aim of distilling essential patterns and themes from the data. Common themes were then identified in order to develop a coding frame. Themes appeared to fit within two overall thematic categories: External Reality, defined as the relationship between people and their physical environment, and Internal Experience, defined as the way the environment mediates meanings, individual feelings and the relationships between people. The categories and their themes were then compared to

issues highlighted in the published literature. The third step involved the creation of a codebook and transcripts were thoroughly coded using the coding frame developed. The final step involved grouping interview statements with similar codes together, keeping patient and family comments separate. This allowed for a thorough analysis of each theme and a way to systematically compare and contrast the two participant groups.

- 1) What are your thoughts about the patient rooms here on the 4th floor?
- 2) What would be your preference for a room if you had a choice? Why?
- 3) How does this room environment make you feel?
- 4) What control do you have over this environment? What would make a difference?
- 5) What do you do for privacy in a 4-bedroom room?
- 6) Do you like to share a room? Why or why not?
- 7) What are your preferences for washrooms on this floor?
- 8) How do you feel about other parts of this hospital?
- 9) If you had a chance to design this unit over again, what would it look like?

Table 1. Interview Questions

	Patients (n=6)	Family Members** (n=6)
<b>Gender</b>		
Male	2	3
Female	4	3
<b>Age Bracket</b>		
40-60	2	4
60-80	2	2
80 and over	2	
<b>Room Type</b>		
Shared room (2)	3	3
Ward room (4)	3	3
<b>Palliative Care Unit Type</b>		
Long-term unit (up to 1 year or more)	1	2
Short-term unit (0-3 months)	5	4

\*Ethics approval was granted under the condition that participants remain anonymous, with no personal information obtained regarding type of illness. Ages have been estimated in order to provide some detail with respect to participants. No information was obtained regarding exact length of stay (only long-term vs. short-term), cultural and ethnic backgrounds, or religious beliefs. More female patients interviewed reflects the higher number of female inpatients in the Bridgepoint PCU.

\*\*Family members included 1 wife, 2 husbands, 1 mother, 1 son and 1 daughter-in-law.

**Table 2.** Demographic Characteristics of Participants\*

## RESULTS & DISCUSSION

### 1. External Reality

In the category of External Reality, eight overall themes were determined to be important aspects of the physical environment for patients and families: room size, noise, light, storage, temperature, colour, washrooms, and social spaces (Table 3).

#### Room Size

Although all of the family members interviewed mentioned room size, only one patient did. Families felt that the rooms at Bridgepoint, approximately 90 square feet per patient, are too small (newer palliative care units allot about 200 square feet per patient): "There is not enough room for families to stand around the dying patient's bed." There is also a lack of storage space, both for personal items and for hospital equipment. One patient suggested incorporating regular service modules into the design of the halls, so that equipment can be stored in these alcoves without obstructing movement through the halls.

#### Light

Natural light was recognized by both participant groups, but more by the families as being "important in the feeling of well-being." Due to the current room configuration, if the patient by the windows keeps the curtain closed, natural light is blocked for the other bed located near the door.

Some patients said that they had not seen daylight from their beds for weeks because of this layout. Artificial light was also mentioned, as there currently exists only a fluorescent fixture over each bed. Participants acknowledged the need for softer light sources.

#### Noise

Patients and families discussed noise as being disturbing, including noise from roommates and other families, as well as staff and hallway noise. However, one patient felt that the noise in the halls from staff was a positive factor as a constant reminder of activity and life. Families prefer not to close the doors to the rooms in order to block the noise, for fear of nobody monitoring their loved ones.

#### Washrooms

The feelings surrounding washroom preferences in a PCU were unanimous amongst all participants. Each patient room, whether shared or private, needs a connecting washroom, with or without bathing and shower facilities. Washrooms located down the hall are not acceptable to patients and families. The PCU currently has one sink per room, but it is not centrally located and tends to be used by only one patient and their family. Suggestions by participants were to have one sink per bed or a central sink for each room, in addition to connected washrooms.

#### Social Spaces

Under the theme of social spaces, it was felt that choice is needed. One patient said, "There should be several options for lounge spaces: some larger ones and a few smaller ones to sit in with a visitor or by oneself." It was generally felt that current lounge spaces on the ward have little privacy and no choice over the television channel selection. Patients and families preferred the smaller "quiet room" on the ward as a more private space that they could reserve for family events, in comparison to the more public lounge spaces.

#### Additional Features

Additional design recommendations included a central nursing station so that nurses can access rooms and observe patients easily, colourful spaces and a more home-like setting for the ward, as palliative care does not require the same amount of medical equipment as other wards and thus the environment can be made less institutional in appearance.

#### Family Concerns

In the category of External Reality, family members raised additional themes to the ones identified by patients: halls as social spaces, ventilation, furniture and PCU location within the hospital. Two family members felt that hallways were a potential space for social interaction, noting that most communication takes place in these circulation spaces versus the specified lounge areas. Four family members discussed ventilation as a fundamental component of a PCU. Toileting at the bedside leads to odours that invade the space of other patients, making it unpleasant for visitors and families. Thus, an efficient air exchange system should

1. External Reality	2. Internal Experience
1) Room size	1) Room type a) preference: single, shared, wardroom b) feeling/mood when in room
2) Storage a) personal b) equipment	2) Autonomy a) privacy b) control
3) Light a) natural b) artificial	3) Shared space a) supportive companionship and social interaction b) patient compatibility c) observable death and dying process d) visitor experiences e) feeling secure as patient is not alone*
4) Noise	4) Stage of care and room type* a) STP vs. LTP b) privacy need as disease progresses
5) Temperature of rooms	5) Patient being moved as indication of death being near*
6) Colour of spaces	6) Spaces creating independence*
7) Washrooms and sinks in patient rooms	
8) Social spaces a) family room, lounges, quiet room b) cafeteria c) main entrance & lobby d) halls*	
9) Air/ventilation*	
10) Furniture*	
11) Kitchen and laundry facilities*	
12) Location of PCU in hospital*	

Note: Themes marked with an asterisk indicate family member preferences, which were not mentioned by patients (all other themes were mentioned by both patients and families). Themes are in no particular order.

**Table 3.** Categories and Themes Identified

be considered for shared inpatient wards. Families felt that at least one comfortable chair is needed next to each patient bed, as current chairs are institutional and uncomfortable for visitors: “I sit in my husband’s wheelchair to watch television with him. I can’t even watch television on the chair that is in the room, it is too uncomfortable.” Two family members felt that the PCU should be located on the main floor of the hospital, so that patients can easily access the outdoors if they are ambulatory. (Architecturally, a terrace or roof garden could be an alternative for higher floors.)

**2. Internal Experience**

In the category of Internal Experience, three overall themes emerged from the data analysis: room type, shared space and autonomy (privacy & control) (Table 3).

**Room Type**

All participants discussed preferences for room type. Three patients said that they would prefer to be cared for in a single room; reasons provided including being a private individual and feeling upset because of noises from room-mates, such as laboured breathing and moaning. Two of the three remaining patients expressed a preference for a

shared room with two beds. Although they acknowledged that a single room yields more privacy, their desire for a shared room was based on companionship and being able to observe the surrounding activity: “I wouldn’t choose a private room – I would rather have a roommate. I would think it would be very lonely in a private room.” However, they acknowledged the need for private rooms to be made available for patients who might prefer this option. The remaining patient was also in favour of a shared space, but for financial reasons felt that a wardroom with four beds would be his first choice.

Similarly, three out of the six family members said that they would prefer a private room; reasons included wanting to visit with their loved ones in private, and their view of dying as a personal process: “A family should have their privacy and should not share the death with three other people. What you say in the heat of the moment – when you announce your love for someone, it is better not to be overheard.” In comparison, two of the three remaining family members said they would prefer shared accommodations, because of the possibility of social interaction and having others around to observe their loved ones in case of emergency. The sixth family member said that she had initially wanted a private room for her husband, but upon spending

time with him in a wardroom and interacting with other families, she now prefers a shared room.

### Shared Space

Due to the frequency with which it was discussed, the theme of shared space was explored further with all participants. Reasons given for this preference were supportive companionship and social interaction, patient compatibility, and observing death and the dying process. Patients with a shared room preference felt that companionship outweighed the desire for the privacy that one could obtain from a single room: "Shared rooms in palliative care are an important part of the environment, with respect to the friendships and comfort that develops between patients." Barriers to communication between patients and families in a shared space included different languages spoken and patients who keep their curtain drawn.

Although several patients brought up the distressing feelings they experienced when watching and listening to their roommates, one patient felt comforted by observing the dying process: "It was good to see that (dying peacefully) because you often hear horror stories surrounding death and dying in a hospital." Families were concerned that noises and the suffering of roommates would distress their loved ones. One mother said that her daughter insisted on keeping the curtain open so that she could constantly check on her dying roommate, to make sure that she was not in distress. Family members brought up an additional benefit of a shared space: the notion of feeling secure, as their loved one is not alone when they cannot be there. In case of a medical emergency, families were eased knowing that roommates could notify medical personnel, as there is limited visibility into the rooms by staff.

Overall, half of the participants interviewed would prefer to have private rooms in a hospital PCU. Individual preferences for room type are shaped by both personality (e.g. being a private person) and events (e.g. seeing a family member, who is a patient, enjoy a shared room). It became clear throughout the data collection that towards the end of life, people still appear to be very adaptable to the environment. Firm beliefs about room type were expected at the outset of the research, but views appear to change for both patients and families, depending on various factors, such as the stage of illness, roommates and witnessing events.

### Patient Compatibility

Patient compatibility was a greater issue than anticipated at the outset of the research. One patient felt that preferences for room type are dependent upon compatibility with roommates: "I would most likely welcome a single room if I was with someone I couldn't get along with." The majority of patients and families said that there should be more attention given to ensuring that patients who are placed together in the same room are similar in terms of health status. They explained that being placed with a roommate who is not compatible would enhance the difficulty of the experience: "The physical environment is always the same, but the feeling shifts according to the roommate." This particular patient felt that a PCU design should focus on separating the ambulatory patients by giving them smaller private

rooms to sleep in, but provide more community spaces where patients can gather and spend the majority of their day.

### Privacy & Control

When asked about privacy and how it is achieved in a shared space, patients said they use the curtain when medical or nursing care is administered, or for personal hygiene reasons. However, even with the curtain fully drawn, patients reported feeling uncomfortable. One patient preferred to keep the curtain fully drawn at all times, while the others expressed a preference for not wanting to feel separated from the activity around them: "I don't like to be shut in, I don't draw the curtain. I like to be aware of things going on around me." All six family members said that there is a complete lack of privacy in the rooms and that a curtain is not sufficient. A curtain does not provide a sound barrier and one family member suggested the use of moveable screens or soundproof partitions as an alternative. Generally, patients appeared to adjust to the space around them and have learned to create a sense of privacy, while families felt that privacy is totally lacking for their loved ones and for them as visitors.

### Family Concerns

Family members again brought up additional themes in the category of Internal Experience (Table 3). In terms of stage of care and room type, one family member felt that patients in a short-term ward could benefit from shared spaces, but in a long-term ward there is more time to observe suffering and death, and so a private room is preferred. Four family members felt that privacy is needed as diseases progress: "If someone is obviously dying, maybe they should be wheeled into a private room where the family can congregate." However, another family member expressed fear in seeing a patient moved to a new space, as this could indicate that death was near. Thus, there is a need for flexibility in room assignments throughout a patient's stay, taking into account patient and family desires. Finally, two family members mentioned the need for spaces that recognize their role as family and promote a feeling of independence, such as laundry and kitchen facilities. These spaces allow families to participate in the care of their loved ones, which is part of the overall philosophy of the palliative care environment.

### Study Limitations

There were certain limitations in this study. Perhaps the most significant limitation is the small sample size and the fact that the researcher was the only individual to collect and code the data. In addition, audio-recording of interview sessions was not possible and no transcripts were produced. In order to address this issue, the data was kept consistent by taking the best notes possible, in addition to strategic listening during the interviews in order to record text to use as quotes in the final research report. Finally, this small sample of participants drawn solely from one hospital setting may limit the ability to generalize results. However, the qualitative literature also argues that a small participant group is not necessarily chosen to represent some part of the larger

### 1. External Reality

Adequate room size, approximately 150-200 square feet per patient.

Alcoves in hall for storing equipment and shelving in rooms for belongings.

Natural light accessible for each patient bed and provision of a reading lamp.

Moveable partitions that create privacy and block noise, as an alternative to curtains.

Colourful spaces and a home-like setting.

Washrooms connected to each room and a sink for each bed or a central sink.

A variety of social spaces, with an allowance for several smaller community areas. Architecturally, the design of halls as possible interaction areas for patients, families and staff has much potential.

Adequate air exchange system, as odours can disturb patients and families.

At least one comfortable, easily moveable chair next to each patient bed.

If the PCU is not on the ground floor, terraces and roof gardens can be designed.

### 2. Internal Experience

Provide a variety of room types: both private rooms and shared two-person rooms.

Allow control over personal space in terms of sound, temperature, lighting, etc.

Place patients with similar health statuses together in a shared space.

Provide ambulatory patients with smaller rooms and larger community spaces.

Consider room type related to stage of care, and consider spatial flexibility as the environment needs to be adaptable to the changing needs of patients.

Provide kitchen and laundry facilities for families, in order to create a sense of independence and allow them to help in the care of the patient.

**Table 4.** Design Recommendations for a PCU

world. According to McCracken (1988), the first principle when selecting respondents is that "less is more and for many research projects, eight respondents will be perfectly sufficient. It is more important to work longer, and with greater care, with a few people than more superficially with many of them."<sup>12</sup> Thus, the results of this research may not be applicable to all palliative care patients and their families, but it does provide a glimpse into the nature of palliative care at one Canadian hospital. These results may also vary across cultures and geographic locations, so this would have to be explored further in future studies. The conclusions and design recommendations made in the following sections are based on the research findings from this study's sample of twelve participants.

### CONCLUSIONS

In this study, seriously ill patients and their family members defined key issues related to the design of the physical environment in palliative care. Patients' individual preferences may depend on their own symptoms and experiences, particularly their interactions with other patients. Therefore, it could be assumed that end-of-life care facilities require a range of room types and sizes to enable patients to select the type that they prefer.

The data obtained from this study supports two interesting conclusions. First, being able to decide what levels of

privacy and community patients and their families want appears to be extremely important to them. Second, being able to control the environment is also essential. Meeting these needs will likely lead to higher levels of comfort for patients and their families towards the end of life. These results demonstrate that matters of privacy versus community and personal control over the environment are fundamental in an inpatient setting and are of great significance to patients and their families.

The results of this study have significant clinical and design guideline implications. The findings suggest that a more tailored or patient-specific approach to palliative care design may be required, given the variability in preferences, both among patients and also between patients and family members. Ultimately, what is needed is a sensitive design approach to an environment for the terminally ill, which takes into account both patient and family preferences.

### RECOMMENDATIONS

An important observation made throughout the interview process and later confirmed with data analysis was the notion of individual variation in the perception of physical environment design. This indicates the need for a variety of patient rooms and public places. More detailed individual assessments are recommended, in order to gain a more thorough understanding of what individual patients and

their families experience. In addition, patient and family preferences for room type may change as death approaches and thus more careful research into the stages of the dying process and how this relates to room preferences must be explored.

Design recommendations for a shared patient room include allowing for privacy through some form of partial walls or soundproof partitions that could then be opened should companionship and social interaction be desired. In addition, there is potential for incorporating the idea of halls as community spaces into a PCU design. The current research results suggest that this type of design concept may support patient and family preferences for rooms that provide privacy, with ample space provided just outside the rooms for social gathering. Patient room sizes could be reduced in order to allow for wider corridors, which would serve as both circulation space and community space. Table 4 outlines a summary of design recommendations for a PCU.

Future directions for this research include expanding the participant population to include hospital staff members and integrating their suggestions with those of patients and families.

The main recommendation arising from the results of this study is the provision of choice in terms of room type. When asked what they would do if they could redesign the unit themselves, all twelve study participants reinforced this design suggestion. One family member from Bridgepoint said, "I think at different stages [of care], you need different things. I think you'll always need the option of single and shared rooms."

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### References

1. Dilani A, editor. Design & Health III: health promotion through environmental design. Proceedings of the 3rd World Congress on Design and Health; 2003 Jun 25-29; Montreal, Quebec. Stockholm: International Academy for Design and Health; 2004.
2. Martin C. Putting patients first: integrating hospital design and care. *Lancet*. 2000 Aug 5; 356(9228):518.
3. MacLeod D. Healthy measures: architecture borrows from evidence-based design medical practices to achieve better design and massive cost savings. *Canadian Architect*. 2005 Oct;15-6.
4. Bridgepoint Health [homepage on the Internet]. Toronto: The Organization; c2002-2005 [cited 2005 Nov 6]. Available from: <http://www.bridgepointhealth.ca/>.
5. Personal communication: Ms. Lori Wilson, Director of program planning and health promotion, Bridgepoint Health. Interview conducted on September 12, 2005.
6. World Health Organization [homepage on the Internet]. Geneva: The Organization; c2006 [cited 2005 Sept 15]. Available from: <http://www.who.int/cancer/palliative/definition/en/>.
7. World Health Organization. The Jakarta Declaration on leading health promotion into the 21st century. Declaration of the Fourth International Conference on Health Promotion: New Players for a New Era - Leading Health Promotion into the 21st Century; 1997 Jul 21-25; Jakarta (Indonesia):World Health Organization; 1997.
8. Personal communication: Ms. Nadia Tobia, Principal, Perkins Eastman Black Architects, Toronto. Interview conducted on September 16, 2005.
9. Kirk S. Patient preferences for a single or shared room in a hospice. *Nurs Times*. 2002 Dec 10-16;98(50):39-41.
10. Pease NJ, Finlay IG. Do patients and their relatives prefer single cubicles or shared wards? *Palliat Med*. 2002 Sep;16(5):445-6.
11. Diekelmann N. Learning as testing: a Heideggerian hermeneutical analysis of the lived experiences of students and teachers in nursing. *ANS Adv Nurs Sci*. 1992 Mar;14(3):72-83.
12. McCracken GD. *The long interview*. Newbury Park (CA): Sage Publications; 1988.