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Editorial

It is with great joy, albeit a bit delayed in it's arrival, that we are publishing this edition of the UAHSJ. We have to thank all the contributors this year, our Editorial board, our Board of Advisers, our sponsors, and all the other people that made this issue possible. We are particularly excited about this issue as we have focused more on the creative works of medical students this year, allowing people to see the various creative minds that somehow find time to produce works while studying for exams. Many of these appear in the Musa column which features both artworks and other creative expressions of students and faculty in the health professions.

This year, we are trying a new approach to peer editing. Instead of having a small coterie of editors who review each article, we expanded the editorial board and allowed there to be more students who review each article. To ensure that the articles we were considering publishing were sound, our editorial board was trained in critically appraising the articles to ensure that whatever we publish, it has to meet our standards. As well, members of the editorial board had more time to spend with each article, helping the contributors produce a polished article of excellent quality. With this new approach, we believe that this has helped us to produce one of our best issues yet.

We hope you agree.

Yours,

Andrew Taylor and Michael Szava-Kovats

Co-chief Editors

Letters

Integrating humanism and science: *The University of Alberta Health Sciences Journal's* Musa columns

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The theme of the *Canadian Conference on Medical Education* (CCME) held in St. John's, Newfoundland this past year was "White Coat, Warm Heart: Integrating Humanism and Science." This was a landmark event! As has been increasingly occurring in the United States, United Kingdom and elsewhere, Canadian health care educators have been exploring approaches to bridging the science/ humanism divide that has emerged with the rise of expanding technological advances in medicine. This meeting highlighted the efforts of medical and health educators in incorporating the arts and humanities as part of the environment in which students are learning to become caring health professionals. In support of this direction, the *Musa: Arts and Humanities in Health and Medicine* column in this journal provides an opportunity for sharing of personal experiences and stories related to health and medicine from the perspective of health care providers, teachers and learners, and also patients.

The Musa column provides a space for art work, poetry, personal narratives and reflection on wide-ranging experiences related to medicine and healthcare. Articles included in the current *UAHSJ* issue provide examples of curriculum experiences and electives available in the Faculty of Medicine & Dentistry at the University of Alberta that include arts and humanities approaches. For example, in previous years as part of her DMED 513 Endocrinology and Metabolism block, Dr. Laurie Mereu introduced "Endocrine Detective Stories" as an innovative approach to reviewing content covered in the. On a voluntary basis, students wrote stories, poems, songs or skits, on their own or as a group, relating to content covered in the block and shared these with their peers in a block review session. Among many excellent creative contributions students have made, we have selected a short story written by Christina Beach (Med 2011) to highlight in this issue. Modeled on the *Encyclopedia Brown* mystery series by Donald J. Sobol, this highly engaging piece considers whether two female Olympic figure skaters awarded gold and silver should be entitled to keep their medals (this essay may cause you to recall the gender dispute Caster Semenya of South Africa faced following her 2009 World 800-metre championship performance).

The Arts & Humanities in Health & Medicine Program offers several undergraduate medical electives. Dr. Deirdre Nunan completed an Arts & Humanities Directed Studies elective as a 4th year visiting medical student from the University of British Columbia. As part of her elective, she completed an essay that considered the role of scars as a motif in two of Michael Ondaatje's novels, *The English Patient* and *Anil's Ghost*. Shortly after this, she began her residency in Orthopedic Surgery in the College of Medicine at the University of Saskatchewan, where she continues to reflect on the meaning and significance of scars on patients' bodies, and how in the face of trauma and injury, healing others can also serve to restore the physician/ healer. Jessica Breton, as an undergraduate medical student, completed an Arts in Medicine elective that allowed her to explore various multidimensional aspects of post-partum depression. Her beautiful and affecting artworks, and the insights that they inspired for her, confirm the oft-quoted observation (frequently attributed to Albert Einstein), that "not everything that can be counted counts, and not everything that counts can be counted." Her artwork is featured on the front and back cover of the current UAHSJ issue.

We have also included a story by Edward Bishop, a professor in the Department of English & Film Studies at the University of Alberta. His travel memoir, *Riding with Rilke: Reflections on Motorcycles and Books* won the 2006 City of Edmonton Book Prize and was a finalist for the 2005 Governor General's Literary Award for Non-Fiction. He first shared his story "Reading the Ward" as part of a panel that also included Dr. Steven Aung and Ted Blodgett at an event that was organized by the Arts & Humanities in Health & Medicine Program and the Friends of University of Hospitals to recognize the interconnections between art and medicine in celebration of the 2009 Alberta Arts Days. Relating some of his experiences and observations as a patient during an extended hospital stay, Ted Bishop's story recalls the many pointed observations of Margaret Edson who wrote the Pulitzer Prize-winning play Wit based on her observations of ward interactions while working in a research hospital as a clerk. Ted Bishop's story is noteworthy for both its candour and the questions it poses

in relation to how we can become more aware of and attuned to patients in the process of caring for them. It also suggests the place of the arts in healing, and also the need to develop a heightened sensitivity to patients' stories, and the part we play in all a patient's experience of suffering and healing. In the fall of 2009, we were saddened by the loss of two senior members of the Faculty of Medicine & Dentistry – Drs. Jody Ginsberg and David Cook, both mentors and leaders who supported and exemplified humanism in medicine. Dr. David Cook was a passionate advocate for inspiring and relevant approaches to teaching medicine, which Dr. Kim Solez has captured in a poem he has entitled, "No passport required for David Cook," which we have also featured as a special *Musa* contribution.

In 2010, we introduced a fundraising campaign which will continue through 2011. Our heartfelt gratitude and appreciation are extended to Dr. Steven K.H. Aung, clinical professor and Order of Canada recipient, for his lecture on medical calligraphy and a fundraising auction of his original calligraphies that occurred this past November in support of the Arts & Humanities in Health & Medicine (AHHM) Program. Donations to the AHHM program, as well as orders for a 2011 calendar featuring Dr. Aung's medical calligraphies can be arranged by emailing pbrett-maclean@med.ualberta.ca. Your generosity will help us to support the dreams and aspirations of students and residents who are committed to bridging existing divides between humanism and science in medicine.

In the context of health professional education that is directed to fostering the development of skilled, caring, reflexive and compassionate practitioners it is helpful to expand the sources and kinds of experience and information that are viewed as valuable, and also to make these accessible to students. My grateful thanks to all our contributors and all those who helped create this issue. We look forward to your response and feedback, and also look forward to any ideas you may have for future *MUSA* columns. It is my hope that this column will help to foster awareness and commitment to integrating the arts and humanities in medicine and health professional education. Given excitement that the 2010 CCME meeting generated, and new developments (for example, a one-day conference on *"Creating Space for Arts and Humanities in the Education of Health Professionals: Where do we go from here? A Canadian perspective"* is planned in conjunction with the 2011 CCME meeting), we have a great future to look forward to! In anticipation of this, we are looking forward to expanding our support for projects and initiatives that consider arts and humanities perspectives in relation to medicine.

Wishing everyone all the best as we begin the new academic year!

Implications of Screening for "Peace of Mind"

Scott McLeod, University of Alberta Medicine, Class of 2012

Technological advances in medicine are happening every day. From pharmaceuticals to improvements in medical imaging, patients have come to expect a lot out of visits to their doctors. Coupled with bombardments from awareness campaigns and fundraisers for every disease imaginable, we are a population preoccupied with health. In catering to patients of today physicians are expected to be knowledgeable about numerous non-traditional health treatments, specialized diets, herbal remedies, and exercise programs. Screening technology is of particular interest to patients because it may detect disease in the early stages before the development of serious ill health. Responding to this demand from patients for more information about their health, radiologists have set up full-body magnetic resonance imaging (MRI) scans promising to detect a wide range of major illnesses. This practice raises several ethical questions regarding the administration of such medical resources. When presented with a fifty-three year old business executive who just wants "peace of mind" regarding his health and who asks for his physician's advice regarding a screening MRI, what advice should be given? A physician must weigh the risks and benefits of screening procedures, being keenly aware of the divergent perspectives between individual patients and the community as a whole.

Screening tests require informed consent before they are conducted (Raffle, 2007). Before MRI screening can safely take place a complete medical history, including details of previous surgeries and details of implanted metal, is needed (Goehde et al., 2005). This information is necessary so that a physician can present advice in a balanced manner to the patient so they can make an informed decision on whether or not to proceed. This involves knowledge of what the procedure entails as well as the associated risks and potential benefits. Patients who request screening tests expect that finding any abnormalities will be beneficial, however, this is not always the case (McKeown, 1968). Ideally, upon identification of a problem patients would be able to subsequently receive treatment and care which would be advantageous to them. According to the classic World Health Organization screening criteria proposed by Wilson and Jungner, all conditions screened for must be important health problems, have an acceptable diagnostic test and treatment available, and be recognizable in early stages (Wilson, 1968). Another major criterion proposed is that screening must not be a "once and for all" exercise (Wilson, 1968). The rationale behind this is that every screen is only one snapshot in time.

There are many positive implications to medical screens such as MRI. Images produced by MRIs contain an immense amount of information. Potential benefits include the detection of

ailments and diseases in major areas of the body such as the head, arteries, lungs, heart, and colon (Goehde et al., 2005). Early detection of disease can lead to better treatment outcomes for the patient, including improved quality of life (McQueen, 2002). An MRI can also give an indication of the extent of disease in certain conditions so that the patient can be made aware of their seriousness. Studies have indicated that when MRI images revealing disease are shown to patients, they function as a "kick in the pants," increasing the likelihood of patients making essential lifestyle modifications (Goehde et al., 2005). Quantification can also provide useful baseline information and may help physicians make correlations when new findings are revealed in future diagnostic imaging. Another major benefit of an MRI screening examination is that new technology has allowed for full-body MRI scans to be completed in approximately fifteen minutes, less time than it takes to go to the laboratory for a complete blood count. For busy business professionals one full-body screen is far less time consuming than multiple visits for medical diagnostic services and follow-up visits with referring physicians. Also, MRIs do not use ionizing radiation resulting in less radiation-related cancer risk when compared with other imaging technologies.

Although there are many benefits to screening with MRIs, there are also many negative implications of which prospective patients must be aware before undergoing the procedure. The results of a screening MRI may reveal conditions that currently have no accepted treatment, are benign in nature, or have no adequate treatment at all (Goehde et al., 2005). While it is sometimes beneficial to identify such conditions there are often significant psychological repercussions to the patient. One must ensure that proper counselling occurs similar to that which happens before and after screening for genetic disorders. The psychological effects of having a disease may affect all aspects of a patient's life including work, hobbies, and family life (Evers-Kiebooms & Decruyenaere, 1998). Currently, there are some technical limitations to the information provided by MRI scanning. For the purpose of detecting tumours in the chest or abdomen a CT scan is usually the first choice, since artifacts from patient movement are common during MRI scans of these areas (Godelman & Haramati, 2008). Due to such limitations, a patient may suffer from anxiety while undergoing and waiting for follow-up testing. Many times, an MRI scan alone may not provide a conclusive diagnosis, and the patient may be subjected to other invasive procedures, each with their own risks. Furthermore, false results will sometimes occur and some patients will leave with a false sense of reassurance while others leave with great anxiety because of suspicions of a disease that is not actually present or is unlikely to progress and cause harm (Raffle, 2007). Another downside to receiving MRI screening is that insurance companies and employers can use diagnostic information as evidence and may change insurance premiums or conditions of employment (Raffle, 2007).

When screening tests become widely utilized the consequences ripple through the community and have a major impact on health care costs. One of these consequences is known as a "popularity paradox" (Raffle, 2007). This occurs when screening results in over-diagnosis and over-treatment. As more people are screened, many are diagnosed and treated even though treatment may be of no major benefit. Regardless of this, many of those receiving screening and treatment believe that they owe their health and sometimes even their lives to the screening test. This can lead to the inappropriate promotion of screening tests. According to recent research, the prostate-specific antigen (PSA) blood test for prostate cancer is a good example of this paradox (Mercer et al., 1997). MRI screening is still under investigation and further evidence must be gathered before it can be recommended. Associated with this case is the dilemma of "universality of health care." In a perfect world, everyone would receive the same quality of treatment regardless of social status and income. However, people can pay to undergo private diagnostic imaging, including MRI screening. Queue jumping may then transpire because, after attending a private diagnostic imaging clinic where a pathological finding is detected, the individual can then re-enter the public system seeking confirmation of the finding as well as follow-up treatment and care. The ability to pay for MRI screening bypasses the public system often leading to faster and more efficient care for the affluent. In this two-tiered system, individuals with similar conditions are not treated equally. Legal implications of MRI screening must also be considered since these may be harmful to the community at large due to the limited resources of our health care system. Screening tests are not always perfect, and after the patient re-enters the public system to undergo potential further investigations, complications from these possibly unnecessary investigations may occur and lawsuits may take place (Raffle, 2007). Alternatively, MRI screening can completely miss some serious developing conditions eroding confidence in diagnostic tests. The burden may fall on physicians and health boards to settle any potential lawsuits, which could place additional strain on the health care system.

No discussion of MRI screening is completely straightforward. Some of the individuals seeking MRI screening may be asymptomatic. A responsible clinician will assess the capacity of the patient making the decision, and advise him or her of the pros and cons associated with the procedure. While many of the ethical concerns may currently prevent physicians from recommending MRI screening to patients, the technology does represent advancement that could have an evidential basis for use in the community at large. Patients will ultimately make up their own minds whether or not to use MRI screening; however, patients should know that MRI screening may not provide the "peace of mind" being sought.

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Combination Therapy with Tumor Necrosis Factor Related Apoptosis Inducing Ligand for Kidney Cancer

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Kidney cancer is the third most common malignancy of the genitourinary system accounting for an estimated 54,390 new cases in North America in 2008. This cancer claims an estimated 13,010 lives each year, contributing to 2.3% of deaths due to all forms of cancer. (1) Renal cell carcinoma (RCC) is the most common histological subtype of kidney cancer and patients presenting with metastatic disease have an estimated survival rate of less than 5%. (2, 3) Conventional cytotoxic chemotherapy has little anti-tumor activity in RCC, which is thought to be due to the over expression of multi-drug resistant pumps, which participate in the normal functioning of these cells. (4) Moreover RCC has shown be to highly resistant to radiation therapy due to a highly active glutathione redox system. (5) RCC is responsive to immunotherapy (α-IFN, IL-2) which has demonstrated a survival benefit in clinical trials. (6, 7) In order to exploit this, the response of RCC to tumor-necrosis-factor related apoptosis-inducing ligand (TRAIL), a mediator of immune response, has been studied.

TRAIL induces apoptosis selectively in cancer cells via activation of the extrinsic and intrinsic (mitochondrial) apoptotic pathways. (Figure. 1) (8) The process involves TRAIL binding to the plasma membrane and inducing a homotrimerization of its receptor. This results in the accumulation of multiple adaptor proteins (FADD, TRADD) at the receptor site leading to the aggregation and activation of initiator caspases 8 and 10. Once assembled, this aggregation of proteins is termed the death inducing signaling complex (DISC). This complex signals downstream to activate executioner caspases 3, 6 and 7 within the cell ultimately leading to cell death. (8) Such signaling is referred to as the extrinsic apoptotic pathway. TRAIL can also signal through the intrinsic or mitochondrial apoptotic pathway through cleavage of Bid by the DISC resulting in the release of cytochrome C from the mitochondria into the cytosol. Once released, cytosolic cytochrome C complexes with caspase 9 to form the apoptosome which results in further proteolytic activation of the executioner caspases 3, 6 and 7. This activity results in further amplification of the apoptotic response. (8) Despite its enormous potential as an anticancer agent, resistance among many cancer cell lines prevents TRAIL from being used on a widespread basis for treatment of metastatic disease. (9)

Interestingly, recent advances in the molecular biology underling the carcinogenesis of RCC have shed light on the interactions between survival signaling and the apoptotic machinery. These interactions have been implicated in TRAIL resistance. (10, 11) It has been shown that up to 80% of sporadic cases of RCC manifest biallelic loss or inactivation in the von hippel lindau (VHL) gene. (10, 11) The product of this gene acts as an ubiquitin protein ligase and causes the degradation of the hypoxia inducible factor 1 (Hif-1) transcription factor. Accumulation of HIF-1 leads to the expression of a myriad of proteins responsible for driving tumourigenesis including those involved in the mitogen activated kinase (MAPK) and Akt/mTOR survival signaling pathways. (10, 11) As aberrant MAPK and Akt/mTOR signaling have been implicated in TRAIL resistance it is logical that attenuating these signaling events poses a novel method of circumventing this resistance. As such, we studied the effect of combination therapy of TRAIL with Sorafenib in RCC due to the multi-caspase inhibitor effects of Sorafenib, which has been shown to attenuate both the MAPK and Akt/mTOR pathways. (12) Moreover as prior work in our lab has shown that Gemcitabine is able to sensitize partially resistant transitional cell carcinoma of the bladder (TCCB) cell lines to TRAIL through its ability to downregulate the levels of the anti-

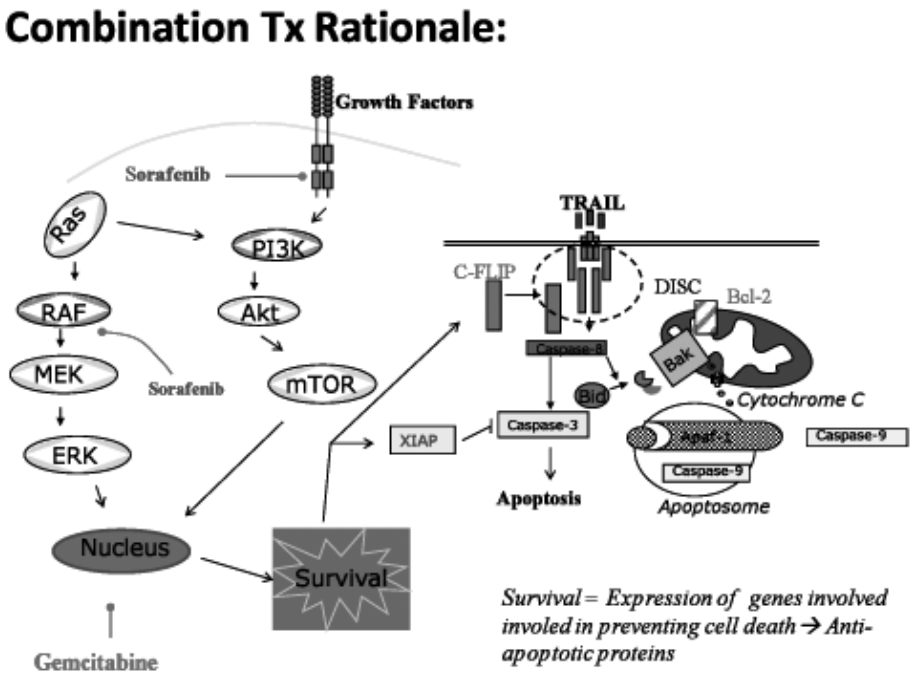

Figure 1. Combination therapy rational. *The PI3K/AKT/mTOR axis and MAPK signaling cascades control the expression of anti-apoptotic proteins, such as Bcl-2, cFLIP and XIAPs. By binding to the catalytic domains of enzymes within these signaling cascades, TKIs, can attenuate these signaling events, prevent the upregulation of these anti-apoptotic proteins and potentially sensitize these resistant cancer cells to TRAIL. Likewise, through modulation of protein translation, gemcitabine may be able to downregulate anti-apoptotic proteins such as Bcl-2 and act as a sensitizer to TRAIL therapy.*

apoptotic Bcl-2 protein (13), we also studied the possibility of synergy between these two drugs in RCC. Thus through combining TRAIL with drugs that target specific survival cell signaling cascades we believe it is possible to sensitize resistant RCC cells to TRAIL. (Figure. 1)

MATERIALS & METHODS

Cell Culture: Five RCC lines (Caki-1, Caki-2, A498, ACHN, 786-O) were cultured at 37C and 5% CO2. Caki-1 and Caki-2 cells were cultured in McCoy's medium. A498 and ACHN cells were cultured in modified Eagle's medium. 786-O cells were cultured in RPMI medium. All medium was supplemented with 10% fetal bovine serum, L-Glu nonessential amino acids-Earle's balanced salt solution, 100 U/ml penicillin, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin-B.

Cell Proliferation (MTT Assay): Cells were seeded at various concentrations into a 96-well plate. Following 24 hours incubation the cells were then treated with various regimes of drugs for specific times dependent on experimental setup. The drug containing medium was then removed and replaced with culture medium. After a 24h incubation period MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide) was prepared using 5mg/ml of PBS and added to medium in each well at a dilution factor of 1:10. Cells were then incubated for 3.5h after which the MTT containing solution was removed and replaced with 150 µM of DMSO to dissolve the resultant formazan crystals. The absorbance at 570nm for each well was then measured using a BIO-RAD mircoplate reader. The percentage cell death was calculated as (1-[absorbance of treated cells/absorbance of untreated cells]) X 100. Each assay was repeated a minimum of three times.

Apoptosis Assay: Cells were seeded at various concentrations into a 96-well plate. Following 24 hours incubation the cells were then treated with various regimes of drugs for specific times dependent on experimental setup. The drug containing medium was removed and replaced with culture medium containing Hoeschst at a 1:2000 dilution factor. The cells were then incubated for 15 mins in darkness after which the Hoeschst containing medium was removed and replaced with Annexin V-FITC staining solution in Annexin Binding Buffer at a 4:100 dilution factor. The cells were then incubated for 30 min at room temperature in darkness. Using an LMP microscope (Zeiss®) pictures were then captured at 5X magnification. Data was acquired using Metamorph® software. Apoptosis was quantified as the number of Annexin V positive cells as a fraction of the number of Hoeschst positive cells.

Western Blot Analysis: Cells were washed in ice-cold, phosphate buffered, saline and lysed at 4 in lysis buffer. (14) After determining the protein content of the extracts by bicinchoninic acid assay (Pierce, Rockford, Illinois) 40 g of protein was electrophoresed in 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, followed by electroblotting onto nitrocellulose. Blots were immunostained with primary antibodies to caspase-9 and 8 (Cell Signaling Technology®) and diluted with 5% nonfat milk to 1:1000. Primary antibodies were detected with horseradish-peroxidase-conjugated secondary antibodies (Jackson ImmunoResearch, West Grove, Pennsylvania) using echochemiluminescence detection reagents (Amersham, Little Chalfont, United Kingdom). (14)

RESULTS

Response of RCC cell lines to TRAIL, sorafenib and gemcitabine

Dose response curves where carried out to determine the response of our panel of RCC cell lines to the drugs TRAIL, gemcitabine and sorafenib. (Figure. 2) In these experiments cells at 80% confluence where trypsinzed and seeded in a 96 well plate at 3000 cells/well (786-O, ACHN) or 5000 cells/well (Caki-1, Caki-2, A498) and incubated for 24h. Following this a drug dilution was carried out and either TRAIL, gemcitabine, or sorafenib were added at various concentrations (10-1000 ng/ml) to each well for 4h. The drug was then removed and FBS containing medium was added to the

wells. Following 48h incubation, an MTT assay was performed to assess cell death following drug treatment. The results of these studies, displayed as the percentage cell death as a function of drug concentration, showed that the cell lines ACHN, Caki-1 and A498 where highly sensitive to TRAIL, whereas Caki-2 was partially resistant and 786-O was strongly resistant. (Figure. 2) All cells lines showed a sigmoidal relationship between cell death and increasing TRAIL concentration, with a maximal biological response at 300 ng/ml. The five RCC cell lines also showed a sigmoidal relationship between cell death and increasing gemcitabine and sorafenib concentration. Similar to TRAIL, the RCC cell lines responded differentially to both gemcitabine and sorafenib and a maximal biological response was seen at 10 µM for gemcitabine and 100 µM for sorafenib.

TRAIL sensitive cells show activation of both the intrinsic and extrinsic apoptotic pathways

To explore the mechanism of cell death in TRAIL treated cells, caspase activation was assessed via western blot analysis. In these experiments TRAIL sensitive (ACHN) and resistant (786-O) RCC cell lines were treated with TRAIL at a concentration of 300 ng/ml for 2 or 6h. Cell lysates were collected and subjected to western blot analysis. In TRAIL sensitive cells cleavage and activation of caspase-8 and caspase-9 was seen following 2h and increased following treatment for 6h. (Figure. 5) This activity was not seen in the TRAIL resistant 786-O cell line. Additionally, these cell lines were treated with sorafenib at a concentration of 10 µM for a period of 2, 6 or 24h. Cell lysates were collected and subjected to western blot analysis. In all conditions, cleavage of caspase-8 and -9 was not seen. (Figure. 5) These experiments where not repeated limiting the validity of these results.

Cytotoxic response of TRAIL resistant 786-O cell line to combination therapy with sorafenib or gemcitabine

To determine the cytotoxic response of our resistant 786-O RCC cell line to combination therapy MTT assays were carried out. Based on our dose response curves (Figure. 2), we used a concentration of 300 ng/ml, 10 µM and 100 µM for treatment of cells with TRAIL, gemcitabine and sorafenib, respectively. Moreover, as previous work has shown that TRAIL resistant leukemia cells can be sensitized to TRAIL with sorafenib at a concentration of 5 or 7.5 µM (15), we choose to also use a concentration of sorafenib at 10 µM during combination therapy with TRAIL. In these experiments, cells were seeded in a 96 well plate at a concentration of 2000 cells/well. Following 24 hours incubation the cells were treated with either sorafenib or gemcitabine for 4h after which the drug containing medium was replaced with FBS containing medium. Following a 24h incubation period, TRAIL was added to the cells for 4h after which the drug containing medium was replaced with FBS containing medium. An MTT assay was preformed 24h later. The results showed an enhanced cytotoxic response for combination therapy of TRAIL with gemcitabine or sorafenib compared to single agent treatments. (Figure. 3) Combination of TRAIL with gemcitabine [10 µM] resulted in the greatest cytotoxic response at 81%, followed by combination of TRAIL with sorafenib at a concentration of 100 µM at 55%. Despite the enhanced cytotoxic response seen following combination therapy of TRAIL with sorafenib at a concentration of 10 or 100 uM, the 786-O cells were still partially resistant and showed a cytotoxic response of 24% and 55%, respectively. (Figure. 3)

Apoptotic response of RCC to combination therapy with Sorafenib or Gemcitabine

To further assess the response of RCC to combination therapy, apoptotic assays utilizing Annexin V and Hoeschst dyes were carried out. Annexin V stains phosphotidyl serine on the outer leaflet of the cell membrane. As this phospholipid normally resides in the inner leaflet and is only present in significant concentrations during apoptosis in the outer leaflet, the degree of apoptotic cell death can be determined following addition of Annexin V to treated cells. In these experiments, cells were seeded at 2000 cells/well in a 96 well plate and incubated for 24h. Cells were then treated with either gemcitabine or sorafenib at a concentration of 10 µM for a period of 4h and then incubated for 20h in fresh medium. Following

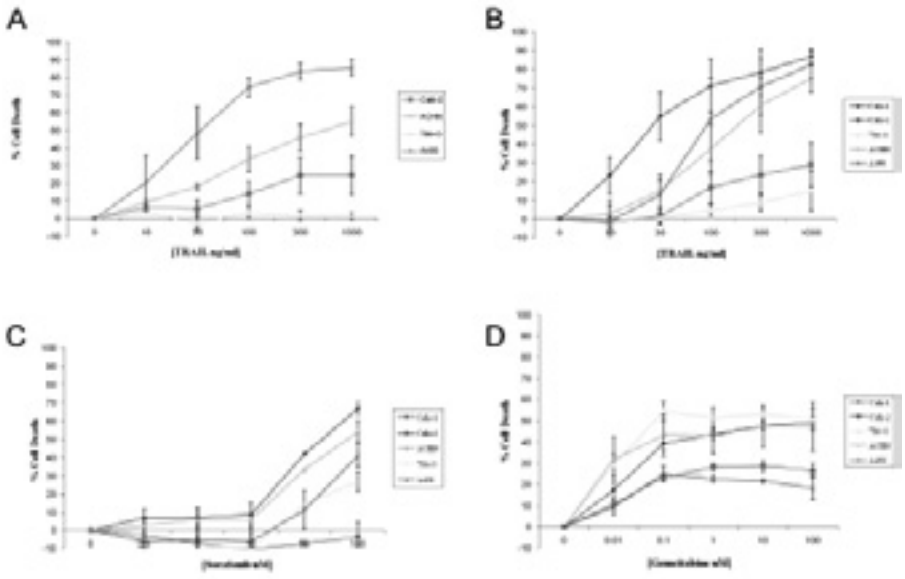

Figure 2. Dose response studies in our panel of RCC cell lines. *Dose response studies were carried out in a panel of RCC cell lines. Cells were seeded in 96 well microtiter plates at a concentration of 3000 (ACHN, 786-O) or 5000 (Caki-1, Caki-2, A498) cells/well. Cells were then treated with either TRAIL (A & B), gemcitabine (C), or sorafenib (D) over a range of concentrations. Cells were then incubated for 24h (A) or 48h (B & C & D) after which an MTT assay was carried out to asses cell death. Data shown represents the mean +/- SEM from at least five independent experiments.*

this, the cells were treated with TRAIL at a concentration of 300 ng/ml for 4h and then stained with Annexin V and Hoeschst. In support of the cytotoxic assays, the results of these experiments showed that combination therapy with gemcitabine or sorafenib resulted in an enhanced apoptotic response when compared to single agent treatment. (Figure. 4) This was seen to the largest extent for combination of gemcitabine with TRAIL which resulted in an apoptotic response in 93% of treated cells. Combination of sorafenib with TRAIL had far less effects, with only 30% of treated cells showing an apoptotic response. (Figure. 5)

DISCUSSION

To assess the response of RCC to TRAIL we initially developed dose response curves via the MTT assay. (Figure. 2) These experiments showed that RCC, like other cancer cell lines, shows a differential response to TRAIL, having cell lines being stratified from highly sensitive to highly resistant. This highlights the difficulty of treating cells via a single agent as even within a given cancer type, cells responded differentially to this drug. In order to determine the optimal concentration of gemcitabine and sorafenib to use in combination we developed dose response curves for our panel of RCC cell lines to these agents as well. (Figure. 2) These results highlighted that like TRAIL, the RCC cell lines showed a differential response to gemcitabine and sorafenib and that a maximal biological response to these agents was seen at 10 µM and 100 µM respectively, accordingly these were the concentrations used in combination therapy. However, despite these dose response studies, other groups have used concentrations of sorafenib 10-fold lower than this to sensitize resistant cells to TRAIL. (16) This suggested that the synergistic effect of these drugs may possibly be reached by using sub-maximal concentrations of sorafenib and because of this a concentration of 10 µM was also used in our combination therapy regimes.

The use of sorafenib in the sensitization of TRAIL has been shown in a number of cell types including human leukemia and colon cancer cell lines. (15, 17) As RCC has an over activity in both the PI3K/Akt/Mtor and MAPK kinase signaling cascades (18, 19, 20), we hypothesized that sorafenib may also have an effect in sensitizing TRAIL resistant RCC cell lines. Despite our initial rationale, the use of sorafenib at a concentration of 10 or 100 µM was unable to sensitize our TRAIL resistant 786-O cell line to TRAIL. (Figure 3, 4) However, as shown in figure 3, the combination of sorafenib at 10 µM or 100 µM with TRAIL resulted in an enhanced cytotoxic response. Despite this, when these values are compared to those for the single agent treatment conditions a synergistic effect is not seen. (Figure. 3) This suggests that the enhanced cytotoxic response between these drugs is due to an additive effect where TRAIL targets a small population of cells that is different from the population of cells targeted by sorafenib. This is further supported by the apoptotic assays in which combination of sorafenib and TRAIL resulted in an enhanced apoptotic response in the TRAIL resistant RCC cell lines. (Figure. 4) However, similar to the cytotoxic assays, this enhanced effect was a result of additive mechanisms and failed to sensitize these cells to TRAIL. (Figure. 4) Thus, unlike in human leukemia and colon cancer cells, sorafenib is unable to target the necessary signaling processes in RCC that are needed to make these cells competent to TRAIL death signals. As such, further investigation of the mechanisms that prevent these sensitizing effects from being mediated in TRAIL resistant RCC cell lines is warranted.

On the basis of previous work highlighting the role of gemcitabine in the sensitization of TCCB to TRAIL (13), we explored its use for the sensitization of RCC to TRAIL. Moreover, work in pancreatic adenocarcinoma cell lines has also supported the role of combination therapy with gemcitabine in both in-vitro and in-vivo model systems further warranting our investigation. (21) Based on the results obtained in our dose response studies (Figure. 2), we used a concentration of 10 µM of gembitabine in our combination therapy regimes. Following pretreatment of cells for 4h with gemcitabine an enhanced

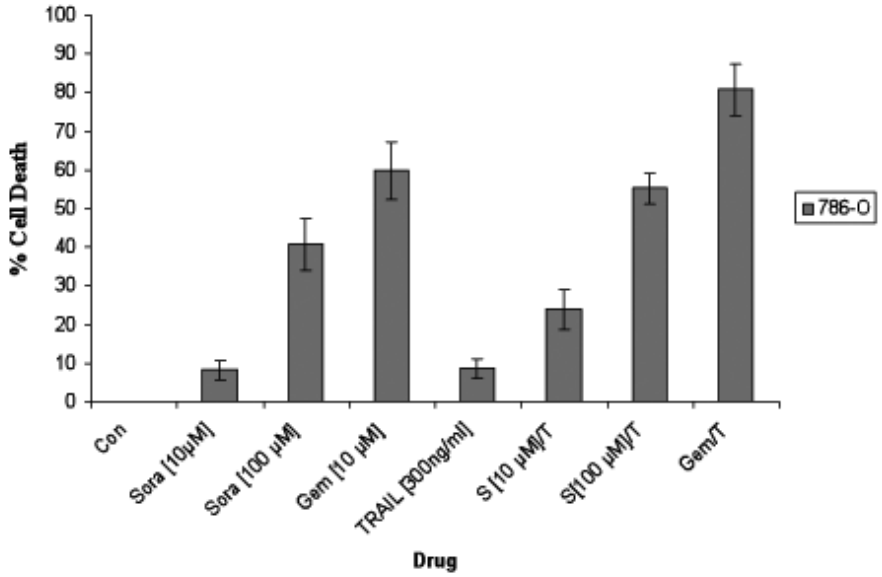

Figure 3. Cytotoxic response of resistant RCC cell line to combination therapy. *Dose response studies were carried out in the TRAIL resistant RCC cell line 786-O. Cells were seeded in 96 well microtiter plates at a concentration of 2000 cells/well. Cells were then treated with either single agent sorafenib, gemcitabine or TRAIL for 4h. Addtionally cells were treated with combination therapy of sorafenib or gemcitabine with TRAIL. A concentration of 10 or 100 uM of sorafenib, 10 uM of gemcitabine or 300ng/ml or TRAIL was used. Cells were then incubated for 24h after which an MTT assay was carried out to assess cell death. Data shown represents the mean +/- SEM from at least three independent experiments. Abbrevations; Sora:Sorafenib, Gem:Gemcitabine, T:TRAIL.*

apoptotic and cytotoxic response of our resistant 786-O RCC cell line was observed following addition of TRAIL (Figure. 3, 4). The cytotoxic response when compared to single agent treatment was not shown to be synergistic, suggesting like sorafenib, gemcitabine enhances cytotoxicity via an additive mechanism (Figure. 3). However, the results from the apoptotic assays did show a synergistic effect where the addition of the apoptotic responses observed for single agent gemcitabine and TRAIL treatment could not account for the 93% apoptotic response observed following combination of these agents (Figure. 4). The discrepancy between the cytotoxic and apoptotic responses of the cells can be accounted for as the treatment of cells with gemcitabine, an anti-metabolite, attenuates cell proliferation. (22) As a result of this, the MTT assays used to assess cytotoxicity are particularly sensitive to the effects of this drug and hence the response of the cell lines to single agent gemcitabine would be expected to be much higher when characterized via the cytotoxic vs. apoptotic assays, thereby making it difficult to obtain a synergistic effect with such a high response from a single agent alone. Taken together this suggests that pretreatment of TRAIL resistant RCC cell lines results in a synergistic apoptotic response and supports previous work done in TCCB. (13)

Activation of caspase 8 by proteolytic cleavage is necessary for the initiation of the extrinsic apoptotic pathway. Moreover for this extrinsic pathway activity to trigger an intrinsic apoptotic response through the mitochondrial pathway, cleavage of both caspase -8 and 9 is required. (8) In our experiments cleavage of caspase-8 and -9 was seen only in the TRAIL sensitive ACHN cell line following treatment of cells with TRAIL for 2h. (Figure. 5) This suggests that TRAIL resistant RCC cell lines are unable to accept extrinsic apoptotic stimuli and as a result cannot initiate cleavage of Bid and amplification of apoptosis via the intrinsic pathway. These effects where not seen for single agent sorafenib treatment lending support to the validity of our cytotoxic and apoptotic assays which showed little cell death following treatment with this drug. (Figure. 5) Importantly, as these interpretations are based on our western blot experiments which were not repeated it is difficult to draw definitive conclusions. Further studies should seek to replicate these results such that the merit of the above conclusions can be determined.

Previous studies have highlighted the role of the transcription factor NFkB in mediating RCC resistance to apoptotic agents such as TRAIL through an upregulation of anti-apoptotic proteins, including Mcl-1. (17) These experiments utilized Bax -/- cells and showed that inhibition of NFkB activity via pretreatment with sorafenib was able to sensitize TRAIL resistant cells. As sorafenib was unable to sensitize our resistant RCC cell line to TRAIL this suggests that the mechanism of NFkB activation is different in RCC compared to this cell system, suggesting sorafenib is unable to target the upstream signaling events responsible for NFkB activation in RCC. As such, future experiments will need to investigate the use of other tyrosine kinase inhibitors to target alternate signaling pathways that have been shown be mediate NFkB activation, such as the mTOR pathway, which can be inhibited via the drug temsirolimus

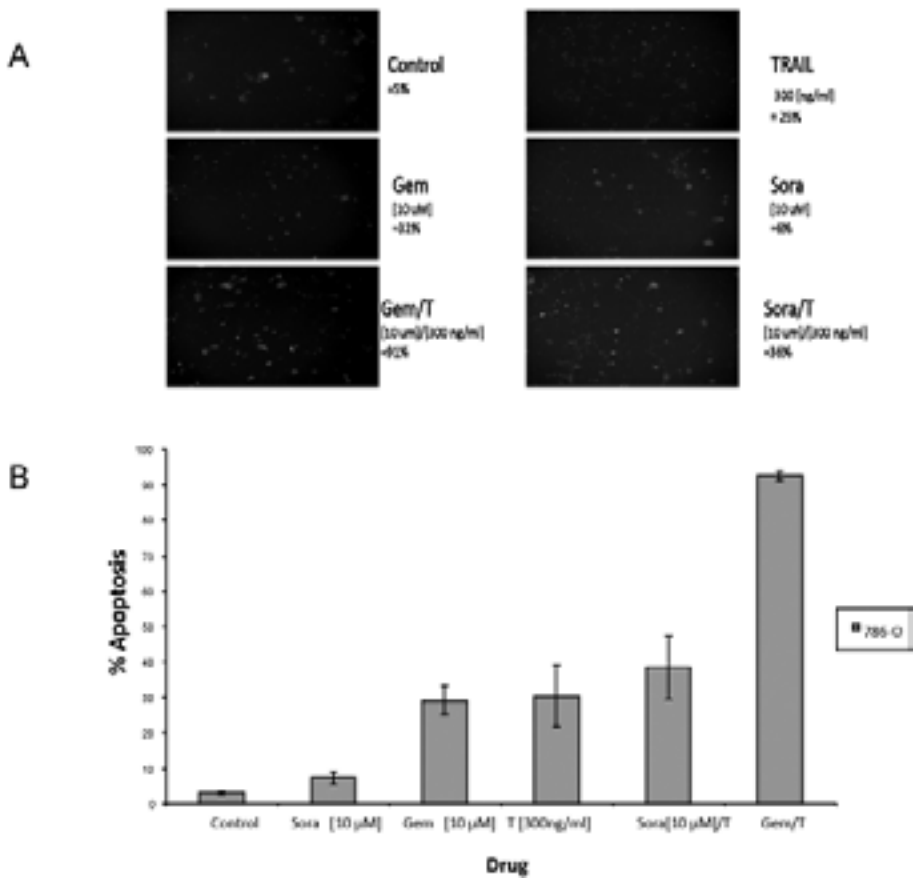

Figure 4. Apoptotic response of resistant RCC cell line to combination therapy. *TRAIL resistant RCC cells (786-O) were seeded in a 96-well microtiter plate. Cells were pretreated with Gemcitabine (10 μM) or Sorafenib (10 μM) for 4h, after which they were cultured in drug-free media for 20h. Cells were then treated with TRAIL (300 ng/ml) for 6h and stained with Hoescht (Blue) dye to visualize the nucleus and Annexin V (Green) to visualize phosphatidyl serine, followed by microscopy. (A) A representative experiment is depicted. % apoptosis is shown. (B) Data shown represents the mean +/- SEM from at least five independent experiments. %Apoptosis expressed as the number of Hoescht (Blue) staining cells incorporating Annexin V (Green) antibody. Abbreviations; Sora:Sorafenib, Gem:Gemcitabine, T:TRAIL*

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Journal excerpts from Birth marks

For more information, see page 13


Baby shower


The Psychoneuroimmunology of Postpartum Depression

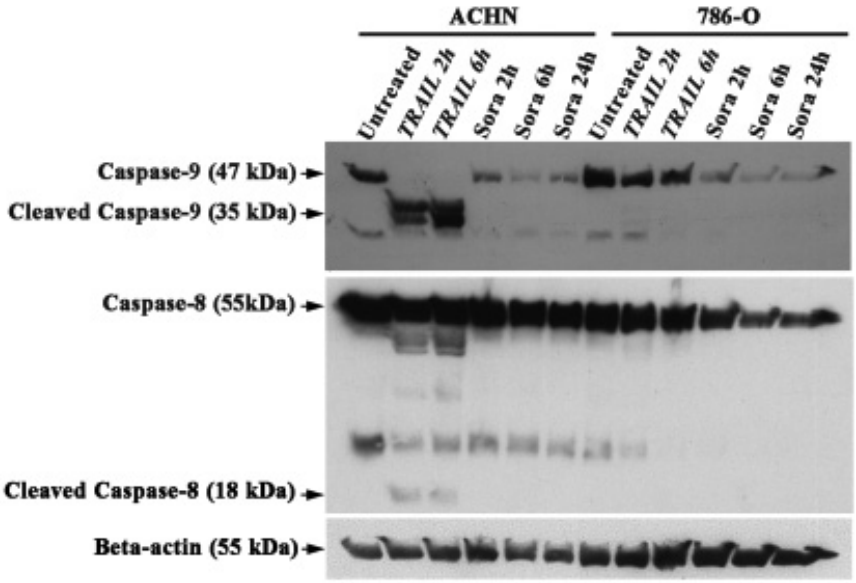

Figure 5. TRAIL induced intrinsic and extrinsic apoptotic signaling pathways. *Activation of both the intrinsic and extrinsic apoptotic pathways is observed upon 2h treatment with TRAIL in the sensitive RCC cells (ACHN), shown by cleavage of caspase-9 and caspase-8, respectively. Activation of these pathways is not seen in TRAIL resistant cells (786-O) or in Sorafenib treated cells. Experiment was not repeated.*

(23, 24). Moreover the mechanisms that prevent sorafenib sensitization of resistant RCC cell lines to TRAIL will be investigated to gain insight into the mechanisms of RCC evasion of apoptosis. Furthermore, as prior research (13) has supported gemcitabine's ability to downregulate the anti-apoptotic protein Bcl-2 in mediating the sensitization of resistant TCCB cell lines to TRAIL, experiments investigating these effects in RCC are warranted to determine whether these effects are mediated by the same cellular processes in both these cancer cell types. Further work investigating the indirect tumor effects of combination therapy by utilizing an in-vivo model of RCC is necessary. Such studies are vital to understanding the therapeutic potential of combination therapy regimes as many of our agents target the tumor microenvironment rather than the tumor cells themselves. This is accomplished through the inhibition of angiogenesis via attenuation of endothelial cell survival signaling. (25)

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Birth marks: An artistic exploration into the medical, personal, societal, and historical dimensions of postpartum depression (PPD) through a collection of sketches, collages, and journalling

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In the early morning of August 11, 2000, Dr. Suzanne Killinger-Johnson left her Toronto home with her 6-month-old son. This 37 year-old woman was a bright and successful doctor. She had been trained in psychotherapy and cared for patients experiencing mental illness. She was described as affluent, attractive, and happily married. She was well liked by family, friends, and neighbours. Yet, on that summer morning in August, she took her son into her arms and threw herself in front of a subway train. The media and the medical community struggled to make sense of this tragic loss. They desperately searched to answer the questions on everyone's mind: why did she do this? But no one could find a satisfactory answer. It didn't seem to make sense.

This is the power of post-partum depression. There is no single cause of this illness. There is no clear predictor for who is at risk and who is safe. There is no simple, logical explanation as to how it can envelop a person's life in darkness. This is why I chose to explore this topic through art. With art, it is possible to transcend the limitations of traditional scientific inquiry and to explore a more human and holistic perspective. My goal was to enrich my knowledge on this topic, to examine my own personal thoughts and biases, and prepare myself to support and be an advocate for my future patients.

Over the course of several months, I created a collection of 24 art works related to the medical, personal, societal, and historical dimensions of post-partum depression. I used a variety of mediums including poetry, collage, sketching, and painting. I tried to avoid having a specific vision or objective for the project, but rather opened myself up to allowing the project to be guided by the art itself. Each piece has its own story which is complete in and of itself. They were not made to be connected to each other in any way. Interestingly, however, when I compiled the pieces together in an album, I noticed recurring elements and images which communicated themes and messages that I had not been consciously aware of.

The medical dimension of post-partum depression was the first area that I explored since, as a medical student, it was the most familiar to me. I learned about the complex interplay between the hormonal, immunological, and psychological forces at work. This was reflected in my art through clippings of brain imagery, anatomy, and study results. I also incorporated pictures from medical text books and juxtaposed them with images related to midwifery and

traditional birth models. The medical images evoked feelings of violation and disempowerment while the midwifery images portrayed warmth and strength. Interestingly, new studies suggest that women who use midwives or who feel more in control of the birth process may be less likely to suffer from post-partum depression.

In order to explore the personal dimension of this illness, I relied on my experiences with patients as well as reading books about survivors of post-partum depression. While each story was unique, I noticed some recurring themes surrounding loss of identity, disappointment, and self-hatred. I incorporated quotations from these stories throughout several of my pieces. Many women also described intrusive and compulsive thoughts of harming themselves or their babies. These thoughts were extremely common yet rarely discussed with others out of fear of being considered a bad person or a monster. I tried to bring this hidden darkness into the forefront by using imagery such as nooses, blood, and rot. I feel that it is important not to hide this part of the illness as it only serves to further feelings of isolation and shame.

The societal dimensions of post-partum depression are broad reaching and include topics such as the construct of motherhood, the value of women in society, and the stigmatization of mental health. In one piece, I examined the words we use for fertility and infertility and what those words say about a woman's worth. In another piece, I gathered clippings from motherhood magazines, and I was astonished by the way in which we celebrate the pregnant form yet revile post-pregnancy bodies. I also tried to illustrate they way in which we set women up for disappointment when it comes to motherhood.

I explored the historical dimensions of this condition by studying literature and old medical texts. I was surprised by many of the misconceptions about women's bodies by some of the great anatomists and physicians of the past. I included artistic representations of beliefs such as the "wandering uterus" and the frailty of women not only because they are so ludicrous but also because these ideas affected the advancement of women's health for hundreds of years. I was also fascinated by The Yellow Wallpaper by Charlotte Perkins which describes a woman's descent into madness in the 19th century. I used some of her haunting imagery throughout my project.

Even though each of my pieces focused on a particular dimension of post-partum depression, there were striking similarities between them. Firstly, the concept of "boundaries" was prominent in many of the pieces in the form of fences, mazes, lines, and divisions. This is reflective of the way in which this illness isolates and traps women. Secondly, "dark garden" images such as dead flowers, insects, and thorns were common. This embodies the dichotomy between life and death, happiness and sorrow, celebration and mourning. Thirdly, the concept of "fragmentation" reappeared in the form of bodies and stories being cut into pieces. This emphasized the way in which women are objectified in our society as well as the sense of loss of self and depersonalization that many women describe following birth. Fourthly, "wounds" appear in many of the pieces. These represent both the physical and emotional wounding that can be associated with post-partum depression. Finally, the idea of "illusion" manifests itself through the idyllic images of motherhood which trivialize the complex emotional identities of women. These illusions are crucial in the sense of disappointment and failure experienced by so many new mothers.

While the purpose of this project was to study post-partum depression, I feel that I have also gained a powerful approach to understanding the world around me. The creative process has enabled me to explore intuitive and abstract aspects of human suffering that are inaccessible through science alone. Most importantly, art has allowed me to find strength and knowledge within the human experience of illness.

Fault lines: Scars as text in Michael Ondaatje's *The English Patient* and *Anil's Ghost*

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Michael Ondaatje's *The English Patient* and *Anil's Ghost* are both ostensibly war novels, the first set as fighting ends in the European theatre of World War II, the latter taking place in the midst of the multilateral terrorism of the Sri Lankan civil war some time before the turn of the 21st century. Geography and physical space are of particular importance in both works; the landscape is as injured by war as are its occupants. Damaged, too, are the books and artwork that add layered depth to the narrative. Both the environs and their creative contents are thus anthropomorphised,

and are portrayed as being wounded by time, by war, and by the novels' human occupants. This personification allows for the inverse interpretation of the human characters as landscape, as literature, and as art. While this may initially seem a tenuous extrapolation, it in fact provides a logical step in a linear argument which culminates in the presentation of scars as readable objects.

In *The English Patient,* the physical landscape is presented as the body of a wounded human; its injuries are, for the most part, fresh and new, a direct result of the war. "[H]igh wounded trees" (273) surround the Villa San Girolamo, which is incarnated as a minor character; its "skin" (39) breached by a "wound" (11). Art, too, is touched by war: murals are marred where "plaster loosened by the bombing [has] fallen away" (7), decapitated statues stand outside, and, in the library, the "skin" of the drowned books bears marks left by their previous peacetime readers (7). Similarly, in *Anil's Ghost,* Ondaatje describes ancient sculptures being carved from stone with "shallowly incised lines" (105), their "edges red, suggesting the wound's incision" (12). Within this imagery, the surgery of creation constitutes butchery of stone, allowing a reading of landscape as body and art as flesh.

Similarly, Ondaatje incarnates the body as text, artwork, and geography, and the scars borne by Ondaatje's characters become words, images, and symbols. In *Anil's Ghost* an identity is established between Palipana's "old, thin body" and "his books and writing tablets," both "aging fast," both "governed only by the elements" (84). Likewise, t*he English Patient* questions whether he is a book "to be read," a house "full of corridors," or a landscape filled with "loose vegetation, pockets of stones" (253). When viewed in this context of the human form as text, art, and landscape or map, the scars borne by Ondaatje's characters become words, images, and symbols. With scars being seen as written or drawn stories, their creation must occur through an act of authorship: we are both artist and canvas, author and text. This graphic representation of our histories on our selves allows for the body to be seen as pastiche, each individual a work of physical intertextuality, similar to the English patient's "commonplace book," his much-altered Herodotus (231).

As the human form is written and overwritten, it is inevitable that meaning is borne in the maps, texts, paintings, and sculpture that our bodies become. The story of a scar begins with scarification itself, but ultimately for Ondaatje the focus is on product, rather than process, and he chooses to write about scarred people rather than about people being scarred. Because of this lack of concrete information and definitive assignation of meaning to the scarred human body, the characters are left to "make a story out of it" (*Ghost* 101), ascribing assumptions and alternate contexts as they see fit.

Scarred forms are "[s]omething to be read" (*Patient* 253), and require an audience. The science of forensic pathology, which is foregrounded throughout *Anil's Ghost,* allows Anil to precisely document such facts as age, occupation, and a person's "last actions" (65), telling her what she believes are "permanent truths" (64). But despite Anil's faith, the reading of scars is an inexact science, a study of "half-perceived interlinear texts" (191). She warns others against what she all too often forgets herself, recommending that they "rethink" their "first impressions," "[a]dmit [they] can make mistakes" (14). She ascribes meaning to injury, but often fails to recognize that she, like Sarath, must "understand the archaeological surround of a fact" (44) because, without context, wounds are easily misinterpreted. There is no "easy translation" (27) from scar to injury, despite their causal relationship, and the potential for "forgery or falsification," (83) intentional or accidental, in their understanding is highlighted by Sarath's fears that they are in danger of misrepresenting the truth in a "flippant gesture" that might lead to new vengeance and slaughter (156-7). This risk is mirrored in the dangers of medical uncertainty, as Gamini examines wounds, determining "how they were probably caused" (287), knowing that "a high index of suspicion" (118) is necessary in diagnosing occult injuries, but that too low a treatment threshold will negate the very purpose of his triage.

In *The English Patient,* there are no scientists trained in the study of injury, only survivors whose experiences must take the place of formal education. But the injuries here are less equivocal, and they are borne by the living, who can explain their origin – should they choose. The Patient, through feigned or real amnesia, allows others to interpret his story, making erroneous conclusions which reflect their own stories while retelling his. Caravaggio, too, is not entirely forthcoming with the story of his scars. He keeps his hands bandaged for much of the novel, "[r]evealing nothing" (27) even after his wounds have healed. These dressings allow him to retain some sense of secrecy, and although they establish him as a "celebrity," a "war hero" (27), the nature and circumstance of his injury remains unknowable until he tells Hana, "They nearly chopped off my fucking hands" (34), and shows her the evidence. The novel's characters – and, by proxy, Ondaatje – view people as "communal histories, communal books" (261), scars being life's commentary on each character, albeit much less readable than the "critical marginalia" "defacing books" in the Sri Lankan doctors' lounge (*Ghost* 230) and in the Italian library.

In continuing to explore the trope of body as medium, and scar as message, one cannot help but progress from the acts of writing and reading to those of editing and censorship – to hide or to heal. Physicians and nurses, highly praised in Ondaatje's demonstration of their selflessness, are "drawn" to patients by their wounds (*Ghost* 211) and "mark" them by their healing (230). The ultimate goal, supposedly, is to create a sort of trompe l'oeil of the flesh, to return a damaged body to one of relative perfection, rewriting the history contained within the skin. Yet while acts of 'editing' in both texts are most often of a practical nature, as doctors and nurses treat the victims of war, in their most poignant portrayals they take on a symbolic role when these same characters reach out and touch the dying and deceased in what becomes an act of self-healing.

These efforts to heal the bodies of both the living and the dead reflect an attempt to impose "some kind of human order" (*Ghost* 128) on the spoils of war. Gamini, in what is arguably the most powerful scene of *Anil's Ghost,* rushes to the side of his dead brother with illogical urgency, wondering how he "could heal his brother […], deal with every wound as if he were alive, as if treating the hundred small traumas would eventually bring him back into his life" (287). Gamini,

practical, cynical, and hard-working to a fault, spends over an hour trying to achieve a "reversal back into love and life" (288) – but not so much for his brother, as for himself. His compulsion to 'treat' Sarath's corpse mirrors earlier scenes in the novel, where Sarath, Anil, and Ananda touch Ruwan Kumara's then-nameless corpse with tenderness and respect (*Ghost* 170). Likewise, in *The English Patient,* Hana revokes all her duties to her living patients, devoting herself instead to the dying English Patient. She "wanted to save him" (52), but, as he knows by her "dead glance[]," she is "more patient than nurse" (95). By the novel's close, Hana has become a source of support and strength for her unlikely cohabitants. In the hopeful but ultimately futile exercise of treating the Patient, instead of deepening her self-imposed isolation, she actually succeeds in repairing her broken self.

While the "last protection" for the unscathed might be to "abandon emotion" (*Ghost* 56), to distance themselves from the injured and merely repair the broken bodies, instead, both novels support the argument that "the only way to survive is to excavate everything," (*Patient* 44) to allow grief to be played out to the fullest extent in an exercise which is not one of respect to the dying or deceased but is rather an act of personal catharsis. As victims die and the relationships of the living are severed, the "ascendancy of the idea" – the commonality of the human experience – is "often the only survivor" (*Ghost* 12). It is in these moments of self-serving tenderness between the living and the dead that the ultimate humanity surfaces in Ondaatje's novels, and that the metaphor of the scarred body as a readable object can be brought to its natural close, as a medium that is written, interpreted, edited, and ultimately assimilated by the reader.

Whether borne by the living, the dying, or the dead, physical scars in Ondaatje's novels serve as portrayals of personal histories which, in being read and interpreted, become an external representation no longer meaningfully couched in individual history, but rather open to the public assignation of meaning. The power held by the reader allows for a self-oriented and narcissistic interpretation of the physical 'text', with a reading as affected by the observer's own history and prejudices as by the events which authored the scar. Ultimately, in both *The English Patient* and *Anil's Ghost,* the meaning of scars is of much more import to the outsider than to the scarred individual. Through the metaphor of body as medium and scars as message, the Other is able to participate not only in the authorship and interpretation of scars, but also in the symbolic rewriting of irreversible events through acts of healing which, while providing little to no benefit to the wounded in *Anil's Ghost* and *The English Patient,* allow the healer to repair his or her self, regaining a sense of control and a modicum of closure.

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Wikipedia Brown solves the case: An endocrine mini-mystery with advance apologies to Donald J. Sobol

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Leroy "Wikipedia" Brown winced as the crowd let out another cheer, and he adjusted the volume on his headphones. On his laptop screen was the live broadcast of the final draw of the men's curling round robin, which was taking place in an arena across the city. Wikipedia considered curling the "thinking man's" sport and much preferred it to the event that was taking place on the ice not a few feet from where he was sitting—women's Olympic figure skating. If not for the occasional spill and the skimpy costumes, he would have skipped out entirely. That, and for the fact that his wife, Sally Kimball-Brown, one of the physicians retained by the U.S. Olympic team, had secured free tickets for them and had insisted that he come along. Oh well. At least he had something to show for this wasted afternoon as he bent down to make sure that the duffel bag containing its precious cargo was still underneath his seat. A box of Wheaties with a picture of the United States' best hope for a gold medal in this event, signed by the athlete herself, Miss Pansy Sheridan. Sally's surprise at Wikipedia's apparent sentimentality quickly turned to chagrin as she realized that he planned to sell it on e-Bay for a profit.

Wikipedia had earned his nickname from his college frat buddies who quickly learned that it was virtually impossible to win a bar bet with him, since he was a limitless repository of information. It was rumoured that he never once had to buy his own beer during the course of his degrees, and that if he opened his mouth to yawn, one could hear the chirping of a dialling modem emanating from within

his body. Sally, always the athlete, had parlayed her love for sports and her brains into a career in sports medicine. Her pretty face was at the moment contorted into a glare.

"Honestly, Leroy, can't you put that thing away for a minute? Pansy's routine is about to begin." Wikipedia sighed and shut his laptop. At least this was the last skater of the competition and a flawless performance here could net him a lot of profit. As the music began, and Pansy started skating, the crowd grew silent. As the tall, well-proportioned 19 year-old entered a spin, Wikipedia leaned toward Sally and whispered, "Well are they or aren't they?"

"Aren't they or aren't they what?"

"You know, her breasts…are they real or fake?"

"Geez, Leroy. Not you too!" The tabloids this week were speculating (again) that Sheridan had undergone breast implant surgery when she was only 13 at the request of her overzealous mother.

"Well, you're a doctor and…" Wikipedia trailed off as Sheridan gathered speed for her final jump. The skater landed it perfectly and a split second later the entire arena went wild. Wikipedia noticed the sports reporters near the ice surface frantically pulling out their cell phones and there seemed to be a commotion at the judges' table. "What just happened?" asked Wikipedia.

"I'm not sure, but I think she just landed a quadruple toe loop, " said the woman seated next to Sally. "That's the first time a woman's ever done that in international competition!" Sheridan finished her routine to an ear-shattering standing ovation. It was obvious that she'd secured the gold.

"USA! USA!" chanted the Americans in the crowd. A few moments later, the announcer confirmed that Sheridan had indeed landed the first-ever quadruple toe loop, and her marks across the board were perfect.

"Let's stay for the medal ceremony," suggested Wikipedia to Sally. "It's not everyday we get to see sports history in the making."

"Wait a sec…" Sally pulled out her cell and read the text message. "They need me down by the dressing rooms. Hope it's not Starling's diabetes again. That girl seriously should consider getting an insulin pump."

"I'm coming with you."

Wikipedia and Sally quickly made their way to the dressing room where they found the coach pacing around and running his hands through his thinning hair.

"Bad news, Sal. We've got some accusations that Pansy's doping."

"From who? The Russians?"

"Nah…it's worse. One of our own—Sonya Starling's claiming that Pansy's been taking steroids." Starling herself skated a solid program with only a few minor mistakes and would receive the silver…unless Sheridan was disqualified. It was a well-known fact that Starling was the type of competitor who would go to any lengths to win.

"Well, what proof does she have?" asked Sally.

"She hasn't had a period since way before we competed in France," piped up a blond young woman in a tracksuit who was liberally popping Timbits from a 40-pack into her mouth and washing them down with a Supreme Iced Capp. Wikipedia recognized her as Sonya Starling. "I know because I asked her then in our hotel if I could borrow a tampon, and she didn't have any on her—said she didn't get a period ever. That's proof she's taking testosterone. I read that it stops women from menstruating. And it probably gave her the strength to land that jump!"

"That's crap!" retorted Sheridan. "I've never taken anything. You're just jealous I beat you. For your information, women can stop having periods during intense physical training—which I've been doing for the past two years to get ready for these Olympics!"

The U.S. coach shook his head. "Ok, look. We have to sort this out before the medal ceremony begins. We've been trying to set an example for the world in these 2010 games here in Vancouver, and we want to show everyone that we're playing by the rules. The IOC has really tightened things up, and this is going to make us look incredibly bad. Now, if either of you has anything to hide, you'd better come clean now!"

"Uh, I might be able to explain what's going on here," volunteered Wikipedia, "but unfortunately, it's going to cost someone a medal."

What did Wikipedia notice that would cast some light on the situation?

Answer:

Sonya Starling has been faking having diabetes in order to get insulin. By claiming to have Type-1 diabetes, she was able to have daily injections of an anabolic substance. Wikipedia thought it was suspicious that a diabetic would eat so many Timbits and have an Iced Capp in one sitting when she was apparently having trouble controlling her blood sugar. Upon questioning, Sonya admitted to paying off an unscrupulous technician in the medical lab where she got her initial blood sugar testing done, so she could appear to get insulin legitimately. She was disqualified and returned to the U.S. in disgrace. A Canadian was awarded the silver medal instead. The Canadians took the gold in curling though, which is where it really counts.

Pansy Sheridan, on the other hand, is a 46 XY genetic male with androgen insensitivity. The tip-off was that she is 19, and has never had a period—unusual for a woman. She is also tall. Genetic testing and a complete history and physical exam helped to confirm the diagnosis. The IOC in an unprecedented ruling allowed Sheridan to keep the gold.

Wikipedia didn't meet his reserve on e-Bay, so he kept the signed box of cereal.

ABOUT THE AUTHOR

A voracious reader, Christina Beach worked as a research technician and bookseller before enrolling in the MD program at the University of Alberta.

Reading the ward

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I used to think all hospital people in white coats were the same: brilliant, infallible, caring, and united in purpose. Somewhere north of Clearwater, British Columbia my motorcycle went into a speed wobble and all that changed.

The unexpected benefit of the crash was a return to the joy of reading. I rented a TV, signed up for the full package, and never used it except to watch the CBC evening news. Instead I found myself reading the way I did when I was a kid. Reading in huge lumps, the same book, all day, until it was done. Someone said that by the time you finish university you're incapable of reading more than thirty pages of one thing at a time. You read 30 pages (the length of the average article) of this, then thirty pages of that.

Here I read until my wrist and arm ached, holding the book above me in my one good hand, thumb and little finger splaying it open. Then on my side, wedging it open with my casted hand, the right-hand page open to the light, then the left-hand page in a dark tent, the book at right angles over it.

Even difficult novels I would read 150 pages at a stretch, discovering a momentum impossible to feel in dip-and-switch reading. It wasn't just aesthetically satisfying, it seemed to answer a visceral need: it felt good. I'll never know whether this was part of my recovery or not.

But I also learned to read the ward. The hospital too is a text. You learn that there's an unacknowledged but very real turf war going on – and you're the turf. The nurses work to rule. The senior doctors, the house staff, work to no rule – or rules revealed only to themselves. Like gods from Olympus they descend at their pleasure. Time means nothing. They come…when they come. It's very Zen.

I'd think the staff physicians had achieved cosmic enlightenment except that you are in deep trouble if you're not ready when they want you. Especially surgeons. Like impatient diners in a steakhouse, they want that meat on a slab and they want it now.

And I learned that if your surgeon says he'll come and see you after the operation and he actually does so, you must call the police immediately. The man's an imposter. Every surgeon says he will come; none of them does. They treat you like a cheap date: they drug you, lay you down, do unspeakable things to your body – and then they don't even call in the morning.

Then there are the physicians-in-training, the residents. They are the slave class, the cannon fodder, the drudges. I would learn that there's a big difference between an R1 and an R4 (a 1st year or a 4th year resident). The first year residents know everything – that's in a book, or that they can find on their iPhones. They just can't always find it on your body because they haven't actually looked at many yet. Fourth year residents are great, you're safe with them. Unless they've been working all night. That haggard slump-shouldered woman in the white coat will be spot-on in her diagnosis, but she just might assign your meds in kilograms instead of milligrams.

The technicians who build your cast or take your blood are the rude mechanicals and they don't care about anything, least of all you, and certainly not what any mere nurse or doctor might have to say. They take an artisan's pride in what they do, but you exist solely in terms of your repair. I tried to figure out where I'd encountered that attitude before, and then I remembered – it was at Midas Mufflers and Jiffy Lube. You're an oil change or a new tail pipe.

That allows them a sense of humour. Nobody else in the hospital makes jokes. These guys make terrible jokes. As I lay immobile with wet strips of something across my back to fit me for my fibreglass back brace, the technician said, "So motorcycle accident eh? Do you know the one about the grandmother riding down the highway on a Harley Davidson knitting a sweater?"

"Glmph." You're on your stomach with your face in the mat but he doesn't care.

"Okay, so there's this grey-haired old grandmother riding down the highway on a big Harley. Going 160 kilometres an hour. And she's knitting a sweater. Hands off the handlebars. Knitting away. Going 160 kilometres an hour. And then she blows past a cop, doesn't even notice him. Just knitting her sweater at 160. So the cop cranks up his bike and takes off after her. Takes him about three miles to catch up with her. Pulls up beside her and says,

'Pull over!'

She just smiles and says, 'Pardon me?'

He shouts again, 'Pull Over!!'

What?' she says.

Now the cop's getting really mad. Here they are roaring down the road at 160 kilometres an hour and she's knitting a sweater, and so he reaches back and gets his megaphone and screams into it,

'PULL OVER!!!'

'Oh no, officer,' she says, 'Cardigan.'"

Get it? Pullover… Okay, I guess you had to be there. Actually even if you had been there it wasn't funny, but it makes you snort and then you're told again not to move.

I learned that no matter how well you learned to read, you needed an interpreter. I was lucky – the woman whose motorcycle I'd crashed was also a physician, and so after the doctor was going on about T2 and L5 and the fracture of the distal whatnot and the something malleolus and the pulmonary contusions and abrusions, and the need

for an NG tube, she was able to tell me "You broke two vertebrae, squashed your lungs, and they're going to stick a tube up your nose."

You also need a guide. When I landed in emergency I was stuck in a hallway on a stretcher, wheezing. My sats were 77%, I was told. That's a B+ in and English class. Not bad, I thought, but I was having trouble breathing. I didn't know "sats" meant "oxygen saturation" and that they should be at 97%. People in green were swirling around like in MASH just after the helicopters land. Someone brought an oxygen bottle, put it on the stretcher, and ran off. I was still wheezing. A kid in green scrubs dashed up and said, "Is this hooked up?"

"No," I gasped.

"Good," he said, grabbed the bottle and took off. It was only when one of the house staff descended from wherever they rest on high that a bed was found, the oxygen retrieved, and I began to breathe.

So you're left in the control of the nurses. They know this. It's like a factory and the ward is the shop floor; decisions may be made in executive boardrooms, but the wards are where the real work is done. And like the teamsters, the nurses work to rule. While the junior residents run around like hamsters, perpetually playing catch-up, if it's time for a nurse's lunch break, he or she stops.

More important, during the sacred ritual of the Shift Change all contact with the patient ceases. Twice a day the on-coming and off-going nurses lock themselves in a sound-proof room, and if you need a bedpan you're out of luck. If you think you'll need a bedpan call before the change or be prepared to grit your teeth and hold it. If you were mobile you could rob your roommate's and be halfway to Red Deer before anyone found out. You don't want to do anything foolish like start to bleed during Shift Change.

I learned all nurses are not created equal. Some even hold you responsible for your illness. In the first days after my accident when I was in Kamloops one asked me to roll over so that she could do something with the sheets. When I explained that I had a broken back she harrumphed like I was getting off on a technicality. Others were fabulous, not just helpful but intuitive, as if they knew what I was feeling, anticipating, not just responding, or slavishly following the chart. So you learn to read name tags, to ask when such-and-such a nurse was coming on.

When the medics flew me back to Edmonton they said, "We're taking you to 'trauma.'" The trauma ward is the hospital equivalent of the drunk tank. This is where you get the people, after the brawls, after those knife fights in north end bars, after the Friday-night auto wrecks. The first night I had half a dozen tubes and monitors connected to me and my very own nurse at the foot of my bed, who would stay there through the night. I was on 24-hour observation. For the first time in this whole business I was afraid. I knew about the nursing shortage, yet here they'd allocated one person to do nothing but sit at the bottom of my bed, and wait. I knew what their cheerful, "We just want to keep an eye on you," meant. It meant, "We think you're going to die and we want to be ready."

But I fooled them. I didn't, and anyway they had other things to do. The next night I woke at 2:00 am to a wrangle at the bed across from me.

"Bill, please. Will you at least let me clean your one good eye for you?"

"Nooofuckinway."

"Bill, let me clean that eye. You'll feel better. I know you will. And I want to give you some pain killer."

"Nooofuckinpainkillers. They're no fuckin' good. You tried to give me bad stuff."

"No Bill, we wouldn't give you anything bad."

"No. They can't fuckin' help me. You know why? You know why??"

"Why Bill?"

"Cause a painkiller can't fix the pain of a broken heart. That's why."

This went on for a long time. A sharp stick and a revolving door seemed to me the best treatment options. But the nurse stayed soft and patient and soothing, and in the end Bill took some pain medication, and had his eye cleaned, and I think maybe had his heart soothed a little as well. An encounter not scripted by a textbook or a chart.

Everybody's got a hospital story. Maybe it's part of the recovery process. Maybe that's something the trauma nurse could read in old Bill. In any case, going into the hospital is like travelling to a foreign country where the food is dodgy, the rhythms strange, and the tribal rivalries unreadable. It's also as fascinating as one of those sprawling novels about slightly dysfunctional eccentric families. To make sense of it all, and really heal, what we need is Tolstoy along with our morphine.

Nervousness

Alim Nagji
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Nervousness. My body didn't give it away, my voice was clear and firm, my fake laugh impervious to doubt. My eyes held the glance of the interviewer with fierce attention and slight playfulness. The only thing that gave away the fear inside me was a barely perceptible tremor in my knees. So much rested on this day – yet in my mind, at that moment, somehow that didn't matter. I was merely playing a role – I was being who they wanted me to be – charming, affable, witty and sensitive; a perfect balance of cautious and confident. A parody of myself that would lead to acceptance into one of the most competitive fields in Canada: Medicine.

A year later I have become my role. I am the epitome of a good person. Mothers hold me up as symbols for their sons declaring, "if only every community could be so lucky as to have an individual like me." But somehow talking to people leaves a bitter taste in my mouth. I should love the sound of my own voice, but it rings hollow and metallic. When I catch my reflection in the mirror, I look away. Mirrors are unnatural, why should we see what we truly are? It has only been a year, so my superiors challenge me: if they survived so long, why then have I become lost so quickly?

I'm in class, at the back because that's where I have always sat. My laptop is open to another powerpoint and the professor flips through another slideshow on the management of some disease. In an hour he will have discussed four conditions, in a week an entire region and in a month a whole system. After one month of sitting in a chair I will be expected to treat someone. I will be invited into their homes and lives, called upon in their weakest moments as the expert. I will stand in front of them, hiding behind a white coat and fancy Latin terms, when truly I will be naked. They will thank me and reward me. All that will betray me is a slight tremor in my knees.

I am no longer a real person. I eat and sleep and regurgitate facts with startling efficiency. I weep when I should and laugh, sometimes inappropriately. It's really the only humanity I have left. I have few outlets to truth: cruelty or laughter. So I laugh at the unfairness of life, the abandonment of the elderly, the neglect of entire populations. I laugh at a God who takes our loved ones from us and laugh even harder at those who think they can stop Him. I laugh, when really you should be laughing, after all it is the best medicine.

No passport required for David Cook

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In Nepal, I found he was traveling

With only a photocopy of his passport.

The rest of us needed documents.

He needed only himself.

In a world of requirements

He made his own rules.

With a twinkle in his eye

The excesses were all good.

He showed up when he didn't have to,

Remembered names when he didn't have to,

Put us at ease when he didn't have to,

Was kind when he didn't have to be.

In the macrocosm,

The microcosm,

And all the in-between cosoms,

He made a difference.

And still is making a difference.

He would be long remembered,

If nothing were named after him,

But many things will be.

Just as he could walk through customs

With none of the usual documents

So he can walk among us still now in spirit

Reminding us the average lecture is appalling.

And we must do better.

And so we shall.

As we build the better medical school

He spoke of so passionately.

Bringing quality health care to all.

And having fun doing it!

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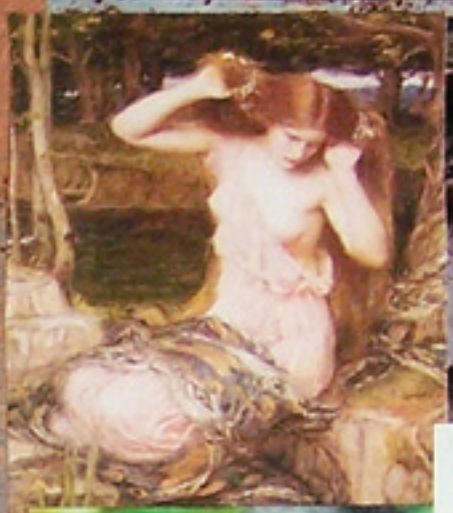
"When a mother lacks support from the father or other family members, she may unconsciously conclude that she cannot successfully raise her infant, and she may reduce her efforts."



Does postpartum depression serve some evolutionary purpose?

—*Clint Johnson, Ridgecrest, Calif.*

Anthropologist **Edward H. Hagen** of Washington State University replies:

POSTPARTUM DEPRESSION (PPD), which afflicts 10 to 15 percent of new mothers, may have evolved as a strategic response to a lack of social support because it helped in passing on genes successfully. Many doctors believe PPD is triggered by the changes in a mother's hormones after giving birth, yet studies have failed to find much evidence for a link between extreme hormone fluctuations and PPD. The fact that fathers, who do not experience such changes, also suffer from PPD is strong evidence that it is not "just hormones."

The finding that PPD often plagues people who have marital problems or little outside support led biologists Randy Thornhill and F. Bryant Furlow of the University of New Mexico and me independently to propose that PPD has an evolved function. Many animals improve their chances of passing on their genes if they desert their young when food or parenting help is scarce. Hu-