MJM

AN INTERNATIONAL FORUM FOR THE ADVANCEMENT OF MEDICAL SCIENCE BY STUDENTS

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EDITORIAL

From the Editor's Desk: Ethics and Current Medical Controversies

Physicians have many responsibilities to their patients first and foremost but also to other patients using the same resources; to their colleagues; to the healthcare system, towards society at large; to their students; and not to be forgotten, to themselves, to maintain one's integrity by respecting one's moral values. While those duties are often prioritized in ethical and professional codes such as the Code of Ethics of the Canadian Medical Association (CMA) (1), many situations arise in which the physician has to make a decision on uncertain ethical grounds. Should an unconscious patient be enrolled in a trial of a new, potentially life-saving therapy without prior consent? Should patients be exposed to the risks of having procedures performed by students, under the justification of learning opportunities to better serve the future? Should physicians refuse to perform a procedure (e.g. abortion) while knowing that the patient will likely undergo the procedure illegally under unsafe conditions?

In the Crossroads section of this issue of the McGill Journal of Medicine, we present two articles that foray into controversial topics, where duties and responsibilities of the physician seem to conflict. In "Blood substitutes: the Polyheme Trials", the author explores the controversy over the clinical trials of Polyheme, an artificial blood substitute that has the potential to revolutionize emergency pre-hospital care, and to be a solution to the world-wide problem of blood donations shortage. It is necessary to allow waiving of patient consent for participation in a trial of emergency treatment, but is it ethical? Should physicians follow a utilitarian approach and make decisions for incapacitated patients in the name of research and potential benefits to the general population? The second Crossroads article, "Paying Kidney Donors: Time to Follow Iran?", describes the converse situation: if a patient wishes to undergo an operation to sell his or her kidney, does the physician have a role in opposing such a decision? If we bear the knowledge that those patients will be facing great risks by selling their kidneys and undergoing the transplant operation in the black market, what is the physician's duty in protecting these patients? The Iranian model of kidney transplants offers financial compensation and life-long healthcare coverage to kidney donors, and is being credited for a significant shortening of transplant waiting lists. The objectification and commercialization of the human body that it entails is however not considered ethically acceptable by most medical associations in Western Europe and North America (2, 3). In Canada, for instance, the only living non-related donations that are currently legally permitted are anonymous, voluntary, and given to the public healthcare associations. In July 2006, the British Columbia Transplant Society in association with the British Columbia branch of the Kidney Society, was the first in North America to start a pilot project of financial compensation of all living kidney donors for the expenses associated with their donations (4). Small steps are being taken in Canada towards forming legislation allowing a government-centered commercial donation system designed to protect both donor and receiver, but it remains to be seen if those projects will garner enough public support and override the current ethical concerns.

Similarly to the issues we present in the Crossroads section, the debate over the privatization of healthcare in Canada is often centered on the duty of physicians to patients: is it more important to serve everyone equally or to improve global delivery of healthcare by reducing the load on the present system, even if it entails positive discrimination? In our Focus section we seek to provide a balanced perspective of the ethical, social, economical, and political implications of a possible reform of the Canadian healthcare system. We have thus invited two experts in the field, Dr. Edwin Coffey, former President of the Quebec Medical Association and Senior Fellow at the Montreal Economic Institute, and Dr. Harvey Barkun, Officer of the Order of Canada, member of the Rochon Commission and President of the Society of Medical Administrators (USA), to respectively discuss the arguments for and against privatization. In addition, we have interviewed two Quebec physicians, Dr. Paul Saba, family physician practicing at the Lachine Hospital and the Médi-Centre de Montréal-Ouest and Co-President of the Coalition of Physicians for Social Justice, and Dr. Lawrence Stein, Chief of the Division of Diagnostic Radiology at the Royal Victoria Hospital (McGill University, Montreal, Qc), to describe their respective experiences with public or private realms of medicine. Lastly, two physicians practicing abroad, Dr. Andrew Vallance-Owen, Medical Director of the British United Provident Association, and Dr. Hisayuki Hamada, Chief of Medical Education at the National Nagasaki Medical Center (Japan), described their respective countries' health care systems.

The current issue of the MJM intentionally raises more questions than provides answers. We hope to encourage students not only to conduct scientific research, but also to participate in ethical debates. Since one will often be confronted with difficult predicaments in clinical practice with no clear right or wrong answers, it is helpful for medical students to discuss abstract

ethical and moral issues from the beginning of their training in order to develop critical thinking skills. As physicians of tomorrow, decisions will someday be ours to make. It therefore becomes our duty, towards ourselves and society at large, to reflect and to shape the ethical cores that define our profession.

Regards,
AS, AYZ, YG

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Ada Stefanescu, M.D., C.M. (2010), and **Alice Yang Zhang**, M.D., C.M. (2010), are the twelfth Editors-in-Chief of the MJM. Ada's research interests include genetics, heart disease and atherosclerosis, areas in which she has participated in projects at Yale University and the Deutsches Herzzentrum Munich (Germany). She is currently working on a project on artificial hemoglobin substitutes in the Artificial Cells and Organs Research Center, McGill University. Alice's past research interests include exploring embryological mechanisms of placenta formation in the murine model. Her current research examines the significance of D-dimer levels in the diagnosis of pulmonary embolism and deep vein thrombosis. Alice is also a national laureate of the Millennium Excellence Award.

Yin Ge, M.D.C.M. (2010), is the Executive Senior Editor of the MJM. His research interests mainly involve the field of cardiovascular medicine. His current research focuses on the use of bone-marrow derived stem cell to regenerate the damaged ischemic heart. For his work, he has received awards from both McGill's Faculty of Medicine and the American Association for Thoracic Surgery (AATS).

LETTERS TO THE MJM

Impressions on an elective abroad

Dear editors,

"In the past, desperate conditions on another continent might cynically be written out of one's memory. The process of globalization has already made such an option impossible… There are no health sanctuaries… The separation between domestic and international health problems is no longer useful."

-Gro Harlem Brundtland
Director General of WHO 1998-2003 (1)

This is the second summer of my medical school years that I spent abroad to learn medicine (first one in Africa, second one in South America). These two very rich experiences pushed me to write and encourage medical students to go abroad and live a different experience in medicine, particularly in developing countries. Although most medical schools in Canada have a highly structured medical course that fits in four short years, I definitely believe that, with enthusiasm, dedication, and perseverance, it is possible for Canadian medical students to arrange and participate in highly rewarding programs abroad. So why should one be promoting that? To expose Canadian medical students to some global health issues, to strengthen their sense of awareness toward health inequalities present in our world, and to reinforce cooperation among international medical students through interaction (2, 3).

What are the benefits of going abroad to learn medicine? Well, first, you will discover a new country, a new population, a new culture, a new weather, a new cuisine, and a new language. You will gain experience in many clinical specialties and broaden your horizons through contact with other medical students and health care staff from this country and probably from all over the world. You will also interact with new professional organizations. You will be in touch with a complete new population, new pathologies, a new spectrum of diseases, and new treatment modalities. You learn to respect new ways of approaching medicine, even if you may disagree. You participate in a system that makes you think differently; where your ideas about everything from patient's approach to treatment modalities are being challenged every day. Through this experience, students see, listen, learn, experience, remember and finally grow tremendously, understanding some global health issues.

There is one important point that needs to be thought about when planning an elective: one needs to make sure that the institution he is going to is well supervised. One of the pros of doing an elective in developing country is students may have more patients and procedure exposure than back home. But, I stress that students should know their limitations.

The problem that sometimes arises during electives in developing countries, with poor supervision, is when the international student is assuming the role of a resident or a doctor when patient load is unbearable for the local medical center (4). It is wrong, in both ethical and legal aspects, and should not happen even if students are encouraged to do so by the local staff. We may all feel this kind of pressure in these types of electives; that is why the definition of one's role should be clear for your supervisor and yourself. Of course, I am sure that many competent students have the skills to take care of a history, physical examination, investigations, impressions, and plan for a patient with a medical problem that is familiar. However, the medical problem is part of a complex structure where unfamiliar culture and other unfamiliar factors are present. A simple unfamiliarity can result in drastic differences in the management of a patient. And here come the principles of beneficence and non-maleficience. Students need to make sure to not hurt the patient; and students cannot offer this if they are not aware of co-existing problems.

On another hand, I also did electives in Canada. The programs are more structured. The role of the student is defined early in the elective, as well as the expectations of the supervisors. There is no pressure about what one can do or not. The spectrum of diseases is similar to the one we see in our local health care system. Basically, the student is more comfortable with a system he already knows.

To conclude, I definitely think it is a good idea to discover other health care systems in developing countries, as long as the student's role and expectations are defined early in the elective. Students should know their strengths and limitations in order to offer the best care to patients. By discovering new populations, new cultures, different diseases the students will have a more global look at health care issues in developing countries.

Sincerely,

Youssef Tahiri
Medical Student, McGill University
Montreal, Canada

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Youssef Tahiri (M.D.C.M 2008) is presently a fourth year medical student at McGill University. Prior to medical school, he did an international French baccalaureat at Stanislas College in Montreal. He is interested in Plastic and Reconstructive surgery. He is presently conducting research in digital microsurgery and wound healing.

ORIGINAL ARTICLE

Injury Severity Score (ISS) vs. ICD-derived Injury Severity Score (ICISS) in a patient population treated in a designated Hong Kong trauma centre

Sydney S.N. Wong,* Gilberto K.K. Leung

ABSTRACT: Trauma and Injury Severity Score (TRISS) has been the benchmark of mortality risk in trauma centers for over 30 years. TRISS utilizes the Injury Severity Score (ISS) as an index of anatomical injury. This study investigated the efficacy of a new type of index of anatomical injury called the ICD-derived Injury Severity Score (ICISS) compared to the ISS using a logistic regression analysis and a global chi-square test of the areas under the Receiver Operator Characteristic (ROC) curves. We found that the empirically derived ICISS performed as well as the consensus derived ISS with no statistical differences between their respective area under the ROC curves.

KEYWORDS: ISS, ICISS, SRR, trauma scoring, TRISS, Receiver Operator Characteristic curve

INTRODUCTION

Background

For a trauma center intending to perform an effective review of their service, as well as for the scientific study of trauma, it is important to have an accurate benchmark of mortality risk. This benchmark serves as a predictor of mortality or "expected" outcome for any patient presenting with certain injuries. The expected result can then be compared to the "actual" outcomes in order to provide quality assurance of care provision. For many years, this benchmark has been the Trauma and Injury Severity Score (TRISS)(1-10). TRISS utilizes the patient's age, type of injury, Revised Trauma Score (RTS), and the Injury Severity Score to estimate the probability of survival. It takes into account the patient's physiological injury, physiological response and anatomic injury. The Injury Severity Score (ISS), first developed by Baker et al., supplies the anatomic index for TRISS, and has been a standard tool for three decades (1).

Lately, there have been new ideas about anatomic trauma scoring that have brought the ISS under a more critical light. One main disadvantage of the ISS is its innate attachment to the Abbreviated Injury Scale (AIS) for severity estimates, as the AIS is a consensus rather than an empirically derived scale (11). Also, the ISS uses data from the top three different anatomic regions with the most severe injuries, neglecting to account for other important injuries within a single region. In many scenarios, one region may have several severe injuries, only one of which will be accounted for, along with two less significant injuries in two other anatomic regions. In addition, because the different regions aren't weighted, a severe foot injury can have the same impact on the score as a moderate head injury. Lastly, the ISS combines injury with therapy in its calculation. A poorly managed minor head injury allowed to progress to coma may result in the same score as a quickly and effectively managed severe head injury. However, despite these important drawbacks, the ISS has remained a robust standard of anatomic trauma scoring during these past thirty years. Past challengers to ISS such as the Anatomic Index (AI) introduced by Champion et al. (2), and the Revised Estimate Survival Probability (RESP) index introduced by Levy et al. have failed to replace the ISS. They were not shown to improve enough upon the ISS as a predictor of survival (6,12).

Recently, a new system has come to the fore. In the middle of the 1990s, Osler introduced the ICD derived Injury Severity Score (ICISS), a survival score based on

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the ICD-9 classification of trauma injuries (13). It was also created in an attempt to address the main limitations of ISS. However, it also has the added feature of convenience, a clear advantage, as most trauma centers already collect and classify patients based on their ICD-9 injuries. Compared to ISS, it is easy to compute. To calculate the ISS score, there must be a trained individual who can correctly apply the AIS/ISS ratio. The ICISS however, is a simple likelihood value. It is based on the assumption that a patient's probability of survival can be predicted based on the survival rates of prior patients with similar injuries as classified by the ICD-9. The ICISS value is the product of survival risk ratios (SRRs) from each injury sustained. These SRRs are established based on trauma data from large patient databases, the original of which was the North Carolina State Discharge Database (13) with data from over 300 000 patients. Using these risk ratios, later studies did in fact show that the ICISS was superior to the ISS alone as a predictor of survival (13-18).

In 2006, a Canadian database was created from the National Trauma Registry (NTR) of Canada, consisting of over one million cases – the largest yet in the world (19). This benchmark database attempted to address an issue of severity overestimation by the ICISS by creating inclusive and exclusive SRRs for each ICD-9 classed trauma injury. Inclusive SRRs are derived from the proportion of patients who survived the injury in question irrespective of other associated injuries present. To determine exclusive SRRs, the patient population with multiple injuries was excluded, resulting in ratios which are thought to be more representative of the "true" risk of the injury. Unsurprisingly, the exclusive SRRs produce ICISS values which are much more optimistic in terms of survival, compared to the inclusive SRR determined ICISS values.

PRESENT STUDY

The objective of the current study is to investigate the predictive value of ICISS compared to ISS. It makes use of the Canadian benchmark to compare inclusive and exclusive ICISS values to ISS values of 1167 trauma patients who presented to Queens Mary Hospital in Hong Kong over a period of 8 years.

At this time, the TRISS coefficients are over fifteen years old. They are derived from studies in the U.S. and may not always be a good predictor of survival in other parts of the world. Therefore, a secondary objective of this study is to examine the effectiveness of the ICISS using Canadian determined SRRs applied to an external database, in a different population.

MATERIALS AND METHODS

Setting

Queen Mary Hospital (QMH) in Hong Kong is one of the five designated trauma centers in Hong Kong as well as the main teaching hospital for the University of Hong Kong Li Ka Shing Faculty of Medicine. It has a well kept registry of trauma patients from 1998 onwards, complete with diagnoses, ISS, ICD-9 codes, and TRISS values calculated by a trained trauma nurse coordinator, along with survival outcomes. QMH has a 24 hour service trauma team with an audit panel, trauma director, and staffed by ATLS trained trauma surgeons. These services render QMH equivalent to a U.S. level 1 trauma centre, with case volume being the only parameter precluding its qualification as such.

SRRs

Survival risk ratios were obtained from tables as published by Bergeron et al. in the Journal of Trauma (19).

ICISS Scores

Inclusive and exclusive ICISS scores were calculated for trauma patients treated at QMH between the years of 1998 and 2005, numbering 1298 cases. Because the SRRs derived from the NTR of Canada do not include penetrating injuries, only blunt trauma cases were included in this study. Instances with incomplete diagnoses or injuries with unclassified SRRs were also excluded, leaving 1167 cases for comparison. An example of Inclusive ICISS score calculation is provided below.

Example trauma case with four diagnoses (inclusive SRRs taken from table 1):

Diagnosis 1: Epidural hematoma (ICD code 852), SRR = 0.8211

Diagnosis 2: Cerebral contusion (ICD code 851), SRR = 0.8816

Diagnosis 3: Fracture of skull base (ICD code 801), SRR = 0.9233

Diagnosis 4: Traumatic pneumothorax (ICD code 860), SRR = 0.9248

ICISS = 0.8211 x 0.8816 x 0.9233 x 0.9248 = 0.6181

Logistic Regression Analysis

Multivariate logistic regression analysis was performed with SPSS v.13.0 (SPSS Inc., USA). Exclusive and inclusive ICISS values were compared separately. In a multivariate logistic regression analysis with age, RTS, mechanism of injury and ISS, both inclusive and exclusive ICISS values were determined to be independent predictors of mortality, as were mechanism of injury, RTS and ISS.

Receiver Operator Characteristic Curves

The predictive value of ISS and ICISS was determined by calculation of the respective receiver operator characteristic (ROC) curves, a graphic representation of the sensitivity divided by 1-specificity of a diagnostic test. A perfect test has a sensitivity of 1 and a 1-specificity of 0, denoting detection of all true positives and no false positives. Graphically, this is represented by a point at the top left corner of the graph and an area under the curve (AUC) equal to 1. Pure chance is represented by the diagonal, and an AUC of 0.5. The higher the AUC of a ROC curve produced by a test, the more effective the test is at discriminating between true positives and false positives. After the ROC curves were found, the AUC between the ISS and ICISS values were compared in a global chi-square test for statistical significance.

Statistical Methods

Basic statistics including mean, range and standard deviation were calculated with Microsoft Excel.

The ROC curves along with AUC for ISS, inclusive ICISS and exclusive ICISS were calculated with SPSS v.13.0.

Statistical analyses for AUC comparison was done with Stata v.9.2 (StataCorp, USA), as SPSS does not feature the function. Stata performs a global chi-square test comparing the AUCs, with a significance level of 0.05.

RESULTS

Basic Statistical Measures

There were a total of 1168 cases suitable for ICISS calculation. The mean age was 45.9 years, ranging from 3 months to 99 years old. 28% of cases were females. The case volume ranged from 115 to 352 cases per year. Overall mortality was 13.78%. (Table 1)

Logistic Regression Analysis

In a multivariate logistic regression analysis with ISS, age, RTS and mechanism of injury, inclusive and exclusive ICISS values were found to be independent predictors of mortality. Odds ratios were 38.086 (95% CI [5.835,248.584]) and 46.954 (95% CI [5.736, 384.356]), $p<0.001$. ISS was also an independent predictor with an odds ratio of 1.057 (95% CI [1.036,1.078]) and $p<0.001$. Hosmer and Lemeshow goodness of fit tests were insignificant at $p=0.255$ for analysis with inclusive ICISS and $p=0.141$ with exclusive ICISS, indicating a reasonably good fit of the logistic regression model with the data (Table 2).

ROC Curves and AUC

The AUC values for ISS, inclusive ICISS and exclusive ICISS were 0.868, 0.851 and 0.838 respectively, with standard errors of 0.015, 0.014 and 0.015 (Table 3).

Comparison of AUC

The global chi-square test with 2 degrees of freedom between the three ROC areas was insignificant. ($p = 0.0734$). In this study, there was no difference between the ICISS and the ISS systems – they are equally predictive of survival. (Table 3)

	Survivors			Mortalities			Overall		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
ISS	13.75	11.82	65	34.32	15.05	75	16.56	14.18	75
Inclusive ICISS	0.87	0.13	0.64	0.67	0.15	0.73	0.84	0.15	0.75
Exclusive ICISS	0.91	0.11	0.49	0.75	0.13	0.76	0.89	0.12	0.76

Table 1: Means, standard deviations and ranges of ISS, inclusive and exclusive ICISS

	df	Sig. Value	Exp(B)*	Lower 95% CI for Exp(B)*	Upper 95% CI for Exp(B)*
Inclusive ICISS	1	0.000	38.086	5.835	248.584
ISS	1	0.000	1.057	1.036	1.078
Age	1	0.082	1.002	1.000	1.005
RTS	1	0.494	0.165	0.001	28.834
Mechanism of Injury	7	0.033			
Exclusive ICISS	1	0.000	46.954	5.736	384.356
ISS	1	0.000	1.062	1.042	1.082
Age	1	0.089	1.002	1.000	1.005
RTS	1	0.000	2.095	1.831	2.397
Mechanism of Injury	7	0.063			

Table 2: Multivariate logistic regression analysis with inclusive and exclusive ICISS
*Exp(B) is an exponentiation of B coefficient, which gives the odds ratio.

	ROC			Asymptomatic Normal	
	Observed	Area	Std. Error	95% CI	
ISS	1166	0.8677	0.0148	0.83873	0.89676
Inclusive ICISS	1166	0.8510	0.0138	0.82400	0.87795
Exclusive ICISS	1166	0.8379	0.0148	0.80893	0.86697

Table 3: Global chi-square analysis of AUC between ISS, inclusive and exclusive ICISS
Area(ISS) = Area(Inclusive ICISS) = Area(Exclusive ICISS)
Chi2 Value = 5.22 Prob>Chi2 (p-value) = 0.0734

DISCUSSION

From the results, ICISS appears to perform as well as ISS given the same dataset. It was not however, able to outperform its predecessor in this study. Despite the somewhat optimistic results, there is an issue which limits this interpretation. At a sample size of only 1167, this is a relatively low powered study. This of course brings the question of whether the non-significance can be due to type II error. In spite of this fact, the current findings may yet have something to offer. It certainly raises interesting questions and provides for speculation of potential solutions.

Other minor limitations may have affected the results. Firstly, the SRRs developed by Bergeron et al (19). do not take into account penetrating injuries. The second issue involves the organization of injury types used by Bergeron et al. The SRRs derived from the NTR are divided into subtypes such that similar injuries within a range of ICD-9 classifications share the same SRR value. This may take away from the specificity of the SRRs and effectively under or over-estimate certain important injuries in those groups (i.e., head injuries).

While there is a recognized risk of interpreting these results too liberally, we can nonetheless safely reflect on the performance of ICISS as long as we qualify these conjectures. Our study suggests that ICISS is a good predictor of survival. For this dataset, its performance was on par with ISS. This conclusion is in keeping with the current literature available. There are several studies showing showing that ICISS consistently performs better than ISS in predicting mortality (13,18,11,20,21). There have also been studies demonstrating that ICISS predicts duration of stay and use of hospital resources more accurately than ISS. (18,22,23). So far, ICISS does not appear to have any glaring deficits.

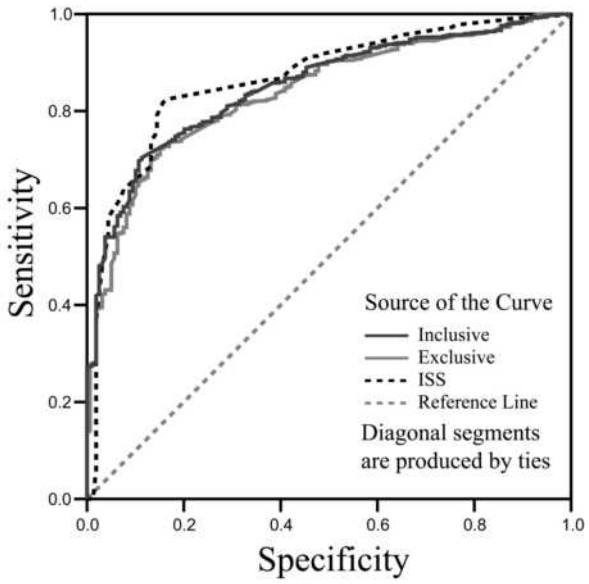

Figure 1: ROC curves of ISS, inclusive ICISS and exclusive ICISS

An interesting focus that this study brings up is the external validity of trauma indices. The literature on this is sparse, but based on results of this study, the SRRs derived by Bergeron et al. appear to function quite adequately in Hong Kong despite being designed for a Canadian population. In future investigations, it would be interesting to compare ISS and ICISS in terms of external validity in different settings. The general opinion to date favours derivation of local SRR databases, theoretically boosting the performance of ICISS with local (similar) populations. But the use of a universal scale has certain advantages as well. For example, it allows for the evaluation and comparison of services around the world, and the determination of a standard of care for all injury types regardless of locality. It enables a service to improve aspects of their care by learning from teams with more experience in the area. Disaster protocols are a good example of a service that could conceivably benefit from a universal scale. ISS has proven useful in this respect for many years, it is one of the few advantages it still holds over the ICISS.

The debate on adopting the new ICISS system doesn't seem likely to end soon and rightly so. There should be a sizeable amount of evidence available before giving up an anatomical index that has proven its worth time and again, yet ICISS appears to be adequately providing it. The evidence of ICISS' advantages is increasing and there is more on the way. In addition to outperforming ISS, ICISS is easier to use. Calculation of ISS can be rather difficult, requiring an individual who is extensively trained in the AIS lexicon. In comparison ICISS is a simple product, the computation of which

offers less opportunity for error. Yet ICISS seemed to perform as well as its predecessor. And because many large hospitals already keep extensive records of ICD-9 diagnoses in trauma cases, there is by now a very large collection of data ready and waiting for conversion into ICISS scores, for analysis, and for SRR dataset development. Several hospitals are already beginning to keep track of both ICISS and ISS for their records, owing mainly to ICISS' simplicity.

CONCLUSION

The push towards an empirical anatomical index in this age of evidence-based medicine has seen more than its share of newcomers. So far, the ISS has proven very robust in the face of these challenges. Yet there is no denying that ICISS is gaining ground quickly. With performance that is at least on par with, and usually above, the standard, its more sophisticated empirically-derived pedigree, and its ease of operation, it appears that the long awaited successor to the ISS may have finally arrived.

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Wendy Ho, Trauma RN, Queen Mary Hospital

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ORIGINAL ARTICLE

Protein expression of MEF2C during the critical period for visual development in vervet monkeys

Daniel M Bernad*, Pascal E Lachance, Avijit Chaudhuri

ABSTRACT: During the early development of the visual cortex, there is a critical period when neuronal connections are highly sensitive to changes in visual input. Deprivation of visual stimuli during the critical period elicits robust anatomical and physiological rearrangements in the monkey visual cortex and serves as an excellent model for activity-dependent neuroplasticity. DNA microarray experiments were previously performed in our lab to analyze gene expression patterns in area V1 of vervet monkeys subjected to monocular deprivation (MD). An interesting candidate identified in its screen was myocyte enhancer-binding factor 2C (MEF2C), a transcription factor linked to neuronal survival. Consistent with the microarray data, we show that there is a qualitative increase in MEF2C protein expression in area V1 of infant as compared to adult vervet monkeys. Our results suggest that the regulation of neuronal survival is one of the molecular mechanisms underlying the critical period for visual cortical neuroplasticity.

KEYWORDS: MEF2C, Neural plasticity, ocular dominance columns, visual cortical development, critical period, CaMK cell-signaling cascade

INTRODUCTION

A set of classic experiments performed by Hubel and Wiesel (1) demonstrated that intercellular communication between neurons is morphologically and physiologically plastic in response to deprivation of visual stimuli. The authors found that the visual cortex is arranged in ocular dominance columns (ODCs), where alternating columns of neurons preferentially respond to visual stimuli presented to either eye (1,2). Also, electrophysiological recording demonstrate that deprivation of visual stimuli to one eye leads to a reduction in neuronal activity in the ODCs that respond to that eye. Furthermore, in infants subjected to monocular deprivation (MD), anatomical rearrangement of ODCs occur such that cortical areas driven by the open eye increase in size at the expense of those initially responding to the deprived eye. However, this process was not observed in adults subjected to MD, indicating that there is a "critical period" during the early development when the brain is capable of adjusting connections in response to changes in the visual environments (3).

The monkey visual system is anatomically and functionally similar to that of human (4). In primates, the plastic nature of the visual cortex in response to external stimuli during the critical period serves as a robust model for cortical neuroplasticity (5,6). Thus, deprivation of visual stimuli can therefore be used as an in vivo model for the study of the molecular mechanisms underling these neuroplastic responses. Previous work employing Microarray analysis identified a novel candidate, myocyte enhancer-binding factor 2C (MEF2C), as a potential regulator of development (7). MEF2C is expressed in a variety of tissues, among which its function in the development of cardiac muscle cells has been well described (8,9). Lachance and Chaudhuri (7) showed MEF2C mRNA expression was increased roughly 2-fold in infants compared to adults. In addition, a trend suggested that the levels of MEF2C mRNA may be further increased by MD (10). This raises the possibility that changes in MEF2C activity are important molecular mechanisms underlying the rearrangements that can occur during the critical period.

Generally, cell-signaling pathways involve

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intracellular protein-protein interactions. In particular, the calcium/calmodulin dependent kinase pathway has been linked to neuroplasticity (11). Upon binding calcium, calmodulin (CaM) activates several proteins including calmodulin-dependent protein kinases (CaMKs). The initiation of these signaling pathways eventually leads to the downstream activation of MEF2C which promotes neuronal cell survival and cortical differentiation (12). The present study will examine MEF2C expression employing visual cortical neuroplasticity as a model system.

In this study, Western blot analyses were performed to validate the MEF2C microarray results at the protein level. Although rates of protein expression often follow changes in mRNA transcription, in numerous cases, gene expression is also regulated at the level of translation (4). It is therefore important to verify that the protein expression profile is similar to that of the mRNA. We hypothesized that MEF2C protein expression is higher in area V1 of infants in comparison to adults, consistent with the microarray expression data. In addition, we investigated whether MEF2C expression is modulated by monocular enucleation (ME), as suggested by a trend observed in the GeneChip® analysis.

MATERIALS & METHODS

Animals and tissue preparation

For this experiment, frozen samples from twelve individual vervet monkeys (Cercopoithecus aethiops) were obtained from a bank of brain tissue. The brain tissues used were from the same animals examined in the microarray analysis performed by Lachance & Chaudhuri (10). As previously described (13), brain tissue was acquired from infant and adult vervet monkeys from our feral population in St. Kitts, West Indies. Briefly, adult and infant (27-35 days of age) monkeys were subjected to ME followed by survival of 1 or 5 days. Control animals were raised with binocular vision. The monkeys were initially sedated with ketamine (10mg/kg, i.m.) and the euthanized via an overdose of sodium pentobarbital (2mg/kg, i.v.). Animals were then perfused transcardially with DEPC-treated phosphate buffered saline (PBS, 2.03 g NaH2PO4, 11.49g Na2HPO4, 85g NaCl). Subsequently, the primary visual cortex (area V1) was removed from the excised brain by blocking along the lunate sulcus and was frozen in liquid nitrogen/isopenate. The tissue specimen was equilibrated in dry ice, transported to Montreal, and stored in a -80°C freezer (14). All experiments were conducted in accordance of standard guidelines of the Canadian Council for Animal Care and were peer-reviewed by an institutional Animal Care Committee.

Western blot analysis

Protein extracts were prepared on ice, from frozen fragments (approx. 2000μg) of visual cortex tissue (area V1), by homogenization in RIPA Buffer (50mM Tris-HCl pH 8.0, 300mN NaCl, 0.5% Nonidet P-40, 0.5% deoxycholate, 0.1% SFS) supplemented with Complete Protease Inhibitor Cocktail, was quantified, and subsequently stored as described by Lalonde et al. (15). Gel electrophoresis was performed as described by Lalonde et al. (15). Proteins were then transferred to a Hybond-C Extra nitrocellulose membrane (Amersham, Peapack, NJ) using the Novex XCell II Blot Module at 20 mA for 2 hours. Confirmation of transfer was assessed by Ponceau S staining. The membrane was blocked in 2% Blotto (2% (w/v) carnation non-fat powdered milk, 0.1 M Tris-HCl pH 7.5, 0.15 M NaCl, 0.1% Tween-20) for 1 hour. The blot was then incubated overnight at 4°C with primary antisera in a sealed plastic bag, washed four times with 2% Blotto for 15 min. Blots were then incubated with Horse Radish Peroxidase (HRP)-conjugated secondary antibody at (1:5000) and washed four times with 2% Blotto for 5 min. Chemiluminescence and visualization was performed as described by Lalonde et al. (15).

Antisera

Antisera were obtained from commercial sources. The polyclonal MEF2C antisera was raised in rabbits against a KLH-coupled synthetic peptide based on the sequence surrounding serine-419 of human MEF2C and purified by protein A and peptide affinity chromatography (New England Biolabs, Ipswich, Ma). The monoclonal serum against GAPDH (glyceraldehydes-3-phosphatedehydrogenase) was raised in mouse cells against GAPDH purified from rabbit muscles (Chemicon International, Temecula, Ca). HRP-conjugated secondary antisera against mouse IgG were obtained from Amersham (Peapack, NJ). GAPDH titration was performed on the same Western blot probed with MEF2C.

RESULTS

To demonstrate that MEF2C protein expression is more elevated in area V1 of infants, we examined its expression in protein extracts harvested from brain tissue of two individual monkeys of each age group (Fig. 1). Our results show that MEF2C expression is qualitatively higher in infants than adults. Furthermore, we observed a single 45 kDa band which was reproducible in the two individual monkeys tested. Incubation with the αGAPDH control confirms that similar amounts of protein extract was loaded in each lane (Fig. 1). Microarray data also raised the possibility that MEF2C expression in the visual cortex is activity-

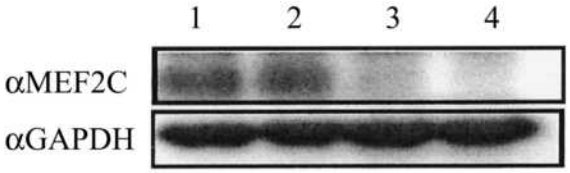

Figure 1: MEF2C protein expression is higher in area V1 of infant compared to adult monkeys. Protein extract from the visual cortex of infants (lanes 1 and 2) and adults (lanes 3 and 4) was assayed with αMEF2C (1:1000 dilution). Incubation of the same blot with αGAPDH (1:50 dilution) controls that similar amounts of protein were leaded in each lane.

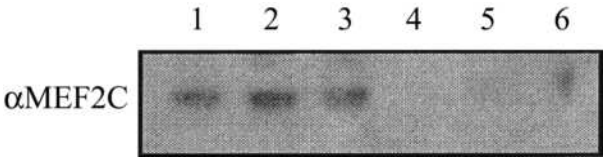

Figure 2: MEF2C protein expression is not modulated in correlation with monocular deprivation. A Western assayed with αMEF2C (1:1000 dilution) was used to compare the levels of MEF2C in area V1 of normal animals (lane 1, infant A; lane 4, adult A) with animals subjected to MD followed by 1 day (lane 2, infant B; lane 15, adult B) or 5 days of survival (lane 3, infant C; lane 6, adult C).

dependent during that critical period (10). To assess whether MEF2C protein expression is modulated by activity, the levels of MEF2C were examined in extracts prepared from normal infants and adults and were compared to animals subjected to ME followed by 1 to 5 day survival (Fig. 2). Although showing a consistently higher expression of MEF2C in all three infant experimental conditions, we did not observe an increase of MEF2C as a result of ME. Our results suggest that MEF2C is expressed at higher levels in area V1 of infant as compared to adult vervet monkeys, and is not modulated in an activity-dependent manner.

DISCUSSION

Based on our results from a microarray screen that identified RNA expression patterns which correlated with neuroplastic rearrangements during the critical period of visual cortical development (10), we examined the protein expression profile of the transcription factor MEF2C. To this end, we characterized the cross-species reactivity of antisera generated against MEF2C and GAPDH to use as tools to study their expression in extracts of area V1 of vervet monkeys. Our results show that MEF2C is expressed at higher levels in area V1 of infant as compared to adult monkeys.

Previous work suggests that the establishment of ODCs occur early during infancy (pre-natal in monkeys) and is independent of the critical period, which peaks at 25-35 days of age in monkeys (16). The increase in MEF2C expression in 27-35 day old infants suggests it may have a role in the molecular events that underlie the critical period. However, to better characterize the correlation between MEF2C expression and the critical period, a more defined time-course of MEF2C expression, one that includes time points before and after the critical period in normal infants, should be performed.

Our results also suggest that MEF2C protein expression in area V1 is not modulated by MD. In corroboration of this finding, Leysen et al. (17) failed to show statistically significant differences in MEF2C protein expression in normal adult cats and those subjected to retinal lesions. In addition, Microarray data suggested a non-significant correlation between elevation of MEF2C mRNA expression and MD (10). One possibility is that in response to MD, the expression of MEF2C mRNA is modulated differently than its translation into protein. However, the trend showing that MEF2C mRNA levels increase in correlation with MD was not replicated in a Northern analysis of MEF2C expression in the same animals (Lachance and Chaudhuri, personal communication). Taken together, these results suggest that the expression of both MEF2C mRNA and protein in the visual cortex is not activity-dependent.

Although MEF2C levels do not change in correlation with MD, it is possible that MEF2C activity is modulated post-translationally in a manner that would correlate with neuroplastic rearrangements in area V1 during the critical period. It has been well characterized that MEF2C activity is positively regulated subsequent to phosphorylation by p38 MAPK and CaMKIV (12).The p38 MAPK and CaMKIV pathways are induced in cells undergoing neuroplastic changes and promote neuronal survival when activating MEF2C during development (12). However, in mature neurons exposed to excitotoxic stresses, the MAPK pathway is pro-apoptotic because it leads to the activation of caspases which cleave MEF2C proteins, including MEF2C (18). It is possible that while the levels of MEF2C remain unaffected, the phosphorylation status of MEF2C may change in correlation with ME in area V1 during the critical period of visual cortical development. This hypothesis could be tested when an antiserum specific for the phosphorylated forms of MEF2C becomes available.

The regulators of MEF2C activity, CaM type 1 and CaMKIV, have also been identified in the microarray screen for genes whose expression is modulated during the critical period of visual cortical neuroplasticity (10). CaM type 1 expression appears elevated in infants in comparison to adults, whereas CaMKIV seems to be induced by ME during the critical period. Future work should focus on the expression of the protein products for these genes to further validate the microarray data.

In addition, the protein expression patterns of other regulators of MEF2C activity, such as P38MAPK, should be examined in similar experimental conditions. Increase in expression of several proteins in the pathway leading to changes in MEF2C activity suggests that the regulation of neuronal survival is one of the molecular mechanisms underlying the critical period for visual cortical neuroplasticity. Directly showing the importance of MEF2C during the critical period of development via gain and loss of function genetic experiments would be helpful in elucidating its definitive role in the neuroplastic response of the visual cortex.

CONCLUSION

This study has demonstrated a qualitative increase in MEF2C protein expression in area V1 of infant as compared to adult vervet monkeys and further suggests that expression is not mediated in an activity-driven manner. Our results suggest that the regulation of neuronal survival is one of the molecular mechanisms underlying the critical period for visual cortical neuroplasticity.

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CASE REPORT

A forme fruste of Shone's anomaly in a 65 year-old patient

Sherif E Moustafa*, Jacques Lesperance, Jean-Lucien Rouleau, Gilbert Gosselin

ABSTRACT: Shone's anomaly, a congenital cardiac malformation complex, consists of multiple levels of left heart obstruction. A rare case of an incomplete form of this anomaly discovered incidentally during cardiac catheterization for an unrelated event is described.

KEYWORDS: Congenital heart disease, Shone's anomaly

INTRODUCTION

In 1963, Shone et al. described a syndrome consisting of multilevel obstruction of all left heart structures. The original features of Shone's complex include mitral supra-annular ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta (CoA) (1).

In clinical practice, the definition of Shone's anomaly has been extended beyond the original Shone complex, to include patients with additional forms of left heart anomalies, such as mitral and aortic valvular lesions and supra-valvular aortic stenosis (SVAS). In the forme fruste, or incomplete form, some of the obstructions are present, whereas others are absent or only of minor relevance. We describe a 65-year-old male patient presenting with congestive heart failure (CHF). Cardiac catheterization revealed a variant of Shone's complex during routine coronary angiography to rule out atherosclerotic coronary artery disease (CAD).

CASE PRESENTATION

An active 65-year-old man was admitted to the hospital service with CHF. History was remarkable for CoA repair (at 11 years of age), sick sinus syndrome with permanent pacemaker implantation 8 years ago, diabetes mellitus and hypothyroidism. Twelve years ago, he presented with CHF. He underwent transthoracic echocardiogram (TTE) that revealed mild apical and anterior wall segmental wall motion abnormalities (SWMA) and normal global ejection fraction (EF) of 50%. Coronary arteries were free from significant atherosclerotic CAD at that time. He remained symptom free on antifailure medications until his recent hospitalization with severe CHF (III/IV NYHA classification). Cardiovascular examination revealed a systolic thrill over the base with a harsh 4/6 ejection systolic murmur best heard over the aortic areas, as well as a soft 3/6 apical holosystolic murmur. Jugular venous pressure was estimated at 18 mmHg. ECG showed atrial fibrillation, pacemaker spikes and left bundle branch block pattern. Laboratory data was notable for raised troponin T 1.6 ng/mL (normal < 0.03 ng/mL) and creatine kinase-MB 51 ng/mL (normal < 6.2 ng/mL).

Coronary angiography did not demonstrate significant atherosclerotic CAD. Selective left ventricle (LV) angiography and aortography revealed mildly dilated LV with severe systolic (EF = 15-20%) and diastolic (restrictive pattern) dysfunction, severe endomyocardial calcification (presumably secondary to fibroelastosis of both ventricles), multiple segmental wall motion abnormalities, severe subvalvular mitral calcification with mild valvular mitral stenosis (MS) (estimated mitral valve area = 2.0 cm^2) and severe (3/4) mitral regurgitation, bicuspid aortic valve (BAV) with moderately severe valvular aortic stenosis (AS) (estimated aortic valve area = 0.7 cm^2), markedly dilated right ventricle with severe pulmonary hypertension (75/40/55 mmHg systolic/diastolic/mean pressure), mild SVAS without a gradient (Figure 1) and mild residual CoA without a gradient (Figure 2). TTE confirmed the aforementioned findings. In addition, it

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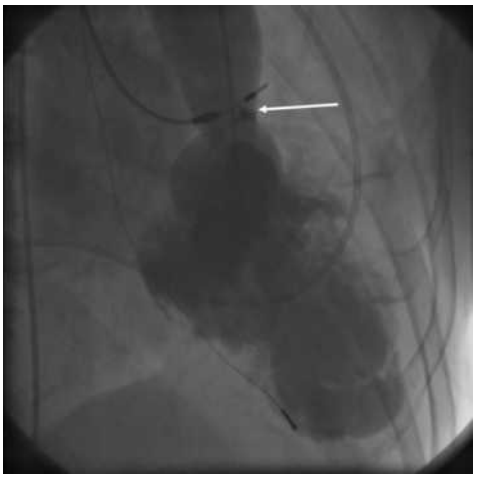

Figure 1: Left ventricular angiography in 1950 showing SVAS (arrow) and akinesia of the whole apex.

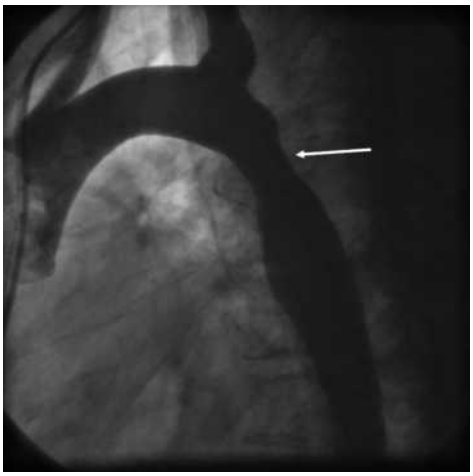

Figure 2: Aortogram in 2004 showing residual CoA repair site (arrow).

uncovered restricted calcified posterior papillary muscle. Dobutamine stress echocardiogram was negative for ischemia.

At that time, the suspected reason for CHF was myocarditis and the patient was followed up closely after hospital dismissal. Three months later, he returned for evaluation for surgical correction. Repeated cardiac catheterization revealed pulmonary vascular resistance of 11.4 which reduced to 4.4 wood's units (Normal range = 0.7 – 1.1 wood's units) with decreased pulmonary pressure from 65/34/47 to 29/13/20 mmHg (systolic/diastolic/mean pressure) after Nitroprusside infusion. EF was 40-46% by TTE and Multiple Gated Acquisition Scan (MUGA). Decision was made for close follow up on antifailure measures including beta blocker (Bisoprolol), acetylsalicylic acid, angiotensin converting enzyme inhibitor (Perindopril) and simvastatin. Surgical correction was declined due to high risk and progressive improvement of EF. The patient's condition improved progressively with a stable EF of 40-45% during follow up in the heart function clinic. There were no major complications or hospitalizations during the follow up period.

DISCUSSION

In this report, we described a case that can be regarded as a forme fruste of Shone's anomaly including subvalvular mitral abnormalities, valvular mitral stenosis, bicuspid aortic valve, valvular aortic stenosis, supravalvular aortic stenosis and coarctation of the aorta with the absence of the supra-annular mitral ring. These anomalies tend to coexist, but the wide range of severity and predominance of each individual lesion may make optimal management troublesome. Even though the incomplete form of this anomaly is prone to be less symptomatic, it is nevertheless surprising that it remained unnoticed in this patient until his mid-sixties. On their own, moderately severe AS and MS can be tolerated for a long time (2).

Our patient presented earlier in his life with CoA as the predominant outflow obstructive lesion. CoA may conceal the presence and potential hemodynamic severity of associated intracardiac lesions (3). Physicians were cautioned to be aware of other left-sided obstructive lesions that could be present in the symptomatic infant with CoA. The correlation of obstructive left-sided anomalies associated with CoA was confirmed by Becker et al. The authors believed that Shone's anomaly should be contemplated in those patients who have ongoing signs of CHF after operative repair of the CoA (4).

Shone et al. (1) noted that mitral valve obstruction appeared to be the most critical problem associated with the anomaly. Mitral commissurotomy alone was not adequate to relieve the obstruction. Bolling et al. confirmed the belief that severity of the mitral valve obstruction correlates inversely with long-term outcome and that operative mortality in patients with this anomaly is negatively influenced by the extent of mitral valve disease. The patients who demonstrated substantially elevated pulmonary artery pressures were those with the worst mitral obstruction and had, in general, the poorest outcome (5). In our case, MS was mild and this correlated well with the patient's longevity.

In conclusion, this rarely reported case of Shone's anomaly in an elderly patient draws attention to the importance of performing a meticulous search for other associated lesions in patients presenting early in life with CoA or any form of left ventricular outflow tract obstruction to prevent later presentation with end stage heart failure or myocardial disease.

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CASE REPORT

A case of postictal psychosis

Lisette Musaib-Ali*

INTRODUCTION

Patients with a long-standing history of seizures are more susceptible to develop major psychiatric disorders including chronic interictal psychosis and episodic psychotic states (1,2). The different psychotic syndromes associated with epilepsy are normally defined based on their chronological relation to the seizures. Interictal psychosis occurs without an antecedent seizure, or an increase in seizure activity (1), and results in persistent psychotic states of varying intervals (3). Postictal psychosis, on the other hand, is an episodic psychotic state that classically follows exacerbations of seizures, particularly clusters of complex partial seizures with or without generalization (4). A lucid period of 12 hours to 6 days after termination of seizure activity precedes the onset of psychiatric symptoms, which often remit spontaneously within days or weeks (5). Patients frequently present with auditory, olfactory, gustatory and/or visceral hallucinations, paranoid ideation, and cognitive dysfunction.

CASE REPORT

Ms. T. is a 31-year-old female who presented in a confused, but alert state after having experienced 3 episodes of seizure activity in 6 days. Upon interviewing she reported that she did not feel like her usual self and feared that something was wrong with her brain. Following her second seizure, she began having visceral hallucinations in her abdomen and groin. Within 24 hours of her third seizure, she had begun to hear voices emerging from her abdomen. The synchronicity of these two symptoms produced a deep anxiety that she was becoming homosexual. The patient also expressed a feeling of responsibility for the suffering of innocent people and as a result, believed that she was being watched. Upon declaration of suicidal intentions, she was started on low dose haloperidol. Her psychoses resolved following two weeks of low dose haloperidol and strict administration of carbamazepine and lamotrigine.

Given our patient's previous hospital admissions for episodes of acute psychosis following a period of poorly controlled seizures, she has an increased risk for developing chronic psychosis from her repeated episodes of postictal psychoses (6,7). While there exists no published trials on the prevention of chronic psychosis, or the symptomatic or prophylactic treatment of postictal psychosis, treatment recommendations based on expert opinion have appeared in the literature in the field of neurology, which were followed for this patient. She was discharged on 200 mg carbamazepine BID, 75 mg lamotrigine BID and 0.5 mg risperidone BID. Follow-up as an outpatient was required in order to monitor her anticonvulsant levels, and to titrate the risperidone up to 1 mg BID, which was discontinued once she had achieved a prolonged period free of seizure activity and psychosis.

DISCUSSION

Epilepsy on average affects up to 1.5% of the general population, of which 0.8% has been admitted to hospital for schizophrenia and 1.5% for schizophrenia-like psychosis (8). Compared to the general population where the risk of developing schizophrenia is 1%, patients with a history of seizures have an increased risk of 2.5% (6). This risk further increases with the number of hospital admissions for epilepsy (6). A latency period of 8 to 15 years was noted between the onset of epilepsy and the patient's first hospital admission for psychiatric issues (5,7). Numerous epidemiological risk factors have been identified, including female sex, early onset epilepsy, long-standing epilepsy, intractable epilepsy, secondary generalization of seizures, and left and/or

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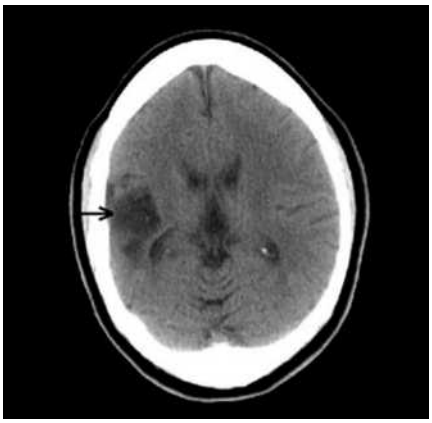

Figure 1a. CT scan, axial section of the brain showing a right middle cerebral artery infacrt limited to the right temporal lobe.

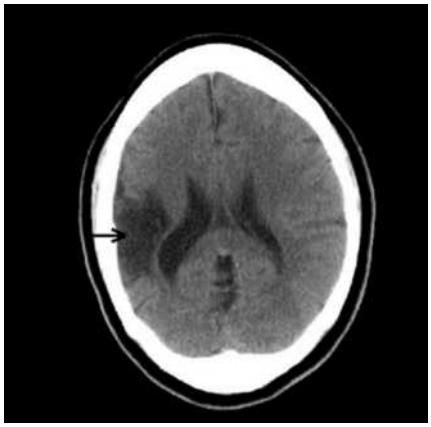

Figure 1b. CT scan, axial section of the brain showing a right middle cerebral artery infacrt limited to the right temporal lobe.

bilateral foci (1).

The propensity to develop postictal psychosis may have some link to the proximity of the seizure focus to limbic structures (8). While the neuropathology of epileptic psychoses remains undetermined, it is believed to be related to abnormal electrical discharges frequently localized to the temporal-frontal lobe and cerebellum (4,7), but can also occur with widespread electrical activity (1). It has been proposed that these epileptiform disturbances result in aberrant regeneration and wiring of neurons, cortical dysgenesis, diffuse brain damage and developmental lesions affecting the connectivity of limbic structures (1).

The patient has a history of seizures in early childhood following a cerebral infarct, compounded by a 10-year history of poorly controlled adult epilepsy. An MRI scan performed 3 years earlier confirmed a pre-existing right middle cerebral artery infarction with sparing of the basal ganglia. During her current admission she underwent computed tomography (CT) and an electroencephalogram (EEG). The CT revealed significant atrophy of the right temporal lobe, but no new lesions or recent infarcts. The EEG confirmed that she was having complex partial seizures with temporal lobe focus and secondary generalization.

While postictal psychosis has been well described in adults, the lack of ICD-10 or DSM-IV classification and the lack of treatment recommendations make the use of prophylactic neuroleptics experimental and problematic. When choosing an antipsychotic medication, it is important to consider the potential additive effect that occurs with the antiepileptic medication. This can increase the number of side effects and toxic effects experienced by the patient, in addition to the pharmacokinetic interactions that can occur during the absorption, distribution, excretion, and biotransformation, resulting in a reduced epileptogenic threshold (ET) and an increase in seizure activity (3). The extent of these adverse effects will vary based on the specific medication, the dosage and duration of use (3). Nevertheless, these numerous unfavorable effects often lead to a high level of non-compliance among patients.

Typical neuroleptics with a low potency such as phenothiazine have been observed to decrease the ET (3). Conversely, highly potent typical neuroleptics like haloperidol demonstrate antipsychotic action at low dose with little effect on the ET, making it one of the safest antipsychotics used to treat postictal psychosis (3). However, haloperidol has a higher risk of extrapyramidal symptoms (EPS), and therefore its use as a first-line treatment for our patient's postictal psychosis was reserved solely for resolving active psychoses. She was then switched to risperidone, an atypical neuroleptic with less EPS side effects, minimal effects on the serum concentration of prolactin, and a positive effect on the negative and dysphoric symptoms of epilepsy that may accompany the psychosis of epilepsy (3).

Both haloperidol and risperidone are weak inhibitors of the hepatic microsomal P450 cytochrome oxidase system (CYP), limiting their effect on the metabolism of concomitantly administered antiepileptic drugs (3). On the other hand, carbamazepine can reduce the plasma concentration of haloperidol and risperidone via induction of CYP3A4, thus compromising the efficacy of psychiatric treatment (3). Lamotrigine, however, is metabolized predominantly by glucuronic acid conjugation with no affect on the cytochrome oxidase system, making it a relatively safe adjunct therapy.

The evaluation and treatment of epileptic patients who present with psychiatric manifestations prove to be complex issues. Although postictal psychoses is relatively rare, this case highlights the importance of seizure control in patients with long-standing epilepsy and the need for prophylactic and treatment protocols for patients at risk of developing epileptic psychoses.

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CASE REPORT

Asian wasp envenomation and acute renal failure: a report of two cases

Rabindra Nath Das,* Keka Mukherjee

ABSTRACT: Acute renal failure is an unusual complication of wasp stings. We report two cases of renal failure after multiple wasp stings (Vespa affinis). Both patients had evidence of intravascular haemolysis, hepatic dysfunction, oligo-anuria and azotaemia and required dialysis. The first patient had severe hemolysis, rhabdomyolysis, pigment and venom nephropathy and died on the 8th day in hospital. The second patient, who recovered completely in 3 weeks time with steroid and antihistaminic therapy, had interstitial nephritis. Although acute renal failure after wasp stings is typically caused by acute tubular necrosis (ATN) in the setting of haemolysis or rhabdomyolysis, in some patients, acute renal failure may result from a direct nephrotoxic effect or acute interstitial nephritis from a hypersensitivity reaction.

KEYWORDS: Wasp envenomation, rhabdomyolysis, interstitial nephritis, acute renal failure, Nepal.

INTRODUCTION

In the Pokhara Valley, Nepal, there are many unpublished cases of wasp poisoning which take a heavy death toll annually. Wasp stings usually cause local allergic reactions but can sometimes lead to intravascular haemolysis, rhabdomyolysis, thrombocytopenia, acute tubular necrosis, acute hepatic injury (1) and even myocardial infarction (2) in addition to various respiratory and neurological (3) manifestations.

Death from wasp envenomation is a rare event and results from acute renal failure (ARF) involving various mechanisms. Although ARF after wasp stings is typically caused by ATN in the setting of haemolysis or rhabdomyolysis, in some patients, renal failure may result from a direct nephrotoxicity of wasp venom or acute interstitial nephritis from a hypersensitivity reaction. We here we report two cases of acute renal failure after wasp stings (Vespa affinis).

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CASE 1

A 55-year-old farmer who had been collecting fodder from a jungle was admitted with dyspnea, hoarse voice and myalgia within 8 hours of being attacked by several wasps. The patient was given intravenous saline, oxygen, salbutamol (β2-adrenergic receptor agonist), chlorpheniramine (antihistamine), cyproheptadine (antihistamine), prednisolone (corticosteroid) and ranitidine (histamine H2-receptor antagonist). He also received fluid, mannitol and furosemide. By the next morning he had haemoptysis and had produced 400 ml of dark urine. On examination, the patient was drowsy, pale, icteric and cyanosed and had approximately one hundred and fifty red and swollen sting marks all over the body. Systemic examination revealed polyphonic wheezes and crepitations at the base of the right lung. Investigations are shown in Table 1. The onset of the oliguric phase was at 12 hours postenvenomation. Chest radiograph showed right basal consolidation. He died on the 8th day following admission despite aggressive therapy with medication, blood transfusions, assisted ventilation, and 16 cycles of dialysis.

CASE 2

A 40-year-old forest guard was attacked by a swarm of wasps. He presented with approximately twenty-five

sting marks in exposed areas of face, throat, hands and legs [Fig.1]. The patient was treated in the primary health centre with rubbing of saliva and papaya slices over the sting marks and referred to teaching hospital almost 24 hours after being stung. He developed anuria and had not passed any urine the previous night. On examination, the patient had a rapid pulse, unrecordable blood pressure, icterus, an urticarial rash in exposed parts of the face, legs and hands, facial puffiness, and a swollen left ankle and right knee joint. The rest of the physical examination was unremarkable. Investigations are shown in Table 1. He was treated with oxygen, salbutamol, chlorpheniramine, cyproheptadine, prednisolone and ranitidine. His hepatic and renal function improved gradually with fluid challenge, furosemide, mannitol, bicarbonate infusion, dopamine, and 12 cycles of dialysis in 3 weeks' time.

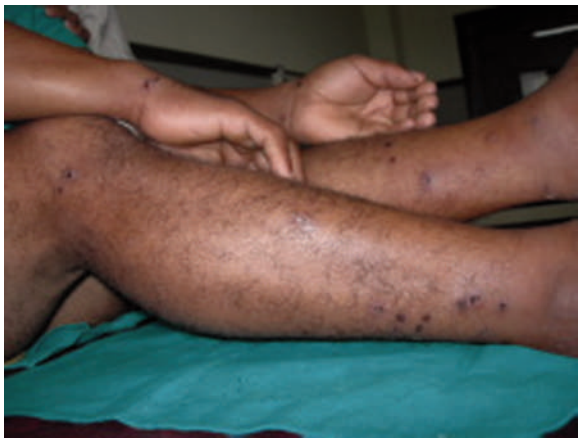

Figure 1: Case 2: Multiple stings & swollen joints.

OBSERVATION

DISCUSSION

Wasp stings are well-known causes of toxic and hypersensitivity reactions. Direct toxicity is rare, but has been reported in cases when a very large amount of venom is injected. Immediate hypersensitivity reactions, such as bronchospasm in the first case and an urticarial rash in the second, are known to occur. In our

Table 1: Pertinent lab results.

	Case 1		Case 2		Normal Range
Day (since admission)	1	2	1	2	
Blood Count					
Hemoglobin	9.8		11.2		12.5- 14.5g%
WBC	11800		12480		4000-11000 cells/cm^2
Eosinophils			37%		1-5%
Reticulocytes			4%		0.2-2%
Prothrombin Time (sec)	78	20	28	14	12.5
Urinalysis					
Specific Gravity	1.028		1.016		1.002-1.018
Albumin	+		+		nil
WBC	6-8		2-4		1-2/hpf
RBC	10-14		1-2		nil/hpf
Hb	+				nil
Urinary Myoglobin	728		6		0-5 ng/mL
Culture	-		-		sterile
Renal Failure Index		3.00		2.98	
Urinary Na+		50		42	50-250 mEq/L/day
FE Na+		2.65		2.90	

	Case 1		Case 2		Normal Range
Day (since admission)	1	2	1	2	
Blood Gases					
pH	7.28				7.35-7.45
PaO^2	88				75-100mmHg
$PaCO^2$	38				35-45mmHg
HCO_3^-	22				22-28mEq/L
General Chemistry					
K^+	6.4	7.2	5.6	4.2	3.5-5mEq/L
Ca^{2+}	8.8	8.2	9.6	10.5	8.5-10.5mg%
PO_4^{2-}	4.2	4.6	4.2	4.6	3.0-4.5mg%
Urea	112	224	76	55	0-20mg%
Creatinine	5.6	13.9	3.6	2.4	0.5-1.5mg%
Bilirubin Indirect	3.4		2.5		0.4-0.8mg%
Bilirubin Direct	0.6		0.7		0.2-0.4mg%
Creatine Kinase		8400		90	<17-167U/L
LDH		4500		340	240-420 U/L
AST	1260	140	1188	78	0-40U/L
Serum Albumin	1.8		3.2		3.5-5.0g%

report, both reactions responded to steroids and antihistaminics. The second patient had swollen joints indicating serum sickness-like reaction in a sensitized individual.

Wasp venom contains toxic melittin, apamine, phospholipases A1, hyaluronidase, acid phosphatase, histamine, and degranulating peptide mastoparan (4). These components have direct and indirect cytotoxic (hepatic, renal and myocyte membrane), hemolytic, neurotoxic and vasoactive properties, which can cause intravascular haemolysis and rhabdomyolysis (5, 6).

Wasp venom can cause ARF by several mechanisms, which include ATN, acute interstitial nephritis, pigment nephropathy resulting from rhabdomyolysis (myoglobinuria) or intravascular haemolysis (haemoglobinuria) and hypotension caused by an anaphylactic reaction (7, 8).

Previously rhabdomyolysis and renal ischemia were thought to be main causes of nephropathy. Sakhuja et al had postulated that direct toxic injury could be one of the possible mechanisms of ARF following wasp poisoning (9).

Many cases of rhabdomyolysis-associated ARF have been published, but those due to wasp stings are rare. The wasp venom has deleterious effect on renal tubules and glomeruli (albuminuria, haematuria and ARF), red blood cells (haemolysis, reticulocytosis, unconjugated hyperbilirubinaemia), muscles (rhabdomyolysis, elevated creatinine phosphokinase and lactate dehydrogenase, myoglobinuria) and liver (elevated transaminases, hypoalbuminaemia and prolonged prothrombin time) (10). Kularatne et al had described similar multi-organ failure with high mortality following wasp poisoning owing to direct toxic effect (11).

In the first case we presented, the patient had myalgia, indicating muscle injury as evidenced by elevated CPK, LDH and AST and myoglobinuria (728 ng/ml). He also had intravascular haemolysis and haemoglobinuria. Toxic pigments might have caused nephropathy resulting in ARF. The alternative mechanism of ARF postulated was direct nephrotoxicity by massive wasp venom.

Zhang R et al. (12) reported for the first time that acute tubulointerstitial nephritis could lead to ARF in wasp sting cases. In the second case we present, the patient had eosinophiluria, indicating interstitial nephritis. He recovered fully with the mentioned treatment. He did not report taking any medication which might have had nephrotoxic side-effects, and no other causes of ATN could be found. Ultrasound abdomen was unremarkable. Kidney biopsy revealed proximal peritubular necrosis and eosinophilic infiltration. Hence it can be hypothesized that the ATN was caused by a hypersensitivity reaction to the wasp venom.

CONCLUSION

Wasp stings pose a great environmental hazard in Nepal and early recognition of anaphylactic shock, hepatic or renal dysfunction, rhabdomyolysis or haemolysis and rapid transport to hospital are essential steps of management to avoid fatalities. ARF due to toxic or pigment nephropathy and tubulointerstitial nephritis should be considered in any oliguric and azotemic patient following wasp attack.

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTION

The second author KG managed the patients with dialysis and conceived the idea for the case report.

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The Dean and CEO, Prof. Satish Dham had inspired the author to write this manuscript. Written informed consent was obtained from the patient's relatives for publication of the study. There is no source of funding for the study and for the manuscript preparation.

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Keka Mukherjee worked with the first author in the medical ward and searched the bibliography for this article. She graduated in December 2006 from Kathmandu University. She is interested in renal diseases.

REVIEW ARTICLE

Anterior cruciate ligament reconstruction: a look at prosthetics - past, present and possible future

Randy Mascarenhas*, Peter B. MacDonald

ABSTRACT: Biological tissue autograft reconstruction using the patellar tendon or quadrupled semitendinosus/gracilis tendons has become the most popular procedure in surgical treatment of a ruptured ACL. This article provides a review of the history of the use of prosthetics with respect to ACL reconstruction grafts including Carbon Fibre, Gore-Tex and Dacron prosthetics as well as the Leeds-Keio Artificial Ligament and the Kennedy Ligament Augmentation Device (LAD). Emphasis is placed on the Ligament Advanced Reinforcement System (LARS) as preliminary investigations of its use have been encouraging. Significant progress has been made recently with respect to the understanding of ACL anatomy, composition, biomechanics, and healing processes, leading to innovative techniques using approaches based in tissue engineering principles and computer – assisted surgery. While research into improved ACL treatment options continues, the synthesis of recent advancements provides a new optimism towards the regeneration of an ACL mirroring its original stability, function, and longevity.

KEY WORDS: anterior cruciate ligament, biomaterials, prosthetics, synthetic grafts, tissue engineering

INTRODUCTION

The anterior cruciate ligament (ACL) is the most frequently injured ligament in the knee and consequently, the majority of research into knee ligament injuries has been directed towards the ACL. While the collateral knee ligaments exhibit strong healing potential and generally respond well to conservative treatment, the anterior cruciate ligament has a poor intrinsic healing ability due to the fact that it is enveloped by synovial fluid and lacks significant vascularization (1). Surgical reconstruction is therefore the most frequent mode of treatment pursued when the ACL is torn. The patients who experience ACL injuries are significantly younger and more active than those who experience many other orthopaedic injuries. The need for reconstruction options that exhibit longevity in the face of great stresses is therefore imperative (2). Historically, options for surgical treatment have included primary repair with or without synthetic augmentation and reconstruction using either biological tissue grafts or prosthetic ligaments. Primary repairs with or without augmentation have tended to fail at restoring stability to the knee and are not a common treatment option today (3). Likewise, prosthetic replacements have traditionally tended to be inadequate due to post-surgical complications arising from wear and degeneration. Hence, biological tissue autograft reconstruction using the patellar tendon or quadrupled semitendinosus/gracilis tendons has become the most popular procedure in surgical treatment of an ACL rupture. However, the frequency of significant anterior knee pain post-surgically and high occurrence of flexion contracture and crepitation in tendon autografts have kept research interests focused on the further development of prosthetic ligament implants. A significant number of early research endeavours into prosthetic ACL replacements failed due to a poor understanding of the biomechanical and physiological

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properties of the ACL. Tremendous gains in understanding have been made in these areas, with significant progress being made in understanding the inter-dependence between ACL anatomy, tissue composition, biomechanics, and the healing processes. Unfortunately, to date, no prosthesis has proven itself as a viable alternative to the patellar or hamstring tendon autografts, currently used in over 90% of ACL reconstructions. This article reviews some of the major historical milestones in ACL reconstruction technology and looks forward to the continuing evolution of this technology. The literature used for this review was obtained using the PubMED database with keywords "anterior cruciate ligament" searched in tandem separately with "prosthetics" and "tissue engineering." It should be noted that many of the studies cited in this review obtained funding from orthopaedic and biomaterial companies that sponsored the implant.

SURGICAL REPAIR: ADVANTAGES AND DISADVANTAGES OF BIOLOGICAL TISSUE GRAFTS

Bone-patellar tendon-bone (BPTB) and semitendinosus/gracilis tendon autografts are currently the most common grafts used in ACL reconstruction. While the BPTB autografts were the former "gold standard", recent studies have identified the quadruple semitendinosus graft as a comparable option for ACL reconstruction (4). Advances in hamstring graft fixation have led to similar strengths of fixation between BPTB and semitendinosus/gracilis grafts (5). Both techniques now offer a high degree of strength and stiffness in the reconstructed ligament. Additionally, use of the patient's own tissue eliminates the risk of rejection and good to excellent results are reported in 85-90% of patients receiving either of these grafts for ACL reconstructions. Nonetheless, with patellar tendon autografts, many patients experience impaired function and significant morbidity at the donor site including secondary anterior knee pain, patellar tendonitis, infrapatellar contracture, and patellar fracture. Likewise, hamstring weakness and saphenous nerve injury can be seen secondary to hamstring harvest in semitendinosus/gracilis autograft ACL reconstruction (6).

To avoid complications resulting from donor site morbidity in autograft reconstructions, allograft reconstruction has also been examined. While eliminating the donor site morbidity, the use of allografts is not currently considered advantageous due to a limited donor tissue supply, delayed biological incorporation, risks of disease transmission and tissue rejection. In an attempt to overcome these concerns, research into the use of synthetic prosthetic ligaments began over 30 years ago and continues today in hopes of eliminating donor site morbidity and reducing the risk of disease transmission and supply shortages. One of the main obstacles in finding an adequate prosthetic replacement for the ACL is the longevity of the graft, with autogenous tissue consistently proving to be a more durable and long-lasting replacement than the many biomaterials that have been applied to ACL replacement (7).

PROSTHETIC BEGINNINGS AND PAST USE

The first attempts at a synthetic ACL reconstruction were conducted by Alwyn-Smith in 1918 using silk sutures; they however failed within 3 months (8). Reconstruction with a prosthetic ligament made of polytetrafluoroethylene (PTFE) with embedded carbon or aluminum oxide fibers (Proplast) was first reported in 1973 (9). Results with this system yielded an average time to breakage of just over 1 year. A report by James et al. suggests that only 52% of reconstructions utilizing this graft yielded satisfactory results (10). Satisfactory results include all grafts that patients were content with and had not ruptured at time of lastest follow-up.

Current classification systems for synthetic replacements of the ACL include grafts, ligament augmentation devices, or total prosthetics. Grafts (polyethylene, PTFE), typically fixed at both ends, were the initial focus of synthetic ACL replacement and were meant to provide stability to the ACL-deficient-knee until secondary reconstruction procedures gained popularity (11). Similarly, ligament augmentation devices (polypropylene, polyester) were intended to provide immediate protection for autogenous tissue grafts until revascularization was complete and the ingrown tissue was capable of withstanding local tensile and compressive forces. Unfortunately, these devices may in fact accomplish the opposite of their intended purpose by stress-shielding autogenous tissue, preventing it from developing adequate mechanical strength. Fixed at both ends like a graft, the total prosthesis was intended as a permanent ACL replacement without any soft-tissue ingrowth that would allow the patient to begin aggressive rehabilitation immediately as no tissue maturation or revascularization was required. While the implantation of a full-strength ACL replacement generally led to excellent short-term results, long-term efficacy results were poor due to wear and ensuing rupture of the prosthesis (11).

Combining the mechanical focus provided by these prior prosthetic approaches with tissue engineering principles has led to the development of a scaffold design intended to serve as a foundation for soft tissue in-growth. Scaffolds may be permanent or may be

intended to gradually degenerate as the host tissue replaces them. Problems associated with the biological incorporation of scaffolds include variability of tissue in-growth, immature degeneration of the implant and insufficient maturation of the host tissue resulting in an inability of the scaffold to withstand inherent mechanical stresses placed on the ACL. Current directions in this area involve the use of tissue engineering focusing on developing a mechanically and biologically functional matrix for the scaffold and the use of in vitro mechanical signals to guide new tissue development (11). Table 1 summarizes the advantages of the various prosthetic ACL graft options that have been attempted and are discussed below.

CARBON FIBRE PROSTHETICS

Some of the earliest attempts to discover an appropriate alternative to the biological graft resulted in a variety of carbon fibre prostheses that varied greatly with respect to material and implantation technique. In 1977, Jenkins et al. were the first to use a flexible carbon fibre implant, and suggested that the carbon fibre induced the formation of tendon in animals and humans (12). However, subsequent studies reported the generation and migration of carbon wear particles into the joint space and regional lymph nodes following implantation of the prosthesis (12). To combat this problem, attempts were made to coat the carbon fibre with collagen and absorbable polymers. Of particular interest was a carbon fibre implant proposed by Alexander et al. coated with a co-polymer of polylactic acid (PLA) and polycapralactone (13). The carbon filaments were thought to act as a scaffold for tissue ingrowth by evenly distributing and reducing the interfacial stress between the implant and soft tissue attachment, while the PLA/polycapralactone would protect the fibre during implantation. Over time, the PLA was meant to resorb and the carbon fibres degrade as new tissue developed, thereby encouraging normal tissue regeneration without permanently replacing it (13). A 24-month study involving 82 patients was conducted by Weiss et al. to further examine the PLA coated prosthesis using a variety of subjective and objective measures (pain, stability, function, and isokinetic strength testing), which revealed significant improvements over the duration of the study (14). Arthroscopic evaluation demonstrated collagenous tissue ingrowth, confirmed by histological studies, to be composed of Type I and III collagen in similar proportions to that found in normal healing ligamentous tissue (14).

A similar design was used in the Surgicraft ABC prosthetic ACL (Surgicraft Ltd., Redditch UK) composed of carbon and polyester fibres oriented in a partial braid by a zig-zag pattern. However, a study by O'Brien et al. with an average follow-up of 34 months showed only 11 of 31 knees (41%) had good results defined as a Lysholm score greater than 76. The Lysholm knee score is an outcome measure that assesses knee function on a 100 point scale. The

Prosthesis	Advantages	Disadvantages
Carbon	Reduction and even distribution of stress between graft and soft tissue attachment Polylactic acid coat protects graft during implantation Encourages ingrowth of collagen into implant	Migration of carbon wear particles Unacceptable incidence of implant stretching and rupture led to poor long-term functional outcomes
Gore-Tex	Tensile strength 3X native human ACL	Progressive long-term loosening
Dacron	Polyester coating serves to protect implant from abrasion	Poor long-term stability
Leeds-Keio Artificial Ligament	Acts as a scaffold for soft tissue ingrowth Excellent max. tensile strength which exceeds that of native ACL	Acts as more of a load-bearing prosthesis, allowing for fibrous tissue ingrowth Large number of long-term graft ruptures
Kennedy Ligament Augmentation Device	Protects autogenous graft from excessive stresses	Weak implant-graft interface Propensity to cause intra-articular inflam. response and resulting synovitis and effusions
LARS Ligament	Mimics natural ACL structure and orientation Reduces shearing forces on the implant Porosity encourages tissue ingrowth	Residual post-operative laxity still present No long-term follow-up studies yet
Tissue-engineered Scaffolds	Duplicate mechanical & structural properties of native ACL Restoration of normal knee joint kinematics Implant can resemble normal ACL over time	Loses strength over time Allogenecity of collagen scaffolds can lead to rejection Consistent reprod. difficult due to batch-to-batch variability Collagen not as modifiable as biodegradable polymers

Table 1: Advantages and disadvantages of various prosthetic ACL grafts.

authors also noted unacceptable stretching and complete rupture as major complications and concluded that the implant is unsuitable for clinical use (15).

GORE-TEX PERMANENT PROSTHESIS

The Gore-Tex ligament prosthesis is composed of a single long fiber of expanded polytetrafluoroethylene (PTFE) arranged into loops. Extensive mechanical testing has shown that the resulting ultimate tensile strength is about 3 times that of the human ACL and the results from cyclical creep tests and bending fatigue testing seem to identify Gore-Tex as the strongest synthetic ACL replacement in terms of pure material stability (16). Bolton and Bruchman reported that 129 out of 130 patients receiving a high strength PTFE ligament showed improved knee stability at 15 months or less (16). Glousman et al. reported an initial improvement upon physical examination and subjective scores. However, at mean follow-up of 18 months, they reported a progressive loosening of the prosthesis (17). Similarly, Woods et al. presented 2- and 3-year follow-up of Gore-Tex ACL reconstructions and showed a similar pattern of early improvement post-operatively, but deterioration over time. They reported an overall failure rate of 33% at 3-year follow-up (18). Indelicato et al.'s follow-up of Gore-Tex implant ACL reconstructions showed a 90% success rate at 2 years versus only a 76% success rate at 3 years or more (19). Despite similar reports describing complications with the Gore-Tex ACL prosthesis, subjective results in several studies remain acceptable at 60-80 % (17, 19). The Gore-Tex ACL prosthesis is currently FDA approved for use in patients who have had a failed autogenous intra-articular graft procedure.

DACRON

With its success as a vascular surgery implant (20), various forms of Dacron grafts have been developed as a scaffold for ACL replacements. The implant is a composite of four tightly woven polyester strips wrapped in a sheath of loosely woven velour, designed to minimize abrasion of the graft and act as a scaffold for fibrous tissue ingrowth. A report by Lukianov et al. reviewed the short-term follow-up (mean 28 months) of 41 patients who underwent ACL reconstruction with the Stryker Dacron ligament prosthesis (3). Seventy-five percent of the patients were found to have a negative Lachman, anterior drawer, and pivot shift at their most recent follow-up. However, Richmond et al. reported failure rates of 37.1% in a study of Dacron reconstruction with mean long-term follow-up of 50 months (21). Likewise, Barrett et al. reported higher failure rates of 47.5% after a four-year follow-up period (22). A clinical study by Lopez-Vazquez et al. examining ACL reconstruction with a Dacron prosthesis showed a similar deterioration of results after the first post-operative year (23). With the initial short-term strength shown by these grafts offset by their poor long-term stability, Dacron grafts should not be considered a viable alternative for ACL reconstruction.

LEEDS-KEIO ARTIFICIAL LIGAMENT

With the desire to design a graft that combined the properties of a permanent prosthesis and a tissue-promoting scaffold, Fujikawa and Seedhom developed the Leeds-Keio artificial ligament: a polyester mesh-like structure anchored to the femur and tibia with bone plugs (24). This mesh was intended as a scaffold for soft tissue ingrowth through the intra-articular and extra-articular sections of the ligament, eventually uniting the bone plugs. The implant was considered sufficiently flexible to be effective with a maximal tensile strength of approximately 2100 Newtons (N), which significantly exceeds that of the average young adults' natural ACL (about 1730 N) (24). Initial descriptions from the inventors also described minimal articular wear with the ligament (24). The inventors of this graft have reported successful clinical results with arthroscopic observations documenting neoligamentous tissue within the implanted Dacron scaffold. Other investigators, however, have reported the ingrowth of non-aligned fibrous tissue (i.e. non-neoligamentous tissue) within the device after implantation and suggested that the Leeds-Keio ligament did not serve as a true scaffolding graft, but instead behaved as a permanent load-bearing prosthesis, subject to long-term failure in the joint (25).

McLoughlin and Smith presented a 3.8 year follow-up study of 25 patients implanted with the Leeds-Keio ligament for chronic ACL instability. They reported a low complication rate and considerable success in the elimination of instability after finding good post-operative results with the anterior drawer test using an arthrometer at 90° of flexion (26). Nevertheless, ensuing long-term follow-up studies showed a deterioration of results after the first post-operative year and a large number of long-term graft ruptures despite excellent early results in stability testing and on the Lysholm scale (27). These findings were similar to earlier results reported by Schindhelm, who found that good early results in a sheep model were not maintained (28). Due to the number of long-term graft ruptures and the lack of long-term stability provided, the Leeds-Keio ligament is no longer suitable for reconstruction of the human ACL (27, 28).

KENNEDY LIGAMENT AUGMENTATION DEVICE (LAD)

Kennedy et al. introduced the concept of the Ligament Augmentation Device (LAD) in 1980 (29). The graft, composed of a band-like braid of polypropylene, was originally developed to reinforce the area of pre-patellar tissue considered to be a weak area of autogenous patellar tendon grafts. Use of this prosthesis employed the MacIntosh/Marshall transfer of a portion of the rectus femoris tendon, pre-patellar tissue, and central third of the patellar tendon in an over-the-top fashion (30). Originally, the graft was developed to protect the autogenous tissue graft from excessive stresses during the initial remodelling phase (characterized by degeneration and revascularization), allowing for earlier resumption of pre-operative activity levels (29). Research has shown that the percentage of load accepted by the LAD varies according to the type of graft employed and method of reconstruction. Comparisons of the patellar tendon and semitendinosus/gracilis LAD composite grafts revealed that the LAD will accept approximately 28% and 45% of the applied load, respectively (31). To prevent excessive stress shielding that would otherwise prevent the autogenous tissue from developing a normal functional tensile strength, the LAD was attached to the bone at only one end. Despite a promising beginning, the suture interface between the LAD and the graft was identified as the weak link of the composite.

Whether collagen fibres become truly incorporated into the LAD remains a controversial issue. Most histological evidence has been derived from animal studies and thus may not be fully indicative of results in humans. Nevertheless, this evidence seems to point to adequate longitudinal collagenization of the graft with inconclusive results on whether or not collagen ingrowth within the LAD has occurred (32). Furthermore, as an intra-articular foreign body, the LAD has been reported to induce an inflammatory response characterized by foreign body giant cells and macrophages in the surrounding tissue. A review by Kumar et al. reported that the majority of complications seen following use of the LAD were characterized as effusions and reactive synovitis, likely a result of LAD-induced inflammatory response (23). The decline in use of the aforementioned MacIntosh/Marshall transfer, combined with the weak graft-prosthetic suture interface and propensity of the LAD to cause high rates of post-operative synovitis have resulted in a lack of widespread use of the device.

THE FUTURE: LIGAMENT ADVANCED REINFORCEMENT SYSTEM (LARS) ARTIFICIAL LIGAMENT

The Ligament Advanced Reinforcement System (LARS) (Arc-sur-Tille, France) artificial ligament consists of fibres made of polyethylene terephthalate (PET). An intra-osseous segment is composed of longitudinal fibres bound together by a transverse knitted structure while an intra-articular segment is composed of parallel longitudinal fibres twisted at 90°. The main innovation of this artificial ligament lies in its ability to mimic the natural ligamentous structure and reduce shearing forces by orientating the free fibers of the intra-articular portion of the graft clockwise or counter-clockwise for use in right and left knees, respectively. Furthermore, the PET fibres of the intra-articular segment are designed to encourage tissue ingrowth due to the porosity of the material, allowing ingrowth from the surrounding osseous tunnels. Ideally, such tissue ingrowth between the ligament fibres would contribute to the viscoelasticity of the graft and protect against friction at the opening of the bony canal and between the fibres themselves (1).

A study by Lavoie et al. examined ACL reconstruction with the use of the LARS artificial ligament. Thirty-eight of forty-seven patients suffered from chronic ruptures of the ACL, while nine others presented with acute or subacute ruptures at a mean follow-up of 21.9 months. Six patients had previously had an unsuccessful ACL reconstruction. The Knee Osteoarthritis Outcome Score (KOOS) was administered to assess patients' opinions regarding their knee, while a modified International Knee Documentation Committee (IKDC) scoring system was used to examine knee stability. The IKDC form initially consisted of seven knee-related parameters that were each rated as either normal, nearly normal, abnormal, and severely abnormal. The worst score amongst the seven categories determined the final score. The form was later modified in 2001 to include subjective factors such as symptoms, sports activities, and ability to function. The Tegner activity scale, a subjective ten point activity scale, was obtained to assess patient activity levels. A Telos radiographic stress system was used to examine anterior knee displacement, which involves obtaining radiographs with the knee in ninety degrees of flexion and a posterior force applied to the knee. When results are compared to the normal knee, this test helps in the assessment of post-operative laxity in the reconstructed knee which may indicate that the graft is failing. None of the patients presented symptoms of synovitis, but longer follow-up time is required to properly draw conclusions with respect to patient outcome. Although Tegner scores improved

significantly following surgery, no patients returned to pre-injury activity levels. Data obtained by the KOOS demonstrated patient satisfaction ranged from 73.5 to 93.0 %. In comparison to the uninjured knee, post-operative Telos stress radiography and the Lachman test indicated an average posterior-anterior displacement of 7.3 mm for the involved knee (28).

A more complete examination of the LARS artificial ligament was provided in a subsequent study by the same authors. Nau et al. conducted a two-year follow-up randomized controlled trial that compared the BPTB autograft with the LARS artificial ligament method of ACL reconstruction in 53 patients with chronic instability (1). Like the preceding study, assessments included clinical examination, anterior laxity testing, as well as the KOOS, IKDC, and Tegner scores. In particular, IKDC evaluation revealed little significant difference between the two methods. Follow-up values for instrumented laxity testing were greater in the LARS group. While similar overall results were obtained for both groups, these results may suggest that a full return to activity may be hastened by using the LARS artificial ligament rather than the conventional BPTB technique (1).

Another recent study by Talbot et al. examined the use of the LARS artificial ligament for ligament reconstruction in knee dislocations (2). Twenty patients were included with a mean follow-up of 27.4 months. Each patient was evaluated using the Lysholm score, underwent clinical examination to identify ligamentous laxity and range of motion, and completed the ACL quality of life (ACL-QoL) questionnaire. The mean Lysholm score was 71.7, which is lower than scores reported by several other studies (range of 74.7 to 91.3) investigating the outcomes of knee dislocations treated with surgery as reported by Fanelli (35). Following the same trend, Telos radiometry revealed a mean residual laxity of 5 mm in patients post-surgery, which is also greater than these previously reported results. The average range of motion post-surgery was 118° with a mean fixed flexion contracture of 2° (2).

Although preliminary investigations into the use of the LARS artificial ligament have been encouraging, concerns regarding the risk of rupture remain and must be addressed through long-term follow-up studies.

TISSUE ENGINEERING ADVANCES

Permanent synthetic prostheses are capable of duplicating the mechanical and structural properties of the ACL. However, they generally tend to lose strength with time. Tissue-based or tissue-aided implants offer the additional possibility of the restoration of normal joint kinematics while the mechanical behaviour of these implants is expected to improve over time as tissues are remodelled within the knee (36). An ideal ACL scaffold must meet the immediate functional mechanical demands within the reconstructed knee, however, they must also degrade at a rate similar to that of tissue ingrowth. Accordingly, the ACL scaffold should lose its mechanical integrity while allowing the remodelled tissues to gain strength and accept an increasing amount of the mechanical demands placed on the ACL. Current research into this novel tissue-engineering approach has focused on seeding either collagen-based scaffolds or synthetic biodegradable polymers with a variety of different cell types. In hopes of stimulating early healing, reducing biomaterial-related inflammatory response and improving neoligament formation, several researchers have sought to adopt a cell sheeting technique to improve the performance of the synthetic ACL scaffold.

Several groups have conducted experiments on this tissue-engineered approach to ACL ligament reconstruction using both fibroblast-seeded synthetic scaffolds and collagen-based prosthetics (37, 38). Bellincampi et al. measured the ingrowth characteristics of rabbit fibroblasts on skin and ACL scaffolds (39). Subsequent in vivo studies suggested that fibroblast-seeded collagen scaffolds were viable after re-implantation into the donor rabbit. The major limitations of these approaches are the allogenicity of the collagen scaffolds, often leading to further complications. Collagen-based constructs also suffer from batch-to-batch variability, making consistent reproduction of these prostheses difficult. Collagen does not offer the same flexibility for modification that is reported with the technology of biodegradable polymers (6).

As an alternative to the scaffolds made of non-degradable polymers, investigators have begun to examine biodegradable materials that would provide immediate stabilization to the repaired ligament but would also act as a scaffold for the ingrowth and/or replacement by host cells. Cao et al. described the generation of neo-tendons in a nude mice model by implanting polyglycolic acid (PGA) scaffolds seeded with bovine tendon fibroblasts in the subcutaneous space of athymic mice (40). Using a similar system, Koski et al. reported the formation of ligament-like structures when fibroblasts isolated from bovine cruciate ligaments were seeded onto PGA scaffolds and implanted subcutaneously in nude mice (6). In both studies, the tissue developed histological characteristics similar to normal tendon and ligament over time.

Ouyang et al. reported that bone marrow stromal cells (bMSCs) seeded onto poly-lactic and -glycolic acid (PLGA) scaffolds grew as a multi-layer of cells intertwined in a collagen matrix synthesized by the cells

themselves. They also noted that the cell sheet formed faster than scaffolds seeded with terminally differentiated cells, such as fibroblasts and smooth muscle cells (41). They reported that degradation of the scaffolds occurred over time, as indicated by a decrease in failure load. Altman et al. seeded 6-cord silk scaffolds with human bone marrow stromal cells and cultured them for 14-21 days. Their results similarly suggested a slow degradation of the scaffolds. However, fatigue analysis and subsequent regression analysis revealed an expected matrix lifetime equivalent to 1 year in vivo. While these reports are an estimate, the authors suggest that this is a marked improvement compared to similar studies using collagen scaffolds (36).

The future of tissue engineering may also require a significant contribution from cell-specific growth factors influencing the maturation and homeostasis of the healing response of ligament tissue. Studies have suggested that individual growth factors may have an important effect on cell division and enhance ligament healing, while others have pointed to the synergistic effect of a combination of growth factors as important to cell outgrowth in ACL explants (42, 43). In a study observing the effects of several growth factors on the cell migration, proliferation and collagen production in human ACL cells, Murray et al. suggested that specific dose-response relationships may exist for the optimal activity of each growth factor (44). These authors observed that the addition of transforming growth factor (TGF)β-1 led to an increased cell population, as well as increased collagen and smooth muscle actin production in human ACL cells cultured on top of a collagen-glycosaminoglycan scaffold. Despite the complex nature of the inter-dependent factors at play during the recovery and rehabilitative period following an ACL reconstruction, much of the literature today suggests that tissue engineering techniques will lead to a new generation of ACL replacements, capable of regenerating a mechanically robust and natural ACL.

COMPUTER-ASSISTED ACL RECONSTRUCTION

In an attempt to improve the accuracy and reproducibility of ACL graft placement, several groups have turned to computer-assisted surgery in an attempt to reduce the incidence of graft failure (45, 46). These systems are capable of modeling the placement and predicting the impingement of an ACL graft based on intra-operative anatomical landmarks and signals received at an opto-electric camera. These studies reported that experience level did not affect the placement of the tunnels. Computer-assisted ACL replacement reduces variance in tunnel placement and allows residents and less experienced surgeons to limit complications and control tunnel positioning (46). Based on the success of navigation systems for total knee and hip replacements, the use of computer-assisted ACL reconstruction may lead to similarly dramatic improvements in technical and functional outcomes.

CONCLUSION

Satisfactory prosthetic replacement of the ACL has been a focus of orthopaedic research endeavours for the past thirty years. Desires to provide immediate mobility and strength to the ACL-deficient knee while avoiding the donor site morbidity caused by the commonly used autograft surgical techniques continually drive new research initiatives. Most of the grafts that have been developed to date have failed due to unsatisfactory long-term physiologic and functional performance. Most permanent ACL prostheses are prone to creep, fatigue, and mechanical failure within several years after implantation (40). Tissue ingrowth scaffolds and ligament augmentation devices require further refinement to provide effective mechanical support while avoiding stress-shielding of the host tissue. In view of these factors, prosthetics are not widely used today in ACL reconstruction, and autogenous tissue grafts remain the gold standard used by the majority of surgeons. Perhaps development of resorbable, tissue-inducing and cell-seeded biomaterials will improve the long-term biomechanical performance of the reconstructed anterior cruciate ligament. Advances in tissue engineering combined with developments in molecular biology and gene therapy may couple with the rapid gains in computer-assisted surgery to provide improved options for the ACL-deficient knee, with a greater potential to restore its pre-injury state.

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REVIEW ARTICLE

Hepatic Fibrosis: Novel Strategies in Detection and Therapy

Venkataramana Bhat, Mamatha Bhat*

INTRODUCTION

Hepatic cirrhosis is the final stage of progressive hepatic fibrosis, and is histologically characterized by collapse of hepatic lobules, formation of fibrous septae, and hepatocyte regeneration (1). Fibrosis as a scarring response to liver damage may be thought of as beneficial, since it contains the injurious process (2). Ultimately however, this progressive scarring can lead to impairment of liver function, development of hepatocellular carcinoma and portal hypertension with all its associated complications. Recently, there has been a growing understanding of the pathophysiology behind fibrosis, which has contributed to the development of agents that could potentially inhibit and even reverse the fibrotic process in the future. Using non-invasive means that are more precise, reproducible, and less fraught with complications would allow the clinician to monitor disease progression, clinical outcomes and response to antifibrotic treatment. In this review article, we will cover the various etiologies of hepatic fibrosis, the currently used diagnostic modalities, serum markers, and transient elastography as novel non-invasive diagnostic modalities, and potential agents that could be used in the future to halt or even reverse fibrosis.

ETIOLOGIES OF HEPATIC FIBROSIS

Hepatic cirrhosis can be the endpoint of various pathologic conditions; however, alcoholic liver disease and viral hepatitis C account for most cases of hepatic cirrhosis in Canada and the U.S. It is estimated that between 210,000 and 275,000 people are currently infected with the hepatitis C virus in Canada, with an additional 5000 people getting infected annually (3). Although there are no detailed epidemiological data from Canada, it is estimated that 600,000 Canadians are chronically infected with hepatitis B, the majority of whom are immigrants from endemic areas (4). Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), hemochromatosis, autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), and Wilson's disease comprise the rest of the etiologies of hepatic cirrhosis.

DIAGNOSIS OF HEPATIC FIBROSIS

These conditions can be elucidated through specific biomarkers and antibody assays. Imaging techniques such as abdominal ultrasound and CT scanning are used to detect and follow structural changes in the liver parenchyma as it progresses from fibrosis to cirrhosis. Liver parameters such as size, appearance of its surface and margin, and the echogenicity of parenchymal texture can be estimated through abdominal ultrasound. However, compensated hepatic cirrhosis can be accurately diagnosed in 80 to 87% of patients (5,6,7) with a specificity of 81.5% (7). This range of sensitivities is based on the following three studies: a prospective study by Gaiani et al. where 212 patients underwent liver biopsies as gold standard and concurrent ultrasonographic assessment (5), a study of 70 patients by Ferral et al.(6), and similar evaluation of 48 patients by Zheng et al (7). The presence of cirrhosis was inferred based on liver surface nodularity, relative enlargement of the caudate lobe as compared to the right lobe, splenomegaly and portal flow velocity. CT scan has been deemed to have a sensitivity of 84% and a specificity of approximately 100% for the detection of cirrhosis (8).

The gold standard to diagnose hepatic fibrosis and cirrhosis is liver biopsy. This is obtained via percutaneous, transjugular, radiographically-guided fine-needle or laparoscopic route, depending upon the clinical setting. The sensitivity of the blind percutaneous liver biopsy when compared to the ultimate gold standard, which is a sizeable biopsy

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obtained laparoscopically, is 82% (9). Histopathological examination enables the clinician to grade the severity of necroinflammation and stage the extent of fibrosis. The Metavir scoring system attributes a score to the stages of fibrosis on a 0–4 scale as follows (10): F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and few septae; F3 = numerous septae without cirrhosis; F4 = cirrhosis.

Liver biopsy is an invasive and costly procedure, and samples only a small portion of the liver. Thus, it cannot afford a global assessment of hepatic fibrosis, and is subject to sampling variation and inter- and intra-observer error. In addition, liver biopsy is associated with a significant morbidity of 3% and a mortality rate of 0.03% (11). Potential complications include local hematoma, infection, and pain related to the procedure.

SERUM MARKERS

Serum markers to monitor the evolution of liver disease are appealing, because they are non-invasive, and repeated testing at regular intervals is more feasible due to lower cost (12). Panels of blood markers have been weighed against the gold standard of liver biopsy, mostly in patients with chronic hepatitis C or cirrhosis due to viral hepatitis C. A meta-analysis of these studies revealed that serum markers can rule in or rule out fibrosis in approximately 35% of patients (13). However, when looking at patients individually, these markers could not reliably differentiate between the various stages of fibrosis. A more recent study by Sebastiani et al. incorporated three panels of serum markers to devise an algorithmic approach that improved diagnostic accuracy (14). The three panels evaluated were the APRI (aspartate transaminase to platelet ratio index), the Forns' index (platelets, gamma-glutamyltranspeptidase, cholesterol) and the Fibrotest (GGT, haptoglobin, bilirubin, apolipoprotein A, alpha-2-macroglobulin). An algorithm consisting of the APRI followed by the Fibrotest boosted the diagnostic accuracy of fibrosis to above 90%. This group estimated that use of this algorithm could obviate the need for up to 50% of liver biopsies. However, the individual stages of fibrosis are not distinguishable using this algorithm. Serum markers are just beginning to be used in clinical practice in order to follow patients with hepatitis of viral etiology, as these are not proven in other types of liver disease. The limitation of these serum markers is the possibility of false positives when there is highly active hepatic inflammation.

FIBROSCAN

Fibroscan is an innovative approach to staging hepatic fibrosis based on elastography, which provides rapid measurement of mean hepatic tissue stiffness (15). A probe is employed to transmit a vibration of low frequency and amplitude into the liver. This vibration wave triggers an elastic shear wave, whose velocity through the liver is directly proportional to tissue stiffness measured in kilopascals (kPa). The Fibroscan technique can measure liver stiffness of a volume that is 100 times greater in size than a standard liver biopsy, thus giving a better overall picture of fibrosis in hepatic parenchyma. Validation studies have reported excellent intra- and inter-operator correlation, and have shown the various degrees of liver stiffness to reliably correlate with the stages of fibrosis (15,16). Sensitivity of the Fibroscan technique ranged from 79 to 95%, and specificity from 78 to 95%, compared to the gold standard of liver biopsy. The limitations of this technique are attenuation of elastic waves in fluid or adipose tissue, which would impair assessment of fibrosis in patients with ascites or morbid obesity. The problem of obesity is especially rampant in North American society, with 30% of the population being overweight or obese.

Use of Fibroscan in conjunction with serum markers of fibrosis (Fibrotest) further enhances accuracy in the staging of fibrosis as reported by Castera et al (17). In this study, there was concordance in staging between Fibroscan and Fibrotest in 70-80% of patients. Combined use of the Fibroscan and Fibrotest assay in these instances resulted in concordance with liver biopsy as follows: 84% for significant fibrosis ($F \geq 2$), 95% for severe fibrosis ($F \geq 3$), and 94% for cirrhosis ($F = 4$). Fibroscan is, however, an expensive instrument with an approximate cost of US$80 000. It is currently in the process of being approved for use in Canada.

EMERGING THERAPIES AGAINST HEPATIC FIBROSIS

Patients with active ongoing hepatic inflammation are often not seen until fibrosis has occurred, as they are asymptomatic most of the time. However, if tests were performed to catch these patients early on the basis of increased liver enzymes, there is the potential to curtail or even reverse hepatic fibrosis. Some agents that stem the development of hepatic fibrosis are already in use. Agents that can reverse fibrosis, however, are only at the investigational stage. Targetting various aspects of fibrotic process would likely have a tremendous impact on the morbidity and mortality in these patients.

The removal of injurious stimuli is a strategy already in use, in the form of antiviral therapy for hepatitis, copper chelation for Wilson's disease, phlebotomy for hemochromatosis, and discontinuation of hepatotoxic medication (18).

Corticosteroids have been used successfully to suppress hepatic inflammation in autoimmune and

alcoholic hepatitis (19). Ursodeoxycholic acid has been proven to increase survival in PBC patients by binding bile acids, and thus also decreasing hepatic inflammation (20). Neutralizing inflammatory cytokines with specific receptor antagonists (TNF-alpha, IL-1 receptor antagonists) and prostaglandin E have been tested in murine models, but not yet in humans (21). Whether colchicine, an anti-mitotic agent, has any antifibrotic activity is still controversial, due to conflicting study results (22,23).

Another attractive target in curtailing hepatic fibrosis is the downregulation of hepatic stellate cell activation. Interferon gamma is already used in combination with ribavirin for therapy of hepatitis C infection. It is postulated that the antifibrotic effects of the interferons may be partially related to downregulation of stellate cell activation. This mechanism could explain the improvement in fibrosis described in patients with viral hepatitis C who do not have a virologic response to interferon alpha (24). Trials of antioxidants (n-acetylcysteine, alpha-tocopherol) are currently underway in humans. Angiotensin II receptors are upregulated in stellate cell activation, thus angiotensin converting enzyme inhibitors and angiotensin receptor blockers have demonstrated antifibrotic activity in vitro and in animals. This has yet to be replicated in humans (25). Hepatic growth factor antagonist and collagen synthesis inhibitors (TGF-B antagonist) have shown promise in animal trials as well (26).

Promoting matrix degradation through matrix metalloproteinases is an antifibrotic strategy shown to be beneficial in a murine model (27). Specific apoptosis of hepatic stellate cells is another interesting theoretical idea, but has not yet been investigated (28).

CONCLUSION

The future of hepatic fibrosis detection and treatment appears bright with novel markers and investigational agents on the horizon. Optimizing the accuracy of non-invasive testing via serum assays and elastography is essential to allowing wider implementation of these tests in clinical practice. When optimized, these tests will be able to provide an 'integrated' readout of liver activity, rather than the limited sampling of a conventional liver biopsy. Early detection of fibrosis, and regular monitoring of fibrosis, would allow for initiation of anti-fibrotic therapies capable of halting and even reversing this process. This would in turn prevent progression to hepatic cirrhosis, and the morbidity and mortality this condition entails. The development of these various early fibrosis detection techniques bodes well for the future care of patients with liver disease.

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REVIEW ARTICLE

The significance of nanoparticles in particle-induced pulmonary fibrosis

James D Byrne*, John A Baugh

ABSTRACT: Exposure to airborne nanoparticles contributes to many chronic pulmonary diseases. Nanoparticles, classified as anthropogenic and natural particles, and fibers of diameters less than 100 nm, have unrestricted access to most areas of the lung due to their size. Size relates to the deposition efficiency of the particle, with particles in the nano-range having the highest efficiencies. The deposition of nanoparticles in the lung can lead to chronic inflammation, epithelial injury, and further to pulmonary fibrosis. Cases of particle-induced pulmonary fibrosis, namely pneumoconiosis, are mostly occupationally influenced, and continue to be documented around the world. The tremendous growth of nanotechnology, however, has spurred fears of increased rates of pulmonary diseases, especially fibrosis. The severity of toxicological consequences warrants further examination of the effects of nanoparticles in humans, possible treatments and increased regulatory measures.

KEYWORDS: Nanoparticles, fibrosis, silicosis, asbestosis, pneumoconiosis, nanotubes

INTRODUCTION

The majority of existing research on particulate causes of pulmonary fibrosis focuses generally on the micron-scale. This review focuses more specifically on nano-scale particles (particles and fibers with diameters less than 0.1 μm), or nanoparticles. In vitro and in vivo studies support that nanoparticles are significant contributors to pulmonary fibrosis, a debilitating condition often leading to death (1). These particles are present in occupational and environmental settings at concentrations dependent upon location, season, and time of day.

Clinical cases of particle-induced pulmonary fibrosis are nearly all occupational in origin. An epidemiological study in Mongolia from 1967-2004 showed that 67.8% of cases involving occupational diseases were diagnosed as dust-induced chronic bronchitis and pneumoconiosis (2). Developing countries continue to be plagued with such cases of pulmonary fibrosis and other chronic pulmonary diseases caused by particles. Recently, China has experienced 10,000 to 15,000 new cases of pneumoconiosis per year, which has increased yearly since 1949. Between 1949 and 2001, China has recorded 569,129 confirmed cases of pneumoconiosis (3). Canada and the U.S. have seen decreasing trends in both diagnosis and mortality rates involving occupational cases of particle-induced pulmonary fibrosis (4). In the U.S., an epidemiological study from 1968-2000 showed that 124,849 deaths were attributed to pneumoconiosis (5). Developed nations experience decreasing trends as a result of improved hygiene conditions in mines, superior dust control, and better use of respiratory protective measures (4). The rapid increase in nanotechnology worldwide has the potential to dramatically increase the exposure of humans to uncharacterized particles and cause an increase in pulmonary disease in many developed areas. For example, engineered nanoparticles, such as carbon nanotubes, have been shown to cause fibrosis in rats (6). The severity of nanoparticle effects warrants further elucidation and increased regulatory measures to protect against human exposure.

EXPOSURE TO AIRBORNE NANOPARTICLES

Exposure to airborne nanoparticles is an unavoidable consequence of the technological advances of combustion engines and engineering and the natural occurrence of dusts, forest fires, and volcanic activity. As the most toxic component of airborne particulate matter, nanoparticles have uncontrolled access to the cells of the airway and even intracellular components

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because of their size (7-9). Central to pulmonary toxicity is nanoparticle deposition in the alveolar spaces of the lung. Nanoparticles have high deposition efficiencies in the lungs of healthy individuals, and even higher efficiencies in individuals with asthma or chronic obstructive pulmonary disease (10, 11).

When inhaled, nanoparticles deposit dispersedly upon the alveolar surface, which likely leads to a scattered chemoattractant signal, resulting in lower recognition and alveolar macrophage responses (12). The deposition of 20 nm particles is 2.7 times greater than 100 nm particles and 4.3 times greater than 200 nm particles (13). Higher deposition efficiencies occur in patients with asthma or chronic obstructive pulmonary disease than in healthy subjects, possibly due to decreased clearance ability (11). Kreyling et al. found that there was less than 25% clearance of 50- and 100-nm particles during the first 24 hours after inhalation (12). The biopersistence of an inhaled particle is an important characteristic dictating the level of inflammation and tissue injury.

Surface Area and Reactivity

The surface area of inhaled nanoparticles favors the formation of free radicals (i.e. superoxide anions or hydroxyl radicals), which drive oxidative stress, an underlying mechanism that promotes inflammatory responses (14, 15). The ratio of surface atoms to total atoms or molecules increases exponentially with decreasing particle size, contributing to the surface reactivity (10). Oberdörster confirmed this by examining a difference in toxicities from nano-sized versus micron-sized titanium dioxide particles of the crystalline type, anatase, when instilled at the same mass dose. The nano-sized particles were more reactive than the micron-sized particles. The data was linearly correlated when the same experiments were performed at the same surface area dose (1).

The lung inflammatory response induced by particles is also dictated by shape, crystallinity, charge, surface modifications, and weathering (10). Many nanoparticles, such as combustion derived nanoparticles, agglomerate readily and move as an aggregate, which decreases particle number, but leaves surface area dosage unaffected. As particles undergo chemical interactions with components of the ambient air pollution cloud, there can be aging of the particles which may change their chemistries (14).

Other constituents of particle clouds also play a large role in pulmonary inflammation and fibrosis. Metals only need to be present in trace quantities to cause inflammatory effects, through the generation of reactive oxygen and nitrogen species (16). Additionally, the capacity of diesel exhaust particles to cause oxidative reactions in vivo has been attributed to their content of metals (17), polyaromatic hydrocarbons (18) and quinones (19). The component responsible for oxidative stress and subsequent pro-inflammatory signaling in diesel exhaust particles is principally the organic fraction (14). The organic fraction contains or can metabolize to components such as quinones, which readily produce reactive oxygen species (19). The surface area of the particle is important in the retention of these constituents, as they remain on or among the airborne particles.

NANOPARTICLE-INDUCED PULMONARY FIBROSIS

A complex set of tissue reactions must occur for the formation and accumulation of fibrous connective tissue that defines pulmonary fibrosis. Traditionally, fibrosis has been viewed as an irreversible process which varies from a restrictive ventilatory defect causing hypoxemia, pulmonary hypertension, and cor pulmonale, to the distortion of lung anatomy inducing bronchiectasis and chronic respiratory infection (20, 21). The pathogenesis of pulmonary fibrosis begins as an inflammatory response to injury when immune cells are excessively or inappropriately activated. These immune cells include macrophages and neutrophils that release toxic mediators, compromising epithelial integrity and promoting tissue injury. The normal repair process involves the recruitment and activation of mesenchymal cells resulting in extracellular matrix deposition, re-epithelialization and restoration of normal lung architecture. In certain patients, however, aberrant tissue remodeling and excessive matrix deposition leads to progressive scarring and fibrosis (22). In the context of particle inhalation it is likely that the inability to clear toxic particles from the lungs via mucociliary clearance or phagocytosis, as well as sustained exposure, may drive an exaggerated inflammatory response that leads to irregular tissue remodeling and fibrosis. Initiation of this cascade may occur due to interactions with alveolar macrophages, epithelial cells, or direct interactions with interstitial fibroblasts.

Nanoparticle exposure activates a number of cytokine/growth factor cascades via an increase in reactive oxygen species. The activation of receptor tyrosine kinases, mitogen-activated protein (MAP) kinases, and transcription factors, such as nuclear factor (NF)-κB and STAT-1, drive transcriptional activation and the expression of genes involved in inflammation and fibrosis (15, 23). Interleukin (IL)-1β and tumor necrosis factor (TNF)-α stimulation increase the expression of pro-fibrotic growth factors and their receptors. TNF-α causes an increase in the production

of transforming growth factor (TGF)-β1, a major stimulator of collagen deposition in fibroblasts (24). IL-1β increases the expression of platelet-derived growth factor (PDGF)-AA and its receptor, PDGF receptor-α, on lung fibroblasts (25). The coordinated secretion of PDGF-AA and PDGF receptor-α attracts fibroblasts from the interstitium and induces proliferation of myofibroblasts. The myofibroblasts form and organize immature collagenous tissue within the lung (15).

The organization of the immature fibrinous tissue with neovascularization, proliferation of myofibroblasts, deposition of increasing amounts of extracellular matrix components and the development of scarring contribute to a loss of tissue function corresponding to the extent of the fibrotic response (26). The removal of the airborne nanoparticle exposure causing lung injury could allow re-epithelialization, dependent upon the state of the basement membrane, collagen and elastic structure of the alveoli. The elimination of immature intra-lumenal collagenous tissue by the fibrinolytic system and apoptosis of the myofibroblasts are important for the re-epithelialization. However, the extent of lung injury may not preserve lung function (27).

The radiographic features of pulmonary fibrosis show patchy ground-glass opacities and numerous centrilobular nodules measuring 2 to 4 mm in diameter. Honeycombing may be seen in advanced fibrotic stages. A progressive decline in diffusion capacity and worsening gas exchange abnormalities with exercise are sensitive indicators of worsening pulmonary fibrosis. Pulmonary function tests show restrictive ventilatory impairment with a reduction in lung volumes, increased elastic recoil and decreased diffusion capacity (28).

CLINICAL CASES OF PARTICLE-INDUCED PULMONARY FIBROSIS

Most cases of particle-induced pulmonary fibrosis are classified as pneumoconioses. Pneumoconiosis, by definition, is an occupational lung disease caused by the inhalation of mineral and metallic particles and nanoparticle dusts. Pneumoconiosis is broken into two forms, fibrotic and nonfibrotic. Fibrotic pneumoconiosis includes silicosis (silica particles), coal worker's pneumoconiosis (washed coal particles), asbestosis (asbestos fibers), berylliosis (beryllium particles), and talcosis (magnesium silicate processing). Nonfibrotic pneumoconioses include siderosis (iron oxide particles), stannosis (tin oxide particles) and baritosis (barium sulfate particles). The most common forms of pneumoconioses are fibrotic, including silicosis, coal worker's pneumoconiosis, and asbestosis (29). In the US, death rates among males in 1968-1981 compared with 1982-2000 have shown a 36% decline in coal worker's pneumoconiosis, 70% decline for silicosis, but a 400% increase in asbestosis (5).

These clinical conditions are not solely influenced by the particle type after which they are named, but by multiple types of particles, varying in size and concentrations. In vivo and in vitro studies suggest that nano-sized particles are the most toxic particle component of particulate clouds, contributing most heavily to fibrogenicity (8, 30). Particle fibroses reviewed here are categorized according to the source of particles, which includes mineral dusts, combustion-derived particles, and engineered nanoparticles. It is important to note that mineral and combustion-derived particle fibroses are occupational diseases mostly prevalent in developing nations. While there have been no documented cases of engineered nanoparticle-induced pulmonary fibrosis in humans, possibly due to exposure levels, exposure to engineered nanoparticles, such as carbon nanotubes, continues to increase as they become more integrated into technology (31, 32). The rest of this review is focused on clinical conditions of particle-induced pulmonary fibrosis, which supports nanoparticles as the most significant particle portion.

MINERAL DUSTS

Mineral dust composition varies by location, and can contain particles of crystalline silica, asbestos, carbon black and other molecules (33). These particles are the most common causes of particle-induced pulmonary fibrosis. For this reason, silicosis and asbestosis are examined in further detail.

Silicosis

Silicosis is caused by the inhalation of crystalline silica particles for extended periods of time. Silica is present in many different crystalline forms that vary in levels of fibrogenicity according to the degree of crystallization. Fibrogenicity increases from the less organized crystal structure of amorphous silica to the more organized crystal structures of quartz, cristobalite, and tridymite (33). As crystallinity plays a role in fibrogenicity, the large surface area per mass of silica nanoparticles allows for a greater production of reactive oxygen species catalyzed by the crystalline surface. The inhalation of silica can also lead to the development of bronchogenic carcinoma (34).

The pathology caused by silica particles involves their phagocytosis by alveolar macrophages. Silica uptake seems to be initiated by MARCO (macrophage receptor with collagenenous structure) as seen in mice by Hamilton et al. (35). Alveolar macrophages are damaged or activated and release cytotoxic oxidant or proteases and inflammatory cytokines such as TNF-α, IL-1 and arachidonic acid metabolites, which provoke

recruitment of inflammatory cells into the alveolar wall and alveolar epithelial surface (22, 36). The generation of oxidants by silica nanoparticles and silica-activated immune cells results in additional macrophage apoptosis, lung damage, inflammation, and cell transformation. The pro-inflammatory cytokines released during inflammation by macrophages and potentially by neutrophils, mast cells and B-lymphocytes participate in the exaggerated deposition of matrix protein and the persistence of transformed cells characterizing silicosis (22). Direct interaction of fibroblasts with silica has also been shown to drive cyclooxygenase-2 and prostaglandin E2 expression, creating a pro-fibrotic cytokine milieu (37). Silicotic nodules caused by silica inhalation consist of fibrotic lesions and are distributed in the upper part of the lungs. The nodule is termed an "onion skin lesion" with collagen fibers concentrically arranged, and dust-laden macrophages surrounding the mature collagen (34, 29). Thin-film computed tomography show numerous bilateral centrilobular nodular ground-glass opacities, multifocal patchy ground-glass opacities and consolidation (29, 38). Figure 1 shows a chest radiograph and CT scan from a male with silicosis who worked in stonecutting for twenty-five years.

Asbestosis

Asbestosis is induced by the inhalation of asbestos fibers. Asbestos is a fibrous silicate mineral used in industry for its heat resistance and tensile strength. The inhalation of asbestos can also lead to the development of other pulmonary diseases, such as benign pleural effusion and plaques, mesothelioma and bronchogenic carcinoma (39).

Deposition of asbestos is based upon its aerodynamic diameter, and the ability of the fiber to align with the airway. The biopersistence and accumulation of asbestos is important in dictating the level of fibrotic response (16). The inhalation of asbestos fibers damages alveolar macrophages and epithelial cells, causing them to release inflammatory mediators and growth factors (38). NF-κB-, protein kinase C- and MAPK-dependent inflammatory pathways are activated as a result. The MAPK ERK1/2 is selectively phosphorylated in lung epithelium after the inhalation of asbestos. The duration of ERK1/2 activation dictates the toxic response to asbestos and related production of reactive oxygen and nitrogen species. ERK1/2 is linked to TNFα and TGF-β1 expression, resulting in inflammation and fibrogenesis (39). Asbestosis appears to be histologically and radiographically similar to idiopathic pulmonary fibrosis with honeycombing being a common feature of late stage asbestosis (29).

COMBUSTION-DERIVED PARTICLES

Combustion-derived nanoparticles cover a large variety of nanoparticles, including diesel exhaust particles, welding-fume particles, fuel oil ash, and coal fly ash (14). These nanoparticles are largely nonfibrogenic, except occupational exposure to coal fly ash, oil fly ash, and welding fume nanoparticles in the cases of boilermakers (40). Diesel exhaust particles have been found to cause fibrotic events in rats as a result of lung overload, but humans are unlikely to ever experience high levels comparable to those issued to experimental rats (14, 41). Combustion-derived nanoparticles may be soluble and release transition metals or organics as their primary pro-inflammatory mechanism. Both transition metals and organics can undergo complex cyclical chemical reactions in the

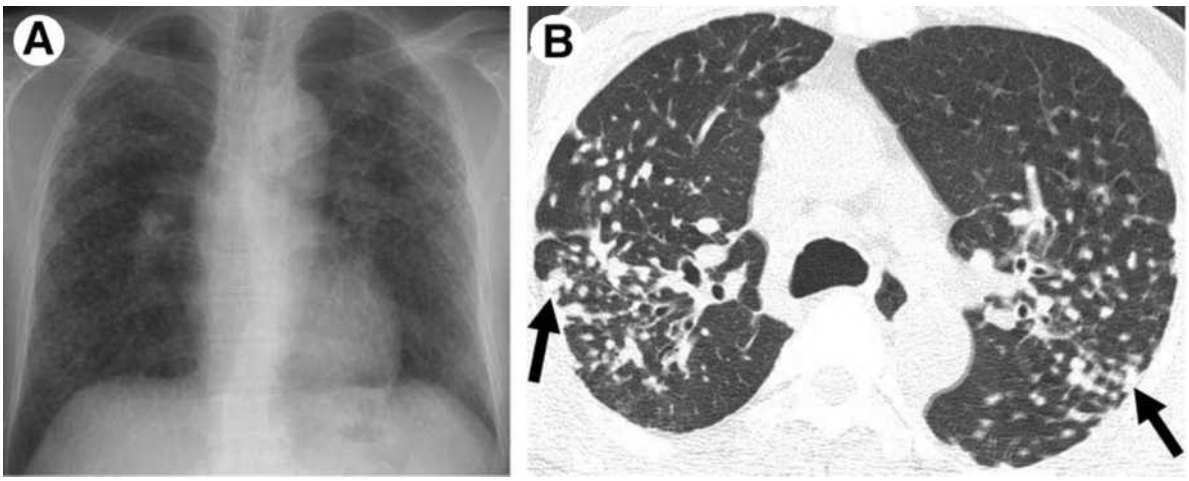

Figure 1: Silicosis in a 56-year-old male who worked in stonecutting for 25 years. (A) Chest radiograph shows multiple variable-sized nodular lesions in both lungs, predominantly in the upper and middle zones. (B) Axial thin-section CT scan (1.0-mm-thick section) obtained at the level of the azygos arch shows multiple small nodules with a perilymphatic (centrilobular plus subpleural) distribution in the upper lobe of both lungs. Note the tendency toward coalescence of the nodules in the lung periphery (arrows). With copyright permission from RSNA and Dr. Kyung Soo Lee (29).

milieu of the lungs that lead to the production of free radicals such as superoxide anion or hydroxyl radical (19). Fibrosis induced by welding fumes and oil fly ash (OFA) are examined in this section.

Welding-Induced Pneumoconiosis

Welding involves the use of electrical currents in excess of 200 amperes and a space-filling metal rod to join two metal objects together. In the process, some of the liquefied metal is aerosolized (42). Most welding materials are alloy mixtures of metals characterized by different steels that may contain iron, manganese, silica, chromium and nickel (43).

Exposure to welding fume nanoparticulate matter in humans is associated with inflammatory cytokine increases in the bronchoalveolar lavage fluid (44). Rats exposed to welding fumes have shown marked pulmonary inflammatory responses and lipid peroxidation indicative of oxidative stress (45). In addition, epithelial cells exposed to welding fumes or the transition metals associated with them exhibited oxidative stress which caused MAPK-dependent NF-κB and AP-1 activation leading to IL-8 upregulation (46). Thus, the soluble transition metals appear to be the primary mechanism of oxidative stress and inflammation (14).

Hull and Abraham examined cases of aluminum-welding particle-induced pneumoconiosis, and found areas of severe dense fibrosis which were interspersed with macrophages containing particles (42). The lung parenchyma display focally dense fibrosis, more severe in the upper lobes, with peripheral honeycombing sparing the lung bases. Figure 2 shows dense fibrotic tissue with alveolar macrophages encapsulating welding particles from an aluminum welder (42).

Oil Fly Ash

Human exposure to oil fly ash (OFA), the inorganic residue from burning carbonaceous materials, occurs where workers, specifically boilermakers, are engaged in the maintenance of oil-fired boilers. Boilermakers that are exposed to OFA have shown dose-dependent decreases in pulmonary function caused by pulmonary inflammation (47).

In these cases of exposure to OFA, the most toxic component appears to be the vanadium pentoxide on the surface of the particle or among the particles. Vanadium pentoxide, a transition metal derived from the burning of petrochemicals, caused the rapid onset of fibrosis in rats (48). In vivo studies by Bonner et al. have shown fibrotic responses through the intratracheal instillation of vanadium pentoxide (48-49). Vanadium compounds

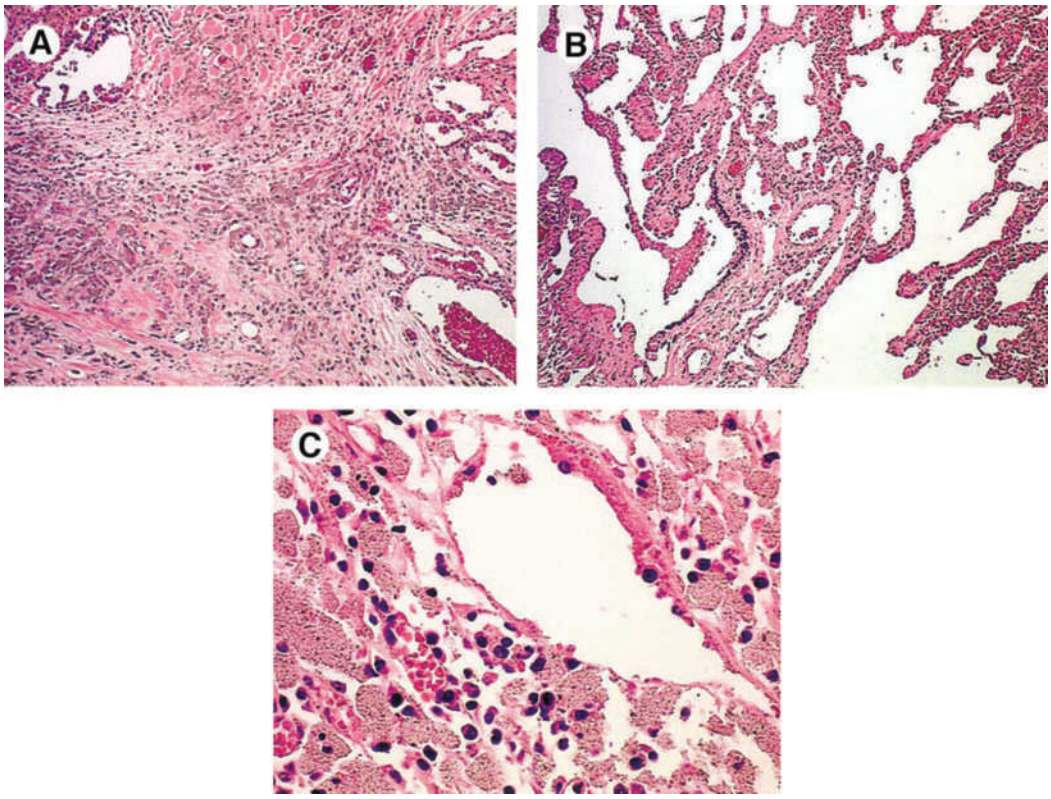

Figure 2: Case 1, LM: (A) Dense fibrotic area of the lung with many aluminum-containing macrophages. (Original magnification x 10.) (B) Lung parenchyma showing peribronchiolar and interstitial aluminum-containing macrophages. (Original magnification x 10.). (C) Aluminum-containing macrophages in lymph node. (Original magnification x 180.) (42). With copyright permission from Elsevier and Dr. Jerrold Abraham.

activate many intracellular signaling pathways via the generation of hydrogen peroxide and many other reactive oxygen species (50). The fibrogenicity of the vanadium pentoxide relates to particle size, as the extent of the surface area is indicative of the chemical carrying nature of the particle.

ENGINEERED NANOPARTICLES

Engineered nanoparticles are particles manufactured to increase surface area and conductivity for materials or to act as delivery agents. These nanoparticles are made from a variety of materials including oxides, metals, carbon, polymers and lipids. Many polymer and lipid nanoparticles have non-reactive surfaces; however, many oxide, metal, and carbon particles are quite reactive (51). The most relevant fibrogenic nanoparticles are carbon nanotubes, which have been compared to asbestos in terms of toxicity. There have been no documented human cases of fibrosis from carbon nanotubes, but exposure to carbon nanotubes is on a steady rise because of their huge potential in industrial applications (6). As the manufacturing costs decrease, it has been predicted that hundreds or thousands of tons of carbon nanotubes could be produced in five to ten years (52).

Carbon Nanotube-induced Fibrosis

Carbon nanotubes have very unique electrical, mechanical and thermal properties, which allow them to have potential application in the electronics, computer and aerospace industries. Carbon nanotubes are found to deposit in the alveolar ducts by aligning their long dimension to the direction of the airstream. Nanotubes longer than 20 μm can cause the same types of pathology as asbestos and other fibers. Carbon nanotubes have a larger surface area than nanoparticles, thus having a higher proclivity to cause more effects. In addition, they have a tendency to get contaminated with metals (53).

Muller et al. were able to show the occurrence of fibrosis in rats after the instillation of multi-wall carbon nanotubes, ground and intact. They ground up carbon nanotubes, and induced a higher degree of inflammation than with intact multi-wall carbon nanotubes. The assessment of lung hydroxyproline (OH-proline) and soluble type I collagen showed a dose-dependent increase in extracellular matrix expression. Histopathologically, collagen-rich granulomas formed in the bronchi, which partially or completely blocked the bronchial lumen. The granulomas reepithelialized, organized around the nanotubes and formed multinuclear giant cells as well as macrophages and other mononuclear inflammatory cells (6). Further carbon nanotube studies showed that carbon nanotubes caused significant increases in lung PDGF mRNA (30). All documented in vivo studies of carbon nanotubes have been by instillation, rather than inhalation. Thus, the fibrogenic effects of the nanotubes could be a result of the complexes formed during the instillation and may not represent a respirable cloud (53).

Lam et al. showed that carbon nanotubes produce profibrogenic lesions similar to those of toxic silica particles (32). Human pulmonary fibrosis caused by inhalation of carbon nanotubes may be very similar to silicosis cases. Overall, in vivo studies point to the induction of fibrosis in humans. Limiting exposure is essential in containing the occurrence of pulmonary fibrosis.

SUMMARY AND FUTURE OUTLOOK

We review particle-induced pulmonary fibrosis and support that nanoparticles are a significant, if not the most significant, particle component contributing to pulmonary fibrosis. The two main factors that contribute most heavily to particle-induced lung diseases are particle surface area and the reactivity or intrinsic toxicity of that surface. In addition, the size of nanoparticles allows them to get deposited in lungs at a greater efficiency than particles of larger sizes, yielding a higher biopersistency.

The ability to produce free radicals is important in the induction of inflammation and fibrosis. The inhalation of nanoparticles can induce fibrosis, based upon the time of exposure, exposure concentration, and ability to produce free radicals. By providing insight into clinical and experimental cases of particle-induced pulmonary fibrosis, we hope to have shown the danger of nanoparticle inhalation.

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REVIEW ARTICLE

The pathophysiology of osteoporotic hip fracture

David Metcalfe*

ABSTRACT: Osteoporotic hip fractures have a profound impact on the physical health and psychosocial wellbeing of patients. In addition, osteoporosis has considerable economic implications and is projected to become an increasing burden on developed economies over the coming decades. Nevertheless, the risk factors for both osteoporosis and hip fracture are both well understood and preventable, often with only minor lifestyle changes. This narrative review explores the pathological process underlying osteoporosis and considers how each of the major risk factors contributes to the pathology of this disease. It is hoped that a greater understanding of individual risk factors will result in renewed efforts to promote increased bone density before patients present with hip fracture.

INTRODUCTION

Osteoporosis is a generalised skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone which leads to fragility and risk of fracture (1). The World Health Organisation (WHO) criteria for osteoporosis are met when bone mineral density (BMD) falls 2.5 standard deviations below the mean found in young adult women (2). Reduced BMD may be caused by a range of factors such as endocrine disturbances, dietary deficiencies, or side effects of pharmacological interventions (3). One consequence of osteoporosis is hip fracture which may also be attributed to extra-skeletal factors such as frailty, failing eyesight, and a tendency to fall (4). The risk factors associated with reduced BMD are described in Table 1.

Although osteoporosis commonly affects the hip and lumbar vertebrae, it may also be found at other sites such as the radius, tibia and ribs (5). One consequence of reduced BMD is that osteoporosis is strongly associated with low trauma fracture. Indeed, up to 51% of fractures in women and 24% of those in men are attributable to osteoporosis (6). In the USA, as many as 1.5 million osteoporotic fractures are recorded annually, including 250,000 hip fractures (7). As a consequence, estimates of the economic burden of osteoporosis in the USA have climbed as high as $17 billion per annum (8). Furthermore, in Switzerland, osteoporosis accounts for more hospital bed occupancy than myocardial infarction, stroke or breast cancer (9).

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In addition to the economic consequences, hip fracture in particular is associated with profound disability and psychosocial sequelae. For example, 50% of hip fracture patients lose the ability to walk without assistance and 25% require domiciliary care thereafter. Furthermore, the mortality rate over the 6 months following hip fracture may be as high as 30% (10).

The causes of osteoporosis and hip fracture are, however, well characterised and offer multiple opportunities both for prevention and disease management. This narrative review considers the pathophysiology of osteoporosis with particular reference to fragility fractures of the hip.

ANATOMY OF THE HIP

The hip is a multiaxial ball-and-socket synovial joint in which the rounded head of the femur articulates with the concave acetabulum of the pelvis. A fibrocartilaginous lip known as the acetabular labrum increases the depth of the acetabulum and grips the femur in position (11). Both joint faces are covered with a dense lubricative layer of articular hyaline cartilage except for the fovea which holds the intracapsular ligament of the femoral head, or ligamentum teres femoris (12). The primary function of this joint is to sustain body weight in both static and dynamic postures.

Although the hip joint is only surpassed in flexibility by the glenohumeral (shoulder) joint, some range of mobility has been sacrificed in favour of further stability (13). This is probably because the weight of the upper body is entirely supported by this joint on standing (12). One consequence of this stability is that the hip joint of a healthy patient should not fracture in

General factors	Female sex Caucasian or Asian ethnicity Advanced age Early menopause Slender habitus Lack of exercise Smoking Family history Excess alcohol Poor nutrition (low calcium or high protein)
Drug products	Corticosteroids Heparin Cyclosporin Cytotoxic drugs
Diseases	
• Endocrine disease	Cushing's syndrome Hyperparathyroidism Hypogonadism Acromegaly Type I diabetes mellitus
• Joint disease	Rheumatoid arthritis
• Other diseases	Chronic renal failure Chronic liver disease Mastocytosis Anorexia nervosa Inflammatory bowel disease Coeliac disease

Table 1: Risk factors predisposing to low BMD (20).

the absence of high energy trauma. Indeed, the femoral head is classically fractured only in high impact road traffic accidents in which the dash board strikes the knee to rupture the joint capsule (14).

However, the femoral head is supported by a relatively thin structure known as the femoral neck which is more prone to fracture than the joint itself is to dislocation (13). The femoral neck is particularly vulnerable in patients suffering from bone disorders such as Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfecta and metabolic bone disease. Femoral neck fractures are also frequently associated with primary tumours of the bone, cancer metastases and infection of the bone (15). However, the majority of patients presenting with femoral neck fractures are those with osteoporosis (16). Although osteoporosis may be caused by multiple factors, all of these are thought to act by subverting the normal physiology of healthy bone.

PHYSIOLOGY OF BONE

Mammalian bones may be classified as long, short, flat, irregular or sesamoid. The long bones, which include the femurs, are a major component of the human skeleton and fulfil a number of different functions. As well as protecting soft tissues and determining posture, long bones also provide a site for haematopoiesis. Furthermore, they are important sites of mineral storage, particularly of calcium and phosphate (17). The multiple functions of bone require a dynamic structure to cope with mineral storage and adaptation to environmental stress. For these reasons, osseous tissue is continually broken down and re-deposited in a process known as 'remodelling'.

Bone remodelling

In healthy adult bone, matrix exists in a dynamic equilibrium of deposition by osteoblasts and resorption by osteoclasts. The latter typically aggregate together and eliminate bone over a period of ~3 weeks, leaving a tunnel of between 0.2mm and 1mm. Osteoblasts then act to deposit new matrix and these cells may be found acting on 4% of the surface of adult human bone at any time (18). New bone is deposited in concentric circles known as lamellae and, in this way, up to 10% of bone is re-deposited in the adult skeleton each year (19). The purposes of continual bone remodelling are twofold:

1. Adjustment of bone shape and thickness in response to environmental and musculoskeletal stresses.
2. Replenishment of old bone which is weaker than newly deposited matrix (19).

AETIOLOGY OF OSTEOPOROSIS

A number of risk factors for reduced BMD exert their effect through subversion of the remodelling process. Indeed, osteoporosis may be seen simply as a failure of bone deposition to match the rate of resorption (19). Many of these risk factors were summarised earlier in Table 1. Although a number affect patients in adulthood, many other risk factors exert their influence during adolescence or earlier in the lifespan when bone deposition initially takes place (19).

Alcohol and tobacco consumption

Many studies have suggested an association between excess alcohol consumption and fragility fractures. One large cohort study has, for example, shown that heavy alcohol consumption (>207ml per week) accompanies an increased risk of fracture in men (RR=1.26) and women (RR=1.54) (21). This relationship is not simply a result of falls under the influence of alcohol as histological changes have also been noted in the bone structure of alcohol abusers (22). However, these may be partially explained by confounding factors associated with alcoholism such as liver damage, hypogonadism and nutritional deficiencies. Nevertheless, alcohol is known to increase parathyroid hormone (PTH) and to reduce concentrations of vitamin D metabolites required for efficient calcium absorption (23). Furthermore, alcohol suppresses bone mineralization by osteoblasts. The consequences of

these effects are calcium excretion in the urine (hypercalciuria), lowered serum calcium (hypocalcaemia) and reduced BMD (23). Despite these risks, a mounting body of evidence suggests that moderate alcohol intake may increase BMD, possibly by increasing oestrogen titres (22).

Individuals who smoke tobacco are at increased risk of developing osteoporosis, even when alcohol is eliminated as a confounding factor. Although the precise mechanism is not understood, there remains a clear dose-dependent relationship between smoking and reduced BMD (24).

High salt diet

Additional dietary risk factors include high salt and high protein diets. Although excessive salt consumption (>9g/day) is not itself a cause of osteoporosis (25), it is known to reduce BMD by increasing renal calcium excretion (26). Indeed, every 100mmol of ingested sodium is thought to deplete the body of around 1mmol of calcium (27). Protein also increases the level of renal calcium excretion. One longitudinal study has, for example, found that high dietary protein causes hypercalciuria and reduced BMD in the elderly (28). Indeed, increasing dietary protein ingestion from 40g to 80g leads to the excretion of an additional 1mmol calcium each day (27). Low protein diets have, however, also been associated with fracture, although this apparent relationship may be explained by confounding factors such as malnutrition and slender habitus (28).

Dietary deficiencies and anorexia nervosa

Poor nutrition is also strongly associated with reduced BMD. According to one meta-analysis of 20 studies, the increased calcium requirement and reduced absorption at menopause may be negated by calcium supplementation (27). Other nutritional factors also affect calcium homeostasis. For example, vitamin D is required for efficient absorption of calcium and one meta-analysis has shown that calcium and vitamin D are more effective than calcium alone in elevating BMD (29). Vitamin D deficiencies, then, are associated with calcium malabsorption, reduced BMD and increased risk of hip fracture (27). As sunlight is a necessary component of vitamin D synthesis, populations exposed less frequently to the sun are at increased risk. Such populations include women dressed according to Shariah law and the homebound elderly. One study has shown that 38% of nursing home residents in the USA had serum levels of 25-hydroxyvitamin D (25-OHD) below 25nM, compared with a normal range of 25-137nM (30). Similarly, the prevalence of vitamin D deficiency and high bone turnover in a cohort of Muslim women living in Australia was found to be 68% and 38.6% respectively (31).

Vitamin K, obtained primarily from leafy green vegetables, is another agent that protects bone matrix. It fulfils this function primarily through facilitating the carboxylation of glutamyl residues on bone proteins such as osteocalcin. One prospective study of 72,237 women, for example, found that those with a low vitamin K intake were significantly more likely to suffer a low trauma hip fracture (32).

These dietary deficiencies, as well as hormonal changes secondary to cachexia, are responsible for the reduced BMD observed in patients with anorexia nervosa. Nutritional rehabilitation can increase the BMD of women with anorexia nervosa beyond that achieved with administration of oestrogen alone (33). Slender habitus is, however, an independent risk factor for osteoporosis with both total fat mass and total lean mass exerting a protective effect on bone in postmenopausal women (34).

Glucocorticoid administration

Glucocorticoids are a class of steroid hormones that bind the intracellular cortisol receptor. They are primarily used for their anti-inflammatory properties in respiratory, musculoskeletal and cutaneous diseases. Indeed, around 0.9% of people on the United Kingdom General Practice Research Database are prescribed glucocorticoids at any one time (35). Glucocorticoids are, however, associated with greatly reduced BMD. They are the most frequent cause of secondary osteoporosis and as many as 50% of patients receiving long-term glucocorticoid therapy sustain a fragility fracture(36). In particular, the relative risk of hip fracture in patients receiving a daily glucocorticoid dose of ≥30mg is 3.13 (95% CI = 1.49-6.59) (37).

These drugs exert their osteoporotic effects through a number of mechanisms. For example, they impair the replication and differentiation of osteoblasts, as well as induce apoptosis in mature osteoblasts (36). Glucocorticoids also downregulate genes encoding matrix proteins such as collagen and osteocalcin(38). Finally, glucocorticoids are associated with reduced intestinal calcium absorption as a result of down-regulating the gene encoding TRPV6, a Ca2+ channel normally expressed in duodenal epithelium (39). Although vitamin D supplementation given alongside glucocorticoids can negate the damage to bone, awareness of glucocorticoid-induced osteoporosis remains low among primary and secondary care physicians (40).

Female sex

Women account for over 80% of osteoporosis

diagnoses (41). Female sex is a risk factor for low BMD both because of the reduced size and cortical thickness characteristic of female bones and the decline in oestrogen titres at menopause (42). Oestrogen has a protective effect on bone, primarily by blocking osteoclast activity. It achieves this through the inhibition of a number of cytokines, including IL-1 and TNF, which otherwise activate mature osteoclasts (43). The bone-sparing properties of oestrogen explain why early menopause predisposes to low BMD and underlies the rationale for using hormone replacement therapy (HRT) to avert osteoporosis. Indeed, postmenopausal oestrogen deficiency is the most significant non-genetic factor in the aetiology of osteoporosis (25).

Pregnancy has, however, also been associated with osteoporosis, particularly with vertebral fragility fractures in the third trimester (44). Nevertheless, long-term studies of postpartum women using dual-energy X-ray absorptiometry (DEXA) have found that reduced BMD during pregnancy and lactation is usually only a temporary phenomenon (45). Although cases of osteoporotic hip fracture have been reported during pregnancy(46), the extent of this relationship has yet to be determined.

Although predominantly a disease of older women, men do suffer from osteoporosis. In Croatia, as many as 5.8% of men over 50 qualify as osteoporotic on analysis of the calcaneus using a quantitative ultrasound (QUS) index (47). Men in the United States account for up to 30% of hip fracture diagnoses (48). Interestingly, male hip fracture patients experience larger rates of morbidity and mortality than their female counterparts (49). Osteoporosis risk factors for men are specifically glucocorticoid or anticonvulsant therapy, testosterone or oestrogen deficiency, smoking, and alcohol consumption (50). In particular, out of the 6.5 million American men projected to suffer from symptomatic androgen deficiency in 2025, 650,000 are expected to suffer a fragility fracture as a consequence (51). Furthermore, many men suffer from idiopathic osteoporosis which can occur at any age (42).

Advanced age

Bone mineral deposition accelerates during childhood and adolescence but trabecular bone loss begins early in midlife and accelerates with increasing age (42). Although menopause accounts for much of the association between age and osteoporosis, bone ageing occurs even before the menopause in many women (52). The actual aetiology of age-related bone loss is unknown, although it is understood to involve an imbalance in bone remodelling. Possible explanations include reduced osteoblast lifespan, increased osteoclast lifespan, abnormal osteocyte signalling or a physiological response to inactivity in old age (53). The efficiency of calcium absorption in the duodenum is also known to decline with age (19).

EXTRA-SKELETAL RISK FACTORS FOR HIP FRACTURE

Although reduced BMD in osteoporosis elevates fracture risk, fracture itself may also be attributed to falling, often from standing height. Table 2 summarises the most significant extra-skeletal risk factors which may lead to falling and subsequent fracture. Falls prevention services have now been implemented by a number of countries and have had some success in reducing the incidence of hip fractures among elderly populations (54).

HEALTH PROMOTION

Health promotion strategies primarily aim to eliminate modifiable risk factors. As osteoporosis screening is not commonplace, these strategies are often targeted at populations considered to be ‘at risk’. Weight bearing exercise is, for example, recommended for elderly community-dwelling people (57). Non-pharmacological interventions include exercise, redress of dietary deficiencies and falls prevention. These health promotion strategies are also an extremely important aspect of fragility fracture management.

Non-pharmacological interventions may be used both as preventative measures and as management strategies following hip fracture. Exercise and dietary intake are important considerations throughout the lifespan as skeletal strength in old age is largely determined by mineral deposition in childhood and adolescence (19).

Exercise

A number of systematic reviews have concluded that weight bearing exercise can increase BMD in both healthy and osteoporotic women (58). In light of this evidence, resistance and strength training are now

Intrinsic Factors	Balance, gait or mobility problems Medications (e.g. sedatives, anti-hypertensive drugs) Visual impairment Impaired cognition Postural hypotension Alcohol
Environmental factors	Poor lighting Steep stairs Carpets or rugs Slippery floors Badly fitting footwear Inaccessible cupboards or windows

Table 2: Extra-skeletal risk factors for hip fracture (55, 56).

commonly found in rehabilitation physiotherapy programmes for osteoporotic fracture patients (59). As exercise should be directed specifically at the site of bone ageing, hip fracture patients are often encouraged to walk with the aid of a stick or frame (59).

Although BMD gains as a result of exercise are reversible, strengthened muscles provide additional support to vulnerable regions such as the femoral neck (19). Furthermore, moderate exercise during childhood is associated with a 10% increase in BMD at the hip which may reduce the risk of fracture in old age (60).

Calcium and vitamin D

Dietary calcium is as effective as pharmacological treatment in maintaining bone health (61). Indeed, one meta-analysis has found that 1000mg dietary calcium a day can reduce fracture risk by 24% (62). Furthermore, dietary calcium is associated with higher oestrogen titres and BMD than is calcium supplementation (63). Supplementation is, however, a useful and economical device for patients unwilling or unable to ingest adequate quantities of dietary calcium. Nevertheless, excess calcium (>1500mg/day) has been associated with advanced prostate cancer in men and kidney stones in those with renal insufficiency (64).

Elderly patients may also be administered 400-800 IU vitamin D daily, in addition to the 700-800mg calcium that is currently recommended (65). Vitamin D and calcium in combination are more effective than calcium supplementation alone as the former is a vital component of calcium absorption (29). Furthermore, vitamin D supplementation is known to increase both parathyroid hormone (PTH) concentrations and BMD, particularly at the femoral neck (19).

Falls prevention

Although there is little to gain from providing falls advice to healthy older people, those who are frail or osteoporotic are known to benefit from referral to a falls prevention service (66).

The most successful falls services are Multifactorial Fall Prevention Programmes (MFPPs). Indeed, there is little evidence in favour of education or environment modification programmes in isolation (67). MFPP teams typically include a consultant geriatrician in addition to allied health care workers such as physiotherapists, nurses, occupational therapists, chiropodists, pharmacists and social workers (64). The programme itself includes a strong element of assessment with each patient treated as an individual and a falls prevention strategy targeted at each of their particular risk factors. There are, however, a number of problems related to the referral of patients to falls services. For example, a high number of referred patients are false positives and may never have been at increased risk of falling (4) A number of systematic reviews have, however, shown that falls interventions can reduce the rate of fracture in the elderly (67).

In addition to falls prevention, patients may use mechanical protection such as hip protectors. Although some trials have shown these to be ineffective, others with longer follow-up times have implied a reduced hip fracture risk (68). One systematic review of seven randomised controlled trials (RCTs) found that hip protectors reduce hip fracture risk by up to 66% (69). Hip protectors are, however, affected by poor compliance, with less than a third of patients using them regularly (70). It is furthermore unclear whether hip protectors are cost-effective (71). For this reason, their use is limited.

CONCLUSION

Although a number of different factors can contribute to osteoporosis, most of these reduce BMD by interfering with the bone remodelling process. Furthermore, many of the risk factors for osteoporosis and hip fracture identified in this review are preventable, particularly if challenged early in the lifespan. For example, exercise and dietary intake are important considerations at an early age, as skeletal strength in old age is largely determined by mineral deposition in childhood and adolescence (19). A greater understanding of the pathophysiology of osteoporosis is likely to inform health promotion strategies aimed both at primary and secondary prevention of this disease. Furthermore, awareness of factors predisposing to falls may help reduce the incidence of hip fracture among those elderly persons already suffering from osteoporosis.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Blood substitutes- the polyheme trials

Sameer S. Apte*

PROLOGUE: A HYPOTHETICAL CASE

A 35 year old female, victim of a motor vehicle accident, sustained life threatening injuries leading to hemorrhagic shock. When paramedics arrived at the scene the patient was unconscious. Due to acute blood loss, the patient's blood pressure and oxygen saturation were critically low, leaving only a short therapeutic window to save the patient. The paramedics were unsure whether the current standard of care, an infusion of saline, would be adequate to sustain the patient's life until the nearest hospital could be reached. These paramedics, however, have been instructed to enroll hemorrhagic shock victims in a phase III clinical trial to test the efficacy and safety of an artificial oxygen carrying fluid or "blood substitute". Like saline, the blood substitute would increase the patient's blood pressure. In addition, it could also help supply tissues with much needed oxygen, potentially reducing the chance of mortality.

Because the patient is unconscious, however, the paramedics are placed at the center of an ethical dilemma. If the injuries are sufficiently severe, infusion of the experimental fluid may maintain the patient's vitals long enough to be safely transported to a trauma center. The patient, however, is incapacitated, so there is no feasible way to obtain proper informed consent.

Polyheme®, a blood substitute, has completed a pivotal phase III clinical trial in which the ethical dilemma exemplified in this hypothetical situation was commonplace (1). Because this clinical trial examines a new emergency therapy, the Food and Drug Administration (FDA) invoked Title 21, Section 50.24, Subpart B of the Code of Federal Regulations in order to grant the creators of Polyheme, Northfield laboratories Inc. (Illinois, USA), an exemption from acquiring informed consent (2-5).

The waiver of informed consent has caused the clinical trial itself to become the center of an intense ethical debate (1, 6-15). Opponents say that Northfield Laboratories has inappropriately influenced regulatory decisions and abused the bureaucratic system in order to gain approval for a questionable experimental protocol (7, 10, 13). Conversely, proponents argue that prolonged suspension of informed consent is a necessity for effective characterization of safety and efficacy of prospective emergency therapies (6, 12, 14). This putative necessity is hinged upon the fact that the majority of patients targeted by new emergency therapies are incapacitated at the time of enrollment (2-4, 16). What is not debated is that the completion of the pivotal phase III clinical trial for Polyheme is surrounded by a cloud of ethical tension…

THE ORIGIN OF BLOOD TRANSFUSIONS & ARTIFICIAL BLOOD

In 1909, the successful characterization of the "ABO" and "Rhesus" blood type antigens on the surface of the red blood cell (RBC) allowed clinicians to begin transfusing trauma patients with whole allogeneic blood (17, 18). Since then, allogeneic blood transfusions have become ubiquitous in clinical medicine (19, 20). Interestingly, even though blood transfusions are the gold standard of care, the efficacy and safety of allogeneic red cell therapy has never been rigorously tested via the clinical trial process (20-22). Indeed, the indications for treatment are largely based on common medical practice, tradition, and expert advice (20-22). Thus, comparing the safety and efficacy of a blood substitute to the standard of care may prove to be difficult.

The most serious motivation for the development of a blood substitute is the worldwide shortage of safe and viable allogeneic donor blood (7). A recent report on blood donations found that during 2001, 12.7% of hospitals reported a cancellation of surgeries due to donor blood shortage and 18.9% reported a shortage of blood for non-surgical purposes (19). In addition, the stress on the donated blood supply is projected to increase in the coming years (23).

In spite of many research initiatives, blood substitute investigations are not yet focused on providing a long

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term alternative for allogeneic whole blood. The acute conditions currently targeted by blood substitutes include hemorrhagic shock or ischemic stroke (24, 25). Because these pathophysiologies are encountered primarily in emergency situations (26, 27), clinical applications of blood substitutes aim only to prolong patient survival until allogeneic blood transfusions become available (27-30).

Outside of the hospital, long-term storage of allogeneic blood is impractical and donor blood type cannot be cross-matched to the recipient (7). Thus, paramedics are restricted to saline, a volume expander, as the standard treatment for hemorrhagic shock (11, 12). Like saline, blood substitutes replenish lost blood volume, do not carry blood type antigens, and are stable for long periods of time at room temperature (31-33). In addition, blood substitutes can facilitate oxygen delivery to ischemic tissues, highlighting an important advantage over the use of saline(34).

In the hospital, in spite of enhanced screening methods for blood-borne illnesses, it is still impossible to be certain that allogeneic transfusions are free of pathogens (6, 30, 35). For example, during the remission periods of retroviral life cycles, viral particles cannot be detected (36). Many serious infections including HIV, hepatitis B & C, malaria, vCJD and cytomegalovirus are still transmitted by transfusions (20, 36). Blood substitutes avoid this risk by undergoing pasteurization, ultrafiltration or other sterilization techniques (32, 36-39).

Lastly, a potential market niche for blood substitutes is the population of patients that refuse allogeneic blood transfusion due to religious beliefs (34, 40). For a blood substitute to be suitable for those with special religious needs, no part can be derived from an animal or human source (21, 28). Compassionate use of Polyheme has already been clinically implemented in cases where allogeneic blood transfusions are refused (41).

The potential for blood substitutes to address the problems with current therapies has been recognized. To date, investigation of blood substitutes has fostered over eighteen clinical trials resulting in granted licensures in multiple foreign countries (26, 27, 33, 37, 42, 43).

AN OVERVIEW OF HEMOGLOBIN-BASED OXYGEN CARRIERS

The founder of the field of blood substitutes is Dr. Thomas Chang of McGill University, who in the late 1950s, encapsulated hemoglobin molecules in a polyvinyl chloride (PVC) membrane (44). Since then, two major categories of blood substitutes have arisen: perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOCs). PFCs are chemically inert organic fluids with the ability to dissolve 20 times as much oxygen as plasma (38, 39, 45). HBOCs, like Polyheme, are solutions of modified hemoglobin in plasma-like fluids. In addition to a reduced side-effect profile, HBOCs deliver oxygen to tissues through facilitated diffusion (via hemoglobin) instead of passive diffusion (27, 46). Thus, HBOCs have proven more efficacious than PFCs in clinical settings (34, 47).

Because extracellular hemoglobin degrades into nephrotoxic dimers, initial attempts to use free-floating or “stroma-free” hemoglobin (SFHb) have failed (46). In addition, because hemoglobin extravasates into endothelial cells and binds the vasodilator nitric oxide, it is a vasoconstrictor (48). To alleviate these problems, various methods to modify hemoglobin including cross-linking, conjugation, and polymerization have been investigated(33).

The earliest endeavours to prevent the dimerization of SFHb used cross-linking agents like diaspirin or glutaraldehyde to covalently bind hemoglobin’s subunits together (49, 50). While nephrotoxicity was reduced somewhat, because cross-linked SFHb is still small enough to extravasate into endothelial cells, its vasoactive properties were still significant (48, 50). Furthermore, cross-linked hemoglobin caused cardiac toxicity (27).

In addition to reducing nephrotoxicity, increasing the molecular weight of SFHb by conjugation with polyethylene glycol or malemide has been shown to lengthen intra-vascular half-life, thereby reducing vasoactivity (51). One pre-market conjugated SFHb solution, Hemospan, has shown moderate efficacy and an acceptable safety profile after phase II clinical trials (47). The manufacturers, Sangart Inc. (California, USA), will soon begin phase III clinical trials (27).

The last common modification of SFHb polymerizes tetramers into macromolecular chains (28). This process affords the same benefits as cross-linking and conjugation (31, 34, 50). By controlling the size of the polymers, oxygen disassociation characteristics and nitric oxide binding properties can also be fine tuned (29, 31, 50). Similarly to Northfield Laboratories’ Polyheme, Biopure Inc. (Massachusetts, USA) has manufactured a polymerized bovine hemoglobin formulation called Hemopure (29). Bovine SFHb comes from a plentiful and renewable resource and has the advantage of not requiring 2,3-diphosphoglycerate to facilitate proper oxygen offloading (27, 33). Hemopure is currently licensed in South Africa and pivotal phase III trials have been completed in North America for use in orthopaedic surgery (46).

Northfield Laboratories’ Polyheme is an HBOC synthesized by polymerization of hemoglobin extracted from expired human donor blood (34). Due to

purification and polymerization, an appreciable vasoconstrictory effect is not associated with Polyheme and no adverse cardiovascular events were reported in preliminary safety studies (31, 34). Recently, Polyheme has completed a controversial pivotal phase III clinical trial and may be the first HBOC to enter Phase IV marketing trials (27, 33, 37).

THE POLYHEME CLINICAL TRIALS: ETHICS AND EDITORIAL

In 1996, the Department for Health and Human Services (DHHS) and the FDA enacted complementary regulations for waiving the requirement for informed consent in certain emergency research protocols (2-4). 21CFR50.24 and 45CFR46 are federal regulations called the 'Emergency Research Waiver' (ERW) rules that allow an incapacitated person to be enrolled in a clinical trial without consent of a legally authorized representative, provided that the following criteria are fulfilled (2-4, 10):

1. The subject must be suffering from a life-threatening condition necessitating immediate treatment.
2. Obtaining informed consent from a legally authorized representative must be infeasible given the time frame in which the subject must be treated.
3. Previous clinical evidence must indicate that the investigated therapy will grant a serious benefit to the subject.
4. The investigators must make an effort to contact a legally authorized representative during the given therapeutic window.
5. An independent committee must review collected data of the ongoing study.
6. Available treatments must be "unproven and unsatisfactory" (2).
7. Principal investigators must meet with the communities from which the subjects will be drawn, and publicly disclose pertinent aspects of the study including the risks and benefits.

Potentially life-saving therapies for which there are no other methods of treatment can also be given special consideration under federal law. A "Special Protocol Assessment" (SPA) is a stipulation outlined in the 1997 US Modernization Act (52, 53) that allows a clinical trial to be streamlined for fast approval; trials which led to the installation of publicly available defibrillators, for instance, were conducted under this stipulation (54) . To be eligible, the experimental therapy must have no existing alternative. The FDA has deemed that Polyheme meets these requirements and has granted Northfield Laboratories SPA status for Polyheme (10, 55).

The FDA and DHHS regulations attempt to find a balance between expediting approval for emergency therapies and ethical practices of clinical investigation. In some cases, however, the interpretation of these regulations can lead to questionable practices.

Having commenced phase I clinical trials in 1991, Polyheme's journey through pivotal phase III studies just recently finished in May 2007 (56, 57). Early trials to determine the efficacy and safety of large volume Polyheme infusions (up to 20 units) were completed in 2002 (56, 58). These secondary studies showed Polyheme's capability to sustain patient survivability in conditions of extreme endogenous hemoglobin deprivation, where death is statistically certain (31, 34). After reviewing the results, the FDA granted Polyheme permission to sponsor a pivotal phase III clinical trial involving 720 hemorrhagic shock victims, pursuant under the ERW (11, 13, 57).

The phase III clinical trial was conducted in conjunction with 32 trauma centers across 19 US states and continued from July 2006 to May 2007 (5, 57). The trial has two distinct phases, a "pre-hospital" phase, and an "in-hospital" phase. In the pre-hospital phase, incapacitated trauma patients are randomized between Polyheme and the current standard of care, saline. Upon arrival at the hospital, patients previously given saline in the pre-hospital phase are given allogeneic blood, while patients previously given Polyheme in the pre-hospital phase are continued on the Polyheme treatment for up to 12 hours. The in-hospital phase of this study uses Polyheme in spite of the availability of allogeneic whole blood (5). Furthermore, if the patient was enrolled in the trial while unable to give informed consent, infusion of Polyheme at the hospital site can be performed without proper notification either the subjects themselves or a legally authorized representative (3, 10, 11).

The pre-hospital phase of this trial is not heavily debated and the necessity of the ERW rule is widely accepted (6-14). The in-hospital phase of this study, however, is heavily debated. The major point of contention comes from the fact that patients who were randomized to the Polyheme group in the pre-hospital phase were not treated with allogeneic whole blood transfusions upon arrival at the hospital (6-14). Previous studies performed under the ERW, most notably the public access defibrillator trial, did not have a protocol with a questionable in-hospital phase (54, 59, 60). Thus, the ethics pertaining to informed consent in the Polyheme clinical trial present a novel situation.

Opponents of the in-hospital phase do not discount the scientific validity of a clinical comparison between

Polyheme and allogeneic whole blood, but they charge that such a comparison must be conducted with the full cooperation and informed consent of patients or power of attorney (10, 13). A further point of contention exists due to dysfunction in the regulatory mechanisms for clinical trials falling under the ERW and the SPA. In particular, in 2006 Kipnis et al. uncovered a number of hindrances to the effectiveness of institutional review board (IRB) and FDA consideration of the Polyheme trial (10).

First, Northfield Laboratories was allowed to maintain secrecy of the specifics of the experimental protocol and research methodologies relevant to the study. Only after signing non-disclosure forms were IRBs and the FDA allowed to review the study protocol (10). In addition, although Northfield Laboratories did discuss aspects of the study including the risks and benefits, the study protocol itself was not disclosed at community meetings; there is no requirement to do so under the ERW (2, 4, 61). It is reasonable that a company should be permitted to protect its intellectual property; the non-disclosure, however, of the Polyheme research protocol seems to be in direct contradiction with stipulations six and seven as previously outlined in the criteria to be granted an ERW (2,4). In the case of an ERW, community consultations are essentially a surrogate method to facilitate informed consent (3, 10, 15). For all intents and purposes, ERW clinical trials enroll an entire community as test subjects. Accordingly, the requirements for surrogate informed consent should be more stringent than for studies where only one subject is being implicated. For example, in a more recent ERW clinical trial that tests the "ResQPump", an automated CPR device, the investigators went to great lengths to fulfill the requirement for community consultations. Specifically, 136 community organizations were contacted, major television and radio networks were sent press releases, 2 local newspapers were informed and multiple public service announcements were aired on television and radio. Because of this effort, attendance at community consultation meetings was tripled over previous ERW Clinical trials (59).

A second obstacle arises because the process by which an IRB reviews a clinical trial protocol is hindered by ineffective regulatory mechanisms and the interplay between ERA and SPA conditions (3, 10, 11). Normally, when an IRB decides to disapprove of a multi-center study protocol, it is required to report their rejection to the sponsor of the study, the local investigator, the FDA, and all other IRBs reviewing the same study or studies with similar protocols (2, 4).

In this case, however, the research of Kipnis et al. revealed two mechanisms utilized by Northfield Laboratories to prevent IRBs from reporting their concerns. Before one IRB evaluation, the principal investigator of the Polyheme trial was privy to information that one member of the IRB had reservations about the in-hospital phase of the trial. Before the IRB convened to deliberate about the study, the application for approval of the trial at that site was withdrawn by Northfield Laboratories (10). In another case, one IRB returned the application for approval to Northfield Laboratories citing concerns pertaining to the in-hospital phase of the study. In order to allow Northfield Laboratories a chance to address these concerns, the IRB requested that they amend and resubmit their request for ERW approval. Northfield Laboratories simply elected not to respond and to pursue study opportunities in other cities. Because the IRB never formally denied the study, a report was never authored, and the FDA and other IRBs were not informed (10, 11).

In the first case, a lack of confidentiality pertaining to IRB proceedings allowed Northfield Laboratories to avoid regulatory mechanisms in order to prevent an unfavourable outcome. In the second instance, an unwarranted decision by an IRB allowed Northfield Laboratories to sidestep regulatory mechanisms. In order to deter clinical trial sponsors from attempting to bypass regulatory procedures, two rules should be enacted:

1. Once a protocol has been submitted for assessment, the sponsor may not retract the submission.
2. Irrespective of whether a sponsor intends to continue pursuing a clinical trial for a submitted protocol, the IRB should evaluate it and officially inform relevant organizations of their findings.

Implementing these two regulations creates an incentive for sponsors to be absolutely certain the submitted protocol is of the highest integrity.

Another notable obstacle to effective review of the Polyheme protocol is the lack of malleability in the regulatory elements of the SPA. The SPA specifies that once the FDA and sponsor confirm an SPA agreement, the study protocol is locked until completion of the study. Furthermore, SPA status can only be granted before the study is evaluated. There are only four allowable exceptions to these rules (52, 53):

1. A mutual written agreement is formulated between sponsor and FDA outlining changes to be made.
2. A "substantial scientific issue essential to determining the safety or effectiveness of the drug" is characterized as unacceptable.
3. The sponsor does not adhere to the agreed upon

study protocol.

4. "The relevant data, assumptions, or information provided by the sponsor in a request for special protocol assessment change are found to be false statements, misstatements or are found to omit relevant facts."

If a sponsor wishes to change a protocol, a new SPA must be applied for (52, 53). Additionally, the ERW implies that protocols should be modified in response to community concerns (2, 4). Taken together, these facts suggest that sponsors may dissuaded from being candid towards community consultations in order to prevent possible reapplication for an SPA to modify the study protocol.

It should also be noted that the four exceptions for change of an SPA do not include any mention of ethical concerns voiced either by IRBs or by the community (52, 62). Because of this, the degree to which the FDA can alter an SPA due to ethical concerns is unknown. Thus, it is unclear whether the concerns voiced about the in-hospital phase of the Polyheme trial could have been legally addressed by the FDA.

In May 2007, Northfield Laboratories released preliminary results of the pivotal phase III clinical trial of Polyheme and have applied for a marketing license from the FDA (57). In spite of the concerns revealed by the research of bioethicists such as Kipnis et al., at the current time, the FDA has not made a public statement regarding the protocol of the Polyheme trials. Furthermore, the ambiguities in the SPA and ERW conditions have not been formally addressed and the regulations remain as is (2, 4, 52, 53).

CONCLUSIONS

The conflict in policy between the SPA guidelines and the ERW creates uncertainty in the regulatory process. The ambiguity of the guidelines for IRB evaluation leaves ample room for clinical trial sponsors to avoid unfavourable outcomes. More tightly regulating the submission and review process could alleviate this problem.

In light of the safety and efficacy demonstrated in pre-phase III trials of Polyheme, the potential clinical benefits to incapacitated subjects by participation in the Polyheme clinical trial clearly outweigh the potential risks. For this reason, it is imperative that regulatory statutes such as the ERW and SPA exist to facilitate speedy investigation of potentially lifesaving therapies like Polyheme. Once, however, an incapacitated subject enters a situation in which a satisfactory treatment is available, he possesses an inherent right to be given the standard treatment. The absence of a requirement in the Polyheme clinical trial to administer allogeneic blood to victims upon arrival at the hospital is unethical. Thus, the regulations concerning the informed consent of incapacitated patients for clinically investigating emergency therapies should be reviewed.

In spite of the concerns surrounding the design of the Phase III clinical trials, Polyheme needed to be given the opportunity to prove its efficacy in a clinical setting. If Polyheme fulfills the promises its creators have made, clinical outcomes for pre-hospital hemorrhagic shock victims will be drastically improved.

APPENDIX – ABBREVIATIONS

RBC – Red Blood Cell
HBOC – Hemoglobin Based Oxygen Carrier
SFHb – Stroma-Free Hemoglobin
PFC – Perfluorochemical
HIV – Human Immunodeficiency Virus
vCJD – Variant Creutzfeldt-Jakob Disease
IRB – Institutional Review Board
FDA – Food and Drug Administration
DHHS – Department of Health and Human Services
ERW – Emergency Research Waiver
SPA – Special Protocol Assessment

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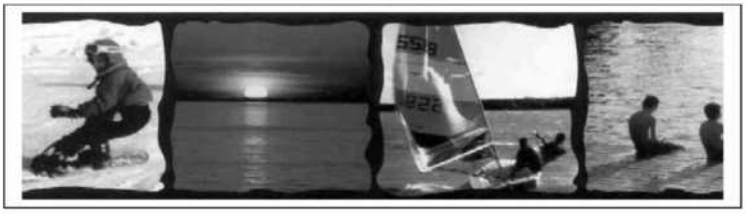

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Paying kidney donors: time to follow Iran?

Rupert WL Major*

Since the first kidney transplant was performed over fifty years ago, it has offered the chance of life and the freedom from dialysis for thousands of people. However, demand for organs has always exceeded supply. The gap between the two is widening due to increased prevalence of diseases common to a 'western' lifestyle such as diabetes and hypertension, leading to more chronic kidney disease and renal failure.

Renal transplants differ from most other transplants because living people are able to donate without significant adverse effects on their own health. Donated kidneys, therefore, have a potential to become a commercial asset. They can be harvested from cadavers or from living human donors. Living Related Donation (LRD) has become the organ source of choice and most common method. Supply, however, is still greatly inferior to demand: the United States Department of Health and Human Services 2006 Annual Report recorded over 82,000 patients on the waiting list for a kidney, up nearly 7% from the previous year (1).

In order to resolve the shortage of donors, some have advocated financial payments being made to donors. Despite being illegal in most countries, the trade appears to be booming in nations such as Turkey, Russia, and South Africa (2). Just as waiting lists and costs motivate some people to travel outside of their country of residence for procedures such as hip replacements and cosmetic surgery - a phenomenon called 'health tourism', a similar phenomenon appears to be occurring on a smaller scale for organ transplants (3). The dilemma physicians and health officials are faced with is whether to close their eyes to this trade, disregarding ethical implications and the adverse effects of surgeries done on the black market, or to legalize it and try to establish boundaries to protect organ donors that receive compensation.

Currently, the World Health Organisation estimates that of the 660,000 people in the world who require any form of transplant, 10% receive one each year (4). Of these, 10% receive their transplant through commercial 'transplant tourism' (4). The lack of donors and the rise of 'transplant tourism' have recently forced regulatory organisms throughout the world to act. The European Union tried to boost organ donations by suggesting a Europe-wide donor card, and has formed a regulatory body to standardize quality and safety within transplantation in an effort to reduce commercial transplants. The People's Republic of China, which performs more transplants per year than any other country except the USA (5), has recently introduced tougher restrictions and penalties for commercial transplantation (5).

One of the few countries that has legalised the sale of organs is Iran (6). The first kidney transplant in Iran took place forty years ago. However, in the following twenty years only one hundred were performed overall within Iran. This was mainly due to the lack of infrastructure available to develop and maintain a kidney transplant network within the country. In the early 1980's, the Iranian government recognized the increasing strain on dialysis resources as the end stage renal failure population grew in Iran. The government began to pay for its citizens to have living related transplants abroad, the majority in the UK. Four hundred such transplants were funded in a five year period (5). As these costs started to spiral, a small network of renal transplantations teams was set up within Iran and just under one hundred transplants were carried out per year from 1985 to 1987 (6). The development of an Iranian renal transplant network of this size was a drop in the ocean compared to over 25,000 people living with end-stage renal disease in Iran, many of which live in rural areas and do not readily have access to medical care (6).

In 1988, Iran legalized living non-related donation (LNRD) of kidneys and established an associated transplantation system. This government-organized system regulated and funded the transplantation process and compensated the donors for their organ. A third-party independent association was set up to arrange contact between donors and recipients. This agency, the Dialysis and Transplant Patients Association (DTPA), still carries out this function to this day and is staffed on a voluntary basis by end-stage renal failure patients. An

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important problem with this system is that human leucocyte antigen (HLA) matching of tissues, necessary to improve the chance of graft survival and prevent host rejection, is not routinely performed. .

Within the first year of the establishment of this system, the number of transplants had almost doubled; nearly four fifths were from living unrelated sources (6). In addition to payment from the government, donors also receive free health insurance and often payment from the recipient or a charity. The receiver of the 'new' kidney is provided with highly subsidized immunosuppression and charitable organizations allow those unable to pay for the transplant themselves to receive a new organ. Importantly, it is illegal for the medical and surgical teams involved or any 'middleman' to receive payment (6). A potential donor is also not allowed to contact anyone on the waiting list. Despite, this, anecdotal stories of young men touting their 'spare' kidney in dialysis clinics are common (7).

There is no nationwide transplant registry in Iran so the outcomes of renal transplantation, regardless of source, are difficult to assess. However, the Hashemi Nejad Hospital (HNH) in Tehran, one of the leading hospitals in Iran, does provide detailed analysis of its data. In the twenty years up to the beginning of 2006, just under two thousand transplants in HNH were performed, three quarters of which were LNRD (4). Despite no HLA matching, results are similar in terms of both graft and patient survival between LNRD and LRD in both Iran and other countries (6, 7). The extrapolation of these results to other, smaller centers in Iran is however limited.

Whilst still illegal in 'Western' nations, could the 'Iranian model' of payment for LNRD be used in North America or Europe to solve the problems of kidney donor shortages? A hotly disputed topic is whether the Iranian system has actually cleared the waiting list for transplants and whether LNRD is the true answer to the problem (7). Advocates of the Iranian model insist that where there was once a significant waiting time in excess of the length in 'Western' nations, there is now no waiting time. Further, there are "no significant differences" in groups of donors and recipients when compared in terms of socioeconomic background (wealth and education level). Thus significant social exploitation is not occurring (7). It should be noted, however, that investment in cadaveric donation programs has allowed them to increase significantly, and they now accounts for more than 10% of transplants (6) (however, this is compared with almost 60% in the US (8)). The Iranian system is known to have ethical and legal loopholes which have been exposed and exploited. One of the earliest problems involved patients from abroad travelling to Iran to receive a kidney donation from an Iranian. This practice was outlawed to prevent the development of true 'transplantation tourism' and international exploitation of Iranian donors. In addition, refugee groups (such as those from Afghanistan) are offered transplants but are not allowed to donate to people outside of their ethnic groups, further decreasing potential exploitation of vulnerable groups (6).

Opponents of the Iranian system insist that the system is not as perfect as it seems. There is evidence to suggest Iran's system has not cleared its waiting list and that trading between socioeconomic classes is a substantial problem (7). Critics of the Iran model would argue that even this well developed system has major flaws and that a ban on payment to LNRD should be maintained in other parts of the world.

Outside of Iran, the issue continues to be highly contentious. The end-stage renal failure population continues to increase in most countries, putting an increasingly heavy load on medical infrastructure. Compensation for living non-related donors, once a taboo subject, has now begun to be discussed openly in transplantation meetings and the medical literature (9, 10, 11). The advocates for legalization argue that each of us has autonomy over our own body in every aspect of our health and that from this stems the right to donate a kidney to a related or non-related patient. Payment for sperm and eggs is legal in many countries, even though they arguably have greater long-term implications due to the potential to create a whole new individual. Similarly to compensation received for participation in some clinical trials, the individual also gains no immediate benefit from putting themselves at risk. However, opponents argue that the donation of a kidney is permanent, which sets it apart from the examples given above. LNRD supporters argue that after the initial peri-operative risk, the donor has no long term increased risk of mortality (12). Furthermore, the risk surrounding the surgical procedures is low in most centers, with a 0.02% risk of death during surgery and its immediate complications and less than a 1% risk of other morbidities (12). Most importantly, in the longer term, a recent meta-analysis has shown that there is no significant acceleration in decrease in glomerular filtration rate (beyond that expected due to aging) in kidney donors fifteen years after transplantation (13).

It could be argued that if the medical profession truly believes in full patient autonomy, care requested with informed consent by a patient should be allowed provided a fair, regulated system is in place. As with recreational drug use, it is a question society faces in many areas: is the harm of the activity in question reduced and better controlled in a regulated market? As ESRF continues to grow in prevalence, the problem of

unregulated organ markets and brokers is likely to become more severe. It is argued that the setting up of regulated markets would 'cut out the middleman' and reduce the exploitation of individuals and developing nations. In situations where there are no regulations, the donors are maximally exploited and are often left with no supportive care once donation has taken place (3). In addition, inferior surgical and medical practice, common on the black market, leave both the donor and recipient at greater risk whilst the broker pockets a large cut of the proceeds.

A possible compromise is a non-monetary reward system. For instance, patients who have previously agreed to be on the transplant list could receive priority health care. It has also been suggested that governments should control the monetary aspects of the transactions rather than payment passing directly from individual to individual. The donor would effectively sell their organ to the state which would then allocate it on the basis of clinical need. By making the process more medically transparent, it may placate to some degree those who accuse pro-monetary transplantation advocates of disregarding the exploitation of the poor by the rich. It is also likely that a 'fair' standard price could be set to prevent those in desperate financial need from being even further exploited. Using economic cost-effectiveness analyses, a figure of approximately $90,000US (£45,000 or 67,000 Euros) has been proposed (14), much less than the estimated cost of dialysis of up to $70,000US per annum per patient (15). Government intervention would also guarantee adequate post-operative care and follow-up for the donor, something which is currently limited.

Finally, the medical profession's view on the ethics of commercial transplantation must be considered. The consensus within the transplantation community is largely against LNRD legalization but increasingly, voices are calling for its allowance. The World Health Organization is strongly opposed to payment for any form of organ (17). This has been partly shown in primary care physicians with 90% and 20% in favour of related and non-related kidney transplants respectively (although there was no mention of commercial payment in the non-related cases) (16). In addition, the overall view appears to be negative towards those who would be actually carrying out the transplantation. The role of commercial transplantation surgeons has cheekily been described in an article in the British Medical Journal as "'Rotten Jobs" that consist of "harm[ing] a poor person and sav[ing] a rich one" (18).

As the pressure of demand for organs continues to increase rapidly, the idea of financial compensation for LNRD of kidneys will continue to be with us. Until an alternative to human donors can be found, either artificial or xenotransplantation (animal) based, then this ethical issue will continue to be discussed and considered within transplantation and wider medical communities. Whether talk will ever be turned to action in favour of monetary payments to donors remains to be seen. The medical profession may not agree with payments on an ethical level but the increasing problems caused by prohibition of LNRD and the prolific black market of transplants are starting to be considered as good reasons for legalization and tight regulation.

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MJM FOCUS

SPECIAL FORUM ON PRIVATIZED MEDICINE WITHIN UNIVERSAL HEALTH CARE SYSTEMS

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FOCUS REVIEW

The case against increased privatization of Canadian health care: whither health care?

Harvey Barkun

The title of this article is that of a submission to the Romanow Commission which published its report in November 2002. The arguments that raged through the years of hearings dealt mainly with funding issues. The federal and provincial governments, who cover approximately 73% of all health-related costs, were in dire financial straits. They were all running huge deficits and federal transfers to the provinces for health and post-secondary education had been cut drastically. With the focus on finances, the country's deputy health ministers commissioned two eminent health economists to produce recommendations on how to curtail costs. Since many of the costs incurred were generated through the practice of medicine (the common wisdom was that each new medical graduate added $250,000 to the national health bill), the experts recommend a 10% drop in admissions to Canada's 16 medical schools. The national number of admissions fell from an average of 1770 students in the 1980's and early 1990's to a low of 1552 in 1997-98. Similar "logic" was applied to schools of nursing. It is estimated that over 5000 nurses were permanently lost to the system. Both physicians and nurses were offered financial incentives and urged to take early retirement. Drastic measures were being implemented to solve the crisis in medicare, which, at the time, was not enough money.

The consequences have been painfully visible in Québec, where overworked and exhausted staff recently left emergency rooms in protest because they could no longer provide patients with proper and safe care.

The critics were most vocal. The public purse could no longer sustain a universal health care system; the private sector could surely run things more efficiently. Patients who could afford it would bear the cost of services while medicare would take care of those who couldn't.

This is the situation presently in the United States. Yet although the US spends over 15% of its gross domestic product (GDP) on health (Canada spends less than 10%), 46 million Americans currently have no health insurance, another 40 million have inadequate coverage, and the US lags behind Canada and most other industrialized nations in health outcomes. These facts should provide enough arguments to dispel any thought of adopting a privately funded system.

But critics maintain that private funding will cure what currently ails the system. They base their arguments on factors that may have been relevant in 1999, but which are no longer pertinent. Indeed, despite millions of dollars provided by the Québec Ministry of Health to the Outaouais Region for emergency room care (where the crisis cited above took place), there were simply not enough health professionals available to solve the problem. The problem in 2007 is *wait times*.

You wait to see a family physician; you wait to see a specialist; you wait in emergency rooms; you wait for elective surgery; you wait for laboratory and radiological procedures. And will an infusion of private money cure these ills? Not at all. These long wait times exist because of a very serious lack of health care personnel. The nationwide financial deficits of the late eighties and early nineties have been reversed. The federal government has declared repeated surpluses, as have many provinces. The feds have increased transfer payments. One only has to look around the country to notice widespread building and renovation of health care facilities; there are daily announcements about the acquisition of state-of-the-art equipment. The only problem is that there are not enough people to run them! The ill-advised decisions of 1991 to 1993 have created a situation where there are not enough doctors, not enough nurses and not enough technicians to staff operating rooms, intensive care units, emergency rooms and radiology installations. The financial deficit has

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become a personnel deficit, and no transfer of activity or responsibility to the private sector will solve the problem. Indeed, if privatization of the system were instituted, the problem would be compounded. As the British National Health System (NHS) has demonstrated, private practice would drain the public service and the current dearth of doctors and nurses would worsen with the movement of these professionals to more lucrative areas of practice.

But take heart! Help is on the way. Governments had realized the folly of their ways in 1999, and by 2001 the number of authorized admissions to medical school had risen to 2025. Nursing schools are turning out many more nurses through their 4-year and 3-year accelerated programs. Unfortunately, although warned, governments now realize that it takes a minimum of six years to turn out a family doc, and up to ten years for certain specialties. Nursing began increasing class sizes in 2002. Results will begin to show in 2008.

Proper treatment requires a proper diagnosis. The diagnosis of our current ill is a lack of people, not lack of money. Privatization is the wrong treatment. The public system is healthy and thriving. With the arrival of newly trained professionals, therapy will provide a vibrant and sustainable health care system. Let no one tinker with it!

Harvey Barkun, OC, MD, FRCPC, was born in Montreal. After receiving an MD degree at the Université de Montpellier (France) in 1957, he completed his residencies at various McGill hospitals. Dr. Barkun was medical director of the Royal Victoria Hospital and was Executive Director of the Montreal General Hospital from 1972 to 1988. He served as the Associate Dean, Professional Affairs, of the Faculty of Medicine, McGill University, from 1977 to 1997. Dr. Barkun was instrumental in creating the first CLSC's in Montreal and chaired the committees which implemented the provincial Departments of Community Health. He was a member of the Rochon Commission and became Executive Director of The Association of Faculties of Medicine of Canada. He is an Officer of the Order of Canada, an Honorary Fellow of the Royal College of Physicians & Surgeons of Canada, and an honorary member of the College of Family Physicians of Canada.

FOCUS REVIEW

The case for increased privatization of Canadian health care

Edwin Coffey

The charter-protected right of all Canadians to purchase private medical and hospital services and insurance for medically required services was implied in the 2005 landmark judgment of the Supreme Court of Canada (SCC) case involving Chaoulli/Zeliotis vs Quebec and Canada. This precedent-setting judgment is now part of Canadian case law and jurisprudence.

In this SCC case, two sections of Quebec's medicare legislation that banned the sale and purchase of private medical and hospital insurance and private medical services in hospitals for services covered by government medicare insurance were declared to be unjustified infringements of the plaintiffs' right to life, personal security, inviolability and freedom.

Coming in the midst of the longstanding public debate over the future roles of the public and private sectors in Canada's health system, the SCC judgment established the following:

1. Confirmed the legality of purchasing and providing private medical and hospital services and insurance;
2. Declared the invalidation of Quebec legislation that prohibits these private health services and insurance;
3. Reassured the opponents of private sector health services and insurance "that the prohibition [of private services] is not necessary to guarantee the integrity of the public medicare plan";
4. Refuted the claims of the Attorney Generals of Quebec and Canada and their expert witnesses, concerning the likely impact of lifting of the ban on private health services and insurance namely: (a) increased overall expenditures, as these would be mainly paid voluntarily by private patients and their insurers; (b) attraction of patients with less acute conditions to the private sector, leaving the sicker patients with the public sector, as the public sector already looks after the sicker patients and would be relieved of many patients with less acute conditions; (c) physicians would tend to lengthen public wait lists in order to direct these patients to their private facilities, since if this should happen the government could establish a framework of practice for public physicians who wished to practice part-time in the private sector.

Canada's deteriorating health system is largely the result of ill-conceived federal and provincial health-financing policy and bad health legislation. During the past four decades, individuals and families have been prohibited from purchasing private alternative or duplicate medical and hospital insurance for services covered by the public insurance plan, even when public services are not available. Patients are not allowed to use their medicare insurance for private non-participating physicians. Physicians in the public system are generally not allowed to treat privately funded or insured patients.

In this context it is not surprising to see the emergence of a strong public desire for health-system reform in the financing, insuring and delivery of essential medical and hospital services. This thirst for reform should not be ignored. The question facing our political leaders is whether the solutions should come from the public or private sector or a mixture of both.

A 2007 international survey of seven countries by the Commonwealth Fund (New York) found that 72% of Canadians think their health care system needs either fundamental changes or complete rebuilding.

A 2006 Léger Poll for the Montreal Economic Institute shows that 48% of Canadians and 60% of Quebecers would find it acceptable if patients were allowed to pay for health care in the private sector while still maintaining the present free universal medicare plan.

Now that the Supreme Court of Canada has invalidated Quebec's legislation and has concluded that access to a private alternative health insurance would

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not endanger the integrity of the public system, it is incumbent upon Quebec and the other provinces with similar legislation to immediately rescind these legislated infringements of the charter rights of patients while retaining present medicare entitlements. This will reduce the associated pain, suffering, and sometimes death that continues to be inflicted on Canadians by this unjust legislation.

The Quebec government recently appointed a Working Group headed by Claude Castonguay, the former Minister of Health who was in office when the current medicare legislation was enacted. His group is examining the present health system and will give recommendations for the future role of the private sector in Quebec's health care system.

It is hoped that the concepts of personal freedom, free market competition, ready access, high quality patient-centred services and patient choice in all health care matters will be reflected in the recommendations of the Castonguay Group early in 2008.

These same concepts for health-system reform in Quebec and Canada form the basis of an earlier proposal, Universal Private Choice: Medicare Plus, co-authored by the writer and Dr. Jacques Chaoulli and published online by the Montreal Economic Institute: www.iedm.org/main/show_publications_en.php?publications_id=30/

In order to restore the lawful and necessary place of private alternative medical and hospital services and insurance alongside publicly funded medicare services, the following measures are suggested for implementation by the respective federal and provincial governments:

1. Retain the universal tax-supported medicare plans and entitlements in the provinces;
2. Reassure Canadians that the restoration of freedom, choice and competition with access to private health-care and health-insurance services will not jeopardize universal access to publicly funded health services;
3. Reaffirm the constitutional jurisdiction of the provinces over health services;
4. Repeal all freedom-infringing and monopolizing provisions in medicare legislation, similar to those invalidated by the 2005 Chaoulli/Zeliotis judgment of the Supreme Court of Canada;
5. Restore the freedom of voluntary non-profit or commercial associations to provide a full range of health insurance services including health savings accounts and health purchasing agencies;
6. Revise the criteria in the Canada Health Act regarding federal cash or tax transfers to the provinces and territories to enhance freedom, quality, access, choice and competition by financially rewarding provinces and territories that undertake the above revisions in their health legislation, rather than penalizing them;
7. Promote a socio-economic environment of individual freedom, personal choice and the opportunity for consumers and providers of medical and hospital services to exercise personal responsibility, innovation and experimentation in the financing, insuring, purchasing and provision of these services, including those covered by medicare.

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FOCUS REVIEW

International perspective on mixed health care: United Kingdom

Andrew Vallance-Owen

When the National Health Service (NHS) was founded in 1948, the consultants–medical and surgical specialists–could only be persuaded to come on board by giving them contracts which allowed them to pursue private practice outside the time they devoted to their NHS work. Nye Bevan, the health minister at the time, was accused of "stuffing their mouths with gold," and many felt the NHS practice would be given lower priority, but the compromise worked and most consultants who have undertaken private practice over the years have also regularly worked more than their contracted hours for the NHS.

The NHS enabled all the people of the country to receive health care for free at the point of need, as it still does to a large extent (prescription charges for drugs being one exception), but some have always wanted additional access to private health care and have been prepared to 'top up' by buying private medical insurance or by paying for private health care directly. Most straightforward private medicine is undertaken in small independent hospitals, but more complex treatment may be undertaken in NHS hospitals, with patients being accommodated in private or pay bed wards.

In many ways the NHS has been very successful; for people who suffer trauma or acute illness the service is excellent, and the primary care system has been second -to-none. However, those with chronic conditions and those needing routine elective surgery have had a less good service which, for the latter, has often meant long waits. Many have argued that health care in the UK has been rationed by waiting; for example, not so long ago many patients could have waited over a year for total hip replacement. Indeed, up to quite recently, the principal reason given for buying private medical insurance (PMI) was to avoid waiting but, despite this issue, PMI uptake in the UK has been running at a fairly stable 12-13% for the last 10 years–partly because it is expensive.

In July 2000, the Labour Government adopted a new strategy for the NHS, the NHS Plan.* Reduction of waiting times became a key priority and, for the first time since the formation of the NHS, ministers decided that the NHS could contract with independent hospitals to use their spare capacity and reduce waiting lists. This was also a tactic, akin to throwing a grenade in a pool, to stir up NHS hospitals and persuade them to be more efficient because, at the same time, a new funding system for hospitals was introduced–payment by results–that brought in competition for patients, each bringing his funding with him.

This short article cannot fully cover the detail of these changes or the nature of the sticks and carrots used but, essentially, waiting times are now dropping significantly and consultants continue to maintain their private practice, although some are worried that the drop in waiting times will threaten the take up of PMI. There are, however, two other factors which might counter that concern.

First, given the problems that many NHS hospitals have been having with methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile, the top reason for purchase of PMI is now clean hospitals; independent hospitals have a much better record in this regard. Second, there have been increasing restrictions on what is available under the NHS. Cosmetic surgery, for instance, has been excluded for some time, and the National Institute for Clinical Excellence (NICE), which assesses the cost effectiveness of new drugs and technologies and acts as

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a gatekeeper for their use in the NHS, is regularly accused of rationing access to certain treatments.

Now, in the last year, private medical insurers and others have been invited to become involved in the demand as opposed to the supply side of the NHS. A separate part of the NHS Plan proposed the devolution of funding decisions from the centre and regions to primary care trusts (PCTs); these would be made more clearly responsible for assessing the needs of their local populations and purchasing (or 'commissioning') appropriate care from local hospitals and community services. The objective of these measures is to wrest power away from the large, expensive hospitals and bring more care, particularly for chronic disease, into the community.

The problem, however, has been that many PCTs have not had the experience to manage the change or the competence to drive this more strategic agenda. Thus, private insurers, who have to be competent in purchasing or commissioning care for private patients, have been asked to tender for contracts to support PCTs in undertaking this and other types of activity.

In summary, therefore, the independent sector in the UK has moved from being almost solely a parallel system to the NHS, with the only point of contact being consultants working in both systems, to a system from which the NHS is increasingly seeking support. Interestingly it is a Labour Government, traditionally opposed to private medicine, which has led this change. Their hope is that the NHS will improve so much that, as a result, the private sector in the UK will shrink and die. Whether this will happen remains to be seen.

* The NHS Plan: a plan for investment, a plan for reform Department of Health, Cm 4818-I July 2000

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FOCUS REVIEW

International perspective on mixed health care: Japan

Hisayuki Hamada, Samuel Lapalme-Remis

Japan's health care system should be the envy of the world. Japan consistently places near the top of the World Health Organization's overall health rankings, and does so while spending the smallest proportion of its GDP on health care than any member of the G7 (8% in 2004; Canada spent 9.9%), making it perhaps the world's best health care bargain. This accomplishment can be traced back to the founding of Japan's national universal insurance health care program in 1961, in which all Japanese could receive equal treatment at any health care facility. This system, however, is in danger of crumbling.

In Japan, patients must pay approximately 30% of their medical expenses (including medications) out of their pocket. In 2004, however, this still left the proportion of all health care costs borne by governments at an exceptionally high 81.5% (Canada: 69.8%). Particularly expensive are the country's drug costs, which make up 18.9% of all medical expenses (Canada: 17.7%). The universal insurance system does exclude certain medical services such as orthodontia and cosmetic surgery; these uninsured services must be paid for out of pocket and are effectively privatized. Japanese law is very strict about the distinction between the provision of insured and uninsured care and prohibits medical institutions from providing both insured and uninsured services as different components of a single series of medical treatments.

Since the late 1990's, however, there has been increasing pressure from the business sector for the government to allow a mixed system in which providers could offer different medical services at the same time, some covered under the public-insurance system and some not. Foreign countries such as the United States have also pressured Japan to introduce market mechanisms and competition to medical care, allowing new insurance plans and medical-service businesses to flourish. In addition, wealthy individuals have expressed a wish to have access to high-level care at the very cutting edge of technology.

In 2001, Prime Minister Jun'ichiro Koizumi formed the Council on Fiscal and Economic Policy to bring Japan's public finances to order, aggressively promoting government-budget reform based on neoliberal principles. With the government's new emphasis on small government, free-market ideology, market-based incentives and increased privatization, Japan's social welfare programs faced major changes. Health care was no exception.

In 2004, a law was passed allowing private companies to participate in running health care institutions under limited parameters in exceptional cases only. Such involvement was restricted to six areas that were already under the category of uninsured medical services and represented cutting-edge medicine:

1) PET scans and other diagnostic imaging
2) Regenerative medicine
3) Medical genetics
4) Cosmetic surgery
5) In-vitro fertilization
6) Others

In 2005, a cosmetic-surgery venture company in Kanagawa Prefecture signed a collaborative contract with a university and became the first such private company to be founded.

However, in response to strong opposition by the Japan Medical Association and concerns by the general population, the Ministry of Health, Labour and Welfare took a cautious approach to the growing number of private companies entering the health care sector throughout Japan and issued a number of reservations

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regarding increased privatization of health care. First, there is a danger that because the medical services required by patients may not be those most profitable to private companies, important medical services may not be made sufficiently available. Second, medical services might no longer be provided in certain geographical regions if service providers withdraw from less profitable areas. Finally, the cost of medical services might increase considerably. In effect, despite the law, private companies are still prevented from forming national chains of health care facilities and the removal of the ban on mixed health care never occurred.

This lack of movement has done nothing to change the fact that the Japanese health care system faces increasingly difficult challenges year by year. By 2005, the proportion of the Japanese population older than 65 years old had exceeded 20% and the birth rate sat at its lowest level ever, 1.26. As a result, Japanese society is fast becoming the oldest society in human history, and the long-predicted collapse of the public health-insurance system is becoming reality. Between 1985 and 2002, the total annual cost of health care in Japan nearly doubled from 16 to 31.1 trillion yen. This funding is split as follows: 51.7% comes from the universal health insurance contributions (shared between employers and employees), 15.3% comes directly from the patient's pocket, 25.1% is paid for by the national government, and 7.9% is paid for by local governments. Yet with an cost increase of 1 trillion yen (CDN$8.7 billion) per year (after the USA, the highest rate of increase in the world), it is difficult to see where the needed funding will come from.

Japan has one of the highest per-capita number of hospitals in the world, with 8.4 hospital beds per 1000 population (Canada: 3.0; USA: 2.8). It is not uncommon for a single physician to run his own hospital, adding to the excess. This is seen as one of the major causes of the unrelenting increase in health care costs. While the government is making an effort to decrease the number of beds that are located in small- and medium-sized hospitals, there is great resistance among the population to dramatic changes in bed distribution, making it necessary for the government to tread carefully. On the other hand, there is a shortage of physicians, with only 2.0 per 1000 population (Canada: 2.1). This problem has been exacerbated in rural areas due the resident-matching system introduced in 2004, which has accelerated the tendency of young doctors to concentrate in urban areas. Rural areas are increasingly likely to lack the necessary doctors and hospitals.

Given this state of crisis, calls for the development of private medicine within the areas permitted by law, as well as for increased application of uninsured and mixed medical care, are increasing among government, business, some physicians (approximately 50% of physicians working in hospitals according to a recent survey) and a minority of patients (about 20%). However, the July 2007 House of Councillors election dealt a crushing loss at the polls to the ruling Liberal Democratic Party that had promoted aggressive fiscal reform, including health-care reform. The majority remains opposed to the increased application of market ideology and free-market competition. The election result highlighted the fact that the population wishes to maintain the current universal health-insurance plan, which it perceives as fair and affordable.

On November 8, 2007, an individual patient successfully sued the government in the Tokyo District Court by claiming that the government violated his constitutional rights by refusing to allow him to apply his public health insurance to any of his cancer treatment because part of his treatment had included uninsured services. The government had insisted that such prohibited “mixed” treatment relieved it of its duty to pay even for the insurable portion of his treatment. In effect, the court ruled that the government's suppression of a mixed system was unconstitutional. In response to this ruling, the Japan Medical Association and patient groups expressed concern that the provision of medical care would now depend on patients’ financial status. Other patient groups applauded the decision. The decision is sure to fan the flames of the debate regarding the removal of the blanket ban on mixed health care.

Based on recent political events, it is clear that the general population in Japan is in favour of maintaining the present national universal insurance health care system. As a result, the debate on the adoption of increased uninsured or mixed medical care is at a standstill. With the nation in a state of political gridlock, there is little indication that battling political parties will be able to come up with any effective solutions to controlling the rapidly escalating costs that threaten to destroy the health care system voters are so eager to preserve.

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FOCUS INTERVIEW

A clinician's view of mixed health care in Quebec

Interview with Dr. Lawrence A. Stein, Radiologist
Interviewed by Samuel Lapalme-Remis for the MJM

MJM: Please describe how your divide you practice on a week-to-week basis.

Dr. Stein: I actually spend about 90% of my time in the hospital system. I've done it that way since 1974. Our group has always had a community clinic. I don't like to use the word "private" clinic, it's a bit of a misnomer because until about quite recently, patients didn't have to pay for the imaging that was available at these clinics—chest x-rays, lumbar/spine, mammography, barium studies. These clinics started in the late 1960's as an outlet for patients to get their outpatient imaging done using their medicare card without relying on an expensive hospital infrastructure. Our group had such a clinic, as did radiologists at most other hospitals.

Then about five or six years ago, these clinics started to include CT, MRI, PET scanning and even nuclear medicine. This was new in that these procedures weren't covered by the medicare card and therefore patients had to pay for that. The Quebec law is very clear regarding radiological procedures; if it's not insured within a hospital, you can charge for it outside a hospital. For some other specialities, there's more of a grey zone.

MJM: What changed five or six years ago?

Dr. Stein: What changed is that CT, MRI and ultrasound just became more used and everyone saw that there was probably a group of patients that would be able to afford or have insurance for these procedures, and who would benefit from them.

At our clinic downtown, we offer everything we offered since 1967, and since 2000 we've added to that these advanced imaging procedures, so 60% of our volume is medicare covered and 40% isn't. It's legal to do this in Quebec, as it is in BC and Alberta. Also, in Quebec, most private health-insurance programs that people are enrolled in as an employment benefit cover these kind of procedures, sometimes up to 100%, and usually about 80%. This is unique to Quebec; if you have a job, you probably have this kind of insurance.

MJM: What was the reaction when you introduced these new services not covered by medicare?

Dr. Stein: Well, in 2000 we moved from a smaller office where we had only offered the covered services and opened a new and larger office where we offered the advanced imaging as well. At the time we developed and opened it, it was fairly unique. Had we done it five years earlier, I think we would have had gotten a very negative response, but at the time we actually did it we got a fairly positive media response. The media were very receptive.

MJM: What were some of the concerns that you heard from the media?

Dr. Stein: The nature of the debate was what people fear most when they hear about private health care, and that's what happening south of us. They do not want the American system in Canada. Quite frankly, I don't think there are many Canadian doctors who want the American system in Canada either, but that's what patients fear. They see spiralling costs and a huge volume of patients who can't afford health care in the United States, and that's what they're bombarded with in the media. Canadians are frightened about that. That's the negative part. What Canadians don't always know is how good the systems in Europe are, like in France, Germany and the UK. These systems offer both government-sponsored and alternative health care working together. Canada is more like Europe overall than like the US. Of course, pressure does need to be maintained on the government to make sure that the public system is properly supported. I've had career-long commitment to and support for a strong, vibrant, well-funded and properly staffed public health care system where there is timely access to quality imaging for all Canadians.

MJM: Per unit time, is it more profitable for a

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radiologist to do a procedure inside or outside a hospital?

Dr. Stein: It's just about the same. It's not to my advantage or disadvantage to work at the clinic over the hospital.

MJM: How would you describe the work you do at the clinic?

Dr. Stein: As I mentioned before, I spend about 90% of my time in the hospital; the clinic is a nice break for me. The hospital is a very high-pressure, difficult, not very efficient environment to work in. Going to the clinic gives me a little bit of a respite.

We're doing very good imaging at the clinic. It's the same community of patients and they're not using hospital resources. Some people accused us at the beginning of catering to the "worried well." In fact, we see more pathology per capita at the clinic than we do at the hospital.

MJM: When a patient pays out of their own pocket, as opposed to when they put down a card and don't have to pay directly, do you sense any difference in the interaction that you have with them?

Dr. Stein: No. Whether a patient is in the hospital or in the clinic, they'll see no difference from me. I don't think they perceive any difference.

MJM: But the patients themselves, they don't demand more?

Dr. Stein: They may be a little more demanding. They will not tolerate waiting. If the appointment is at nine o'clock, they expect to be seen at nine. In the hospital you can often have a patient who has been waiting for a considerable amount of time. That won't be tolerated at the clinic.

It's interesting because that carries over to the patients in the clinic who use their medicare card. They expect to be taken care of on time too. It's just the environment.

MJM: How else does the population at the clinic differ from that of the hospital?

Dr. Stein: Obviously, in the hospital we see sicker patients, patients who are less ambulatory. Also, there's two groups at the clinic, those who use their medicare card and those who are paying or have insurance. Those who are paying are probably a higher socio-economic group.

MJM: Is that a concern of yours?

Dr. Stein: Yes and no. I look on that in two ways. The first thing is, whose fault is it? If a patient needs a CT scan and can't get it in an appropriate length of time, it's the government's fault. So the fact that we're offering it to some patients who can afford it or can get the insurance, does it bother me? Yes, it bothers me; I'm concerned about it. But it's the fault of the government for not providing the resources that are necessary to deal with the ageing population and higher technology. In imaging, medicare is no longer sustainable. It may have been good for 1967 to 1997, but it can't keep up with the high cost in imaging. Something has to give, the money has to come from somewhere.

MJM: Where would you hope that the money will come from in the future?

Dr. Stein: I think that for the future, we have to allow both parts, the state-supported and the alternative have to be supported and allowed to thrive. And there may even be situations where there's a link between the two. The government may see that it's more worthwhile to have things done in the clinic than in the hospital. But right now they'd rather have the patient wait.

What I'm for is timely access to quality imaging. Full stop. I fight every day of my life to get more resources in the hospital. We don't have enough receptionists, typists, technologists, radiologists. It's hard. Right now we're capped by the number of radiologists, yet our volume of work in hospital has increased. It's forcing us all to work too hard. In the hospital, I'm often forced to manage three patients at the same time when it should be one patient at one time. It's hard to get a day's work done without constant interruptions.

I don't have that at the clinic. At the clinic, 100% of the time I'm attentive to what I'm doing and dealing with the patient at hand.

MJM: Do you find this makes a big difference in terms of the quality of care that you're able to provide?

Dr. Stein: You learn how to practice in the hospital. You learn how to do it well. If you can't do it, you will leave the hospital. I've had medical students ask me, "how can you practice like that?"; they can see the interruptions that I deal with. I just say, "you learn how to do it."

There are times where I have thought that each of us is trying to do too much. I have to think that that is prone to making errors.

MJM: What advice would you give a young radiologist beginning their practice in Quebec?

Dr. Stein: I would say that the type of practice you want is a combined hospital and outside-clinic practice. We have a beautiful profession in that we can do both of these things. The hospital allows us to do many things you could never do in a clinic. You might be bored as a young radiologist doing just an outside practice.

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FOCUS INTERVIEW

A clinician's view of public health care in Quebec

Interview with Dr. Paul Saba, Family Physician
Interviewed by Samuel Lapalme-Remis for the MJM

MJM: Please describe how your divide you practice on a week-to-week basis.

Dr. Saba: I work about one week a month doing hospitalization at the Lachine Hospital in Montreal. I do another week of mixed hospitalization, either with intensive care or without intensive care. I do about two weeks a month altogether in practice at my clinic; I try to be in my office at least three weeks out of four, two to three days a week. I also work at the emergency room whenever they need me; I probably put in about six shifts a month. So I do a pretty wide spectrum of medical practice, which I find very interesting.

MJM: What led you to pursue this kind of career?

Dr. Saba: I had always worked a little bit in everything; at one point my practice leaned more toward office practice but then around 2000, when there was a big cry for doctors in emergency rooms, I answered the call and started working in rural areas part-time. I believe in the public system and I thought that if we're going to make the public system work, we have to participate in helping where the need is. Then about four years ago, my colleagues asked me to come to Lachine Hospital because there was a shortage of doctors. Then there was a push to downsize the hospital and turn it into a clinic, so I became president of the local chapter of physicians and took on a leadership role to fight to maintain it as a community hospital. That's what I've been doing recently.

In the past, after graduating from the Faculty of Medicine at McGill University in 1980, like a lot of my colleagues, I left Quebec. I did my residency in internal medicine in the United States and stayed on to work there for several years. Then from 1994 to 1996, I participated in a Canadian project in the Ivory Coast, I was the director of a community health project there. Working there, I realized that I really appreciated what Canada had. I decided in 1996 that I wanted to come back to Quebec and I've been here ever since.

MJM: What originally prompted you to leave Quebec?

Dr. Saba: Part of it was that when I first left Quebec, I felt that as an Anglophone I didn't really have a part in the society here. There was always political unrest; you never knew if Quebec would separate or not. I felt that there wasn't any future for anglophone doctors practicing in Quebec in the long run. I've since changed my mind on that.

MJM: What made you change your opinion?

Dr. Saba: I think that we have a wonderful model of health care, despite the waiting times and cutbacks. Secondly, as anglophones, we can master French adequately to practice and be comfortable, and to help in the development of Quebec. Whatever Quebec's political future, as physicians our focus should be on providing health care. If anything, we can help build bridges. Here I've been very involved, as an anglophone, to defend the only francophone hospital in the West Island of Montreal [Lachine Hospital]. I play the same role as co-president of the Coalition of Physicians for Social Justice in defending publicly-funded health care in Quebec. I think it shows that we as anglophones can play an essential role in defending social justice and health care needs of the poor in Quebec, whether they're anglophone or francophone.

By remaining here, it shows that we're not here just for our own financial interest, because we do have opportunities as anglophones to practice elsewhere. By making a decision to stay here, I think it shows that we care. We have a great opportunity here to heal physically, spiritually and even politically. As physicians we should see ourselves as healers of people

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and not of one or another political party. We are ambassadors for health.

MJM: Does assuming such a role require personal sacrifice?

Dr. Saba: If I didn't get involved in fighting for things that I believe in, whether that be saving a hospital or saving public health care...there is a cost. There's a cost in term of time. I'm often torn because of my family responsibilities, leaving my young children, sometimes to have to go to a meeting or do an interview. But in the long term it's less frustrating, I sleep better at night and I'm not as angry.

I see some of my colleagues sometimes who feel very flustered and frustrated, who feel like victims of a system that's gone awry. So I tell them, "get involved, spend some time to promote and defend our health care system, try to improve it. If you believe that public health care is the way to go, do everything you can to ensure that it works to its maximum."

MJM: Why are you committed to working within and promoting the public health care system?

Dr. Saba: I prefer to live in a system that is striving for more equity, ensuring a fair health care system for all, including our neighbours, friends, people we don't know, or relatives who are less well-off financially. There are lots of studies that show that public health care offers better medical care. Publicly funded health care offers better outcomes at a better cost than private health care. Given the evidence, we can't help but support a system that has worked well in the past.

MJM: What makes government the most appropriate provider of health care?

Dr. Saba: It's not so much government but a government-based insurance. When patients receive care not based on their own pocketbook, studies have shown that patients get more timely access to care and they also get guaranteed access. There are delays but the people who are most acutely ill get the care they need. Where money becomes a factor, people delay getting care or they don't get it at all.

However, the government needs to offer adequate salaries to health care providers and ensure that doctors working in offices can cover their expenses. This is necessary to provide the quality of care that people need and also to keep health care workers in the province. In Quebec, our per-capita health care expenditure is often the lowest in Canada. You can't get by on the cheap. So that's a proviso.

MJM: In your opinion, is that what the government is trying to do?

Dr. Saba: Yes. And that's unacceptable. And it's created this situation where medical graduates, on whom we spend lots of money to train, are leaving the province. We need to do everything we can to make it attractive for graduates to stay. It's not just a question of increasing enrolments, but also making sure they have a position once they graduate and that they can practice where they want to. If you really want them to go to rural areas, you can't do it by coercion.

MJM: What are some of the frustrations involved with dealing with the present system?

Dr. Saba: I think that we are overstaffed with administrators. I'm not talking about the ward clerk who works very hard on the floors or the support staff in the hospitals. I'm talking about the administrative assistants to the directors, the people at higher levels. Each health care institution has its own character and the administrators don't always respect or understand that. The money that goes to funding these extra layers of bureaucracy would be better spent on health care workers.

MJM: Why wouldn't introducing private health care put pressure on these institutions to be more efficient?

Dr. Saba: Where competitive models have been introduced, like in Australia or New Zealand, there was either a slight improvement or no improvement in efficiency, and eventually it winds up costing more. It would be a dangerous path to follow to jump into a system where the evidence shows no benefit.

MJM: Clearly there are major problems with the system as it is. How can improvements be made?

Dr. Saba: For waiting times, for example, with cardiac surgery in Ontario they have a coordinator that looks at waiting times from hospital to hospital and gets people who need surgery from one place to another. Just listing the waiting times at different hospitals on the internet and expecting the person with chest pains to make the call is not a solution. That's unquestionable. We need to coordinate that to direct people to hospitals where there are shorter waiting times. We don't need to offload patients to private clinics; within our own hospitals we can provide care.

Where there are excessive waiting times everywhere, we need to increase the efficiency of our operating rooms. Right now we have zero-deficit so each hospital is allocated a certain amount of money. If they go above that amount, they're penalized. There's got to be more flexibility in the budget. If a hospital gets more cases than it expects, it should get the budget it needs to deal with them. You can pay extra hours to staff; everyone needs a bit of extra money. You can do all this within the system, you don't need all these extra private clinics.

MJM: But you do need to spend more money.

Dr. Saba: You need the budget to provide the care. Right now there's no margin. Budgets are planned a year ahead and administrators get bonuses if they can stay within budget or go below budget. So administrators are paid to *decrease* the amount of care

that goes to patients. It shouldn't be like that.

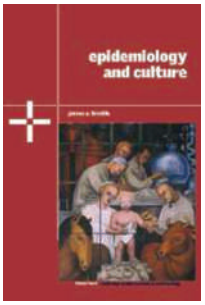
MJM: What advice would you give a young person beginning a career in medicine as a physician?

Dr. Saba: Go into the field of medicine that you most want to do. Don't let the money put you into an area that you don't want, otherwise you'll be very frustrated and very unhappy. Choose the path that's most fulfilling. Whether you go into the private or the public sector, follow your convictions.

It's a sacrifice, whatever field of medicine you go into. Don't allow the frustrations, the bureaucrats, the bureaucracy, the government, to take away your joy of medicine. If you feel something's wrong, fight to make it right.

Paul Saba, MD, is a graduate of the McGill University Faculty of Medicine. He is currently on active staff at the Lachine Hospital and in practice at Médi-Centre de Montréal-Ouest in family medicine. He is Co-President of the Coalition of Physicians for Social Justice, which advocates for publicly-funded health care.

BOOK REVIEW



Book Review by Olubukunola Ayeni, Laurentian University, Sudbury, by James Trostle

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Throughout life, humans are faced with dualisms: female or male, right or wrong, black or white. However, what accounts for the area between these two distinct points? In the aforementioned examples, how does one interpret androgyny, both right and wrong, or gray areas? In line with the thoughts of Adorno and Horkheimer, many aspects of life present a pseudo-individuality when, in reality, these disparate ideas are quite similar or can be molded to reach the same end result (1). Essentially, synergy is achieved in supplementing benefits from one area with another.

In particular, health and medicine contains many dualistic ideals. For example, whether medicine is an art or a science and whether physicians should base decisions on theory or use practice as a guideline are persistent questions (2). In a recent book, entitled Epidemiology and Culture, James Trostle attempts to rectify a novel medical dualism. He masterfully addresses the division of ideas between epidemiologists and medical anthropologists.

In order to understand the scope of this book, one must first assess the background information, the key themes that are presented, and the future direction of the author's arguments. The purpose of this review is to provide an analysis of Epidemiology and Culture in terms of social dimensions of health and illness. As a result, this discussion will begin with the foundations of health and illness, according to James Trostle.

Trostle describes health as an ideal that is unique to each person and culture. In fact, he claims that there are "distinctions in our seemingly universal view of health and disease.(3)". This belief is shared by many scholars (4, 5) and Trostle presents epilepsy as a prime example of a disease with multiple meanings and definitions. He notes that epilepsy results from a culmination of social, natural, and cultural forces (3). He argues that no definition of health and illness is complete without taking into account the elements of classification, meaning, risk perception, behaviour, and cultural constructs (3). These pieces of background information are extremely pertinent to the key themes presented within this book.

Trostle defines culture as a dynamic process that produces change. In keeping with this definition is the principle that culture has the ability to shape disease. Unfortunately, clinicians have long had poor training about the multifaceted aspects of culture and how these affect health (3). As a result, culture is treated as a single variable; often referred to as 'race'. In reality, clinicians should aim to understand the effect of culture on disease. There are many associations between culture and illness. For instance, why is it that AIDS was historically associated with homosexuality in Western society?

The cultural perception of death is another issue that is important to address when understanding health and illness. There is no universal definition for death or even a universal guideline to determine if someone is considered dead. Margaret Lock explains that although brain death is the legitimized end of life in North America, the Japanese affirm that the end of life is a social event and reject the notion of death as a measurable endpoint (6). Overall, Trostle (2005) explains how social and cultural meaning can be translated to mortality patterns. Clearly, culture has a significant effect on health and illness. However, it is equally important to understand the meaning and concept of risk amongst different cultures.

Risk is judged and understood differently amongst those from disparate cultural backgrounds. Trostle indicates that risk perception, at times viewed as individual, relies heavily on those around the individual and their culture (3). Deborah Lupton perfectly corroborates this point by adding that, "risk discourse in public health can be separated loosely into two perspectives. (7)" The first she describes as external (environmental), while the other is referred to as individual (focusing on lifestyle choice).

Similarly, Trostle believes that risk should be viewed in two dimensions: individual and social risk (3). The former describes people's motivation to seek treatment or take individual action for their risk, such as

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improving lifestyle practices after the diagnosis of heart disease (3). Social risk explains why some groups are marginalized to unhealthy environments. For example, AIDS among gay men in San Francisco was not labeled a crisis for quite a long time (3). Trostle and Lupton both agree that literature on risk in the health domain fail to explain the significance of social and cultural contexts (3, 7).

Understanding people's conception of culture and risk are central to gaining insight on health and illness at the individual and population levels. Consequently, it is imperative not to undermine such meanings by categorizing them merely as variables. This form of reductionism is often the practice in many research studies (3). Representing a group of people under a single variable such as "race" takes away from the unique attributes of each individual (8). To represent humans as "mass-produced objects on a factory production line" is further reductionist (8). In order to move away from this style of reductionism, Trostle suggests 'unpacking variables' correctly (3).

These variables, such as race or ethnicity, seem to fit perfectly into predictive models and have been used to explain scientific patterns for years (3). Many of today's research studies involve categorizing individual responses based on demographic information including race, gender, and age. However, a more effective and comprehensive approach is to 'unpack' these variables by understanding the social and cultural components of common epidemiologic variables (3). Trostle recommends creating 'auxiliary measurement theories' that take into account the ideas shaped by theories and their relation to the indicators used to measure them (3). In essence, auxiliary theories "guide the selection of specific variables and measures that are said to represent the underlying theory."

The author further explains, through examples, how the variables of person, place, and time can be unpacked incorrectly, resulting in a loss of individual complexity and cultural significance within each variable. Consider how the following ethnic groups are commonly listed within research: African Americans, Asian Americans, Hispanics/Latinos, Native Americans, and Pacific Islanders. Initially, this seems unbiased; however, it is important to note that some groups are listed by geographic region, while others are listed by language (3). This simplified list of groups could easily lead to the preconception that upper class Pakistani Muslims, middle class Thai Buddhists, and working class Catholic Filipinos share a unified Asian identity (3). As a result, evidence about social stratification is often misinterpreted as racial differences (3). With these explanations, Trostle validates the use of auxiliary measurement theory in research design and practice.

Trostle indicates that a prime example of this theory in practice would be to measure religiosity through prayer instead of using church attendance (3). The advantage of this practice would be to link religiosity to performance of faith instead of physical presence and network development within the church. Thus, unpacking variables serves to justify and guide selection of measures and strengthen quantitative research design; a valuable benefit to future research. Contemporary researchers can adopt this method of "unpacking variables" by ensuring that studies incorporate a broad sense of contextual elements (person, place, and time). As an example, a team of physicians, epidemiologists, and biologists would be able to unpack the complex variables involved with the relationship between tuberculosis and physical environment. Consequently, a multidisciplinary approach should be employed to further develop research studies.

The advent of processes such as research design that includes sociocultural variables and technological advances for integrated research, have fostered the development of the epidemiology and anthropology movement throughout the 20th century (3). Both anthropology and epidemiology are disciplines that offer unique contributions to the health care field. However, both also have shortcomings within their structure (3). A potential solution to this issue would be a multidisciplinary field that encompasses the strengths and contributions of both disciplines.

The result of this approach would provide an immense benefit to community-based interventions as well as health education and promotion (3). Two cases that illustrate a multidisciplinary approach are the Five-City Project and the investigation of cholera in Latin America (9, 10). In the Five-City Project, an integrated approach was utilized. Research was conducted by informal and formal networks, and culture was stressed in interpretation, leading to a comprehensive and representative picture of that community (3).

The unexpected resurgence of cholera in the Americas sparked interest and concern. Although the political, emotional, and economical toll was devastating, this incident allowed for a tremendous expansion of knowledge about individual as well as population health and illness. In this case, the researchers uncovered individual and group risk, health system adaptation to disease, government reaction to disease, and population reaction to interventions (3). Consequently, the integrative approach allowed for historical, political, and cultural data to be combined in order to better understand the initiation and spread of epidemic disease (3).

In essence, these studies, with the use of the integrated

approach, permitted anthropologists and epidemiologists to conduct more comprehensive, community-adapted interventions. However, there are still many obstacles in the way of developing a holistic approach. As with any new theoretical development, a novel multidisciplinary field will be met with resistance. One challenge that needs to be addressed is how to unify detailed individual analysis (i.e. case studies) with larger social and cultural constructs across populations. Trostle reiterates the magnitude of this test by adding that a challenge lies in combining individual cases and statistical accounts without distorting either (3). Nonetheless, combining anthropology and epidemiology would form a very comprehensive integrated approach.

Overall, I am thoroughly impressed with James Trostle's discourse on the state of anthropology and epidemiology. He succinctly portrays the necessity for a collaborative approach for understanding health and illness around the world. His masterful writing and ideas are corroborated with well-documented research. He also provides limitations and some areas of improvement within peer-reviewed research methodology. Also, an honest initiative by Trostle is evident in his acknowledgement of the limitations and challenges to his idea of a multidisciplinary approach. In fact, it is evident that the style of this book may be repellent to those within the medical forum as it is not presented in a typical scientific configuration. As a result, this may deter many health professionals from reading this piece of work.

Ultimately, this book implies that in order for society to develop heath initiatives progressively from epidemiology and medical anthropology, each field must recognize the unique contributions of the counterpart's discipline instead of competing (3). In reading this book, I have become more aware of the importance of cultural, political, and historical influences on health. I would recommend this book to any health care professional interested in gaining an appreciation of the evolution of cultural epidemiology. Further, this book is recommended for those who wish to understand the significance of the complex socio-cultural variables that exist within medicine.

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ABSTRACTS

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Investigation of positional and orientational contributions to visual shape integration in amblyopic patients

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Background information: Our ability to discriminate the shape of objects is very well developed and something we take for granted, yet little is known about the nature of the underlying neural mechanisms responsible. For instance, in amblyopia, a disorder characterized by an impaired processing in the visual areas of the brain in an otherwise normal eye, patients have difficulties judging the shape of highly visible objects, and traditional treatment consists of patching the fellow eye to let the amblyopic eye develop. Moreover, it is known that in order to process the shape of an object, the information relating both to the position and the orientation of the object is used. Furthering scientific understanding on the basis for the shape processing disorder in amblyopia may lead to a more comprehensive approach to therapy as well as refining our current knowledge on normal vision. **Purpose of the study**: By measuring the discrimination of contour shape in amblyopic patients, our aim is to find the relative contributions of positional versus orientational coding of visual information to the amblyopic deficit for shape discrimination. **Methods**: Amblyopic patients and controls are tested on their ability to discriminate between a circle and a slightly deformed one, using images that allow us to distinguish between orientational and positional information in the stimulus. Data is collected using a psychophysics threshold derived form a two- alternatives forced choice type experiment. **Results**: It was found that amblyopic subjects as well as normal subjects are better at tasks using pure orientational information than positional information. Moreover, when deriving the circular contour frequency from the stimuli parameters (CCF: number of radial modulations per unit of visual angle), amblyopes as well as controls do better at the task as CCF increases (as the stimulus distance rises). **Conclusion**: It was concluded that both orientation and position pooling mechanisms are affected in amblyopes. While position and orientation seem to be varying similarly as CCF increases within the range tested, preliminary evidence show some discrepancy at higher CCFs. Further investigations at even higher circular contour frequency will probably lead to additional results and conclusions regarding shape integration in amblyopic vision.
Keywords: shape integration, amblyopia, circular contour frequency

Nrf2 and Cul3 are potential biomarkers for the evaluation of chemoresistant breast cancer

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Background information: Cancer cells can induce the expression of detoxifying enzymes, which can nullify the activity of chemotherapeutic agents and prevent successful treatment. Recently, the transcription factor Nuclear Factor Erythroid-Like 2 (Nrf2) was implicated in a potential chemoresistance pathway in breast cancer. Nrf2 can induce the expression of phase II detoxifying enzymes which can lead to chemoresistance to doxorubicin and paclitaxel. Nrf2 expression is negatively regulated by the E3 ubiquitin ligase Cullin 3 (Cul3) by targeting it for proteasomal degradation. It has been shown that silencing of Cul3 using small interfering RNA leads to increased Nrf2 activity and dramatic chemoresistance. In a pilot study, breast cancer biopsies (8/10) showed high levels of Cul3 and low levels of Nrf2 and phase II detoxifying enzymes, but expression was not correlated with the chemoresistance status of the patients. **Purpose of the study**: We hypothesize that a higher ratio of Nrf2 versus Cul3 expression is a useful biomarker to determine the chemoresistant status of breast cancer. **Methods**: A tissue micro-array (TMA) set used was composed of 1622 core biopsies of breast tissue samples from 219 patients for prognosis and an additional 40 patients with follow-up biopsies. For the TMA, small 0.6mm and 1.0mm wide cylindrical core biopsies were punched from paraffin-embedded fixed tissue blocks. The cylindrical cores were then arranged in a new paraffin block in a precise array. Serial sections from the TMA set were stained using avidin-biotin based immunohistochemistry (IHC) techniques using human specific antibodies for Nrf2 and Cul3. **Results**: Positive staining was mostly seen in epithelial cells and epitheloid cancer cells. Nrf2 demonstrated mostly granular cytoplasmic staining while Cul3 demonstrated both cytoplasmic and nuclear staining. Quantification of staining intensity and percent staining of the epithelial cells was performed for the entire TMA set. In readable cores with epithelial cells, Nrf2 showed variable expression (44% no staining, 13% low intensity, 22% moderate intensity and 21% high intensity) while most cores showed high Cul3 staining intensity (2% no staining, 13% low intensity, 41%

moderate intensity and 45% high intensity). Variability, suggests patient differences, possibly due to the chemoresistance status of the patients. This cannot be determined yet as the IHC data at present still needs to be evaluated with respect to basic clinical-pathologic data such as tumor type, grade, therapy, relapse and disease-specific survival. At the same time, staining of Nrf2 versus Cul3 is being correlated with the different clinical parameters by a biostatician.
Conclusions: Once statistically significant relationships are determined, more definite conclusions can be drawn with respect to Nrf2 and Cul3 expression profiles and their use as markers for chemoresistance.
Keywords: breast cancer, chemoresistance, Nuclear Factor Erythroid-Like 2, E3 ubiquitin ligase Cullin 3, tissue microarray

Dealing with unscheduled patients in an outpatient clinic: a simulation modeling approach

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Background information: As the oncology outpatient clinic at Montreal General Hospital is looking for ways to improve efficiency and reduce patients' waiting times, the following question has been raised: at a given daily arrival rate of unscheduled patients, what is the best way to serve this clientele as to minimize their impact on the daily clinic's operations and the waiting times for all scheduled patients. **Purpose of the study**: In this study, a simulation modeling approach is used to answer the question previously raised. **Methods**: The data was collected through interviews and direct observation of the clinic. Additional information, such as the number of visits per day, type of procedures performed, and the number of physicians working was obtained from MedVisit database of the clinic. Process mapping was done to understand the patients' flow through the system. Simul8 V9 software package was used to build a simulation model to depict the oncology clinic at work. Modifications were then introduced to the basic model and the performance of these modified scenarios was compared to the performance of the original unmodified scenario. The sensitivity of performance was examined under four realistic environmental factors: no show, variance of consultation time, walk-in arrival rates and scheduled patients' arrival patterns. **Results**: While the patients' average waiting time was the measure of interest, the model also allowed evaluating other parameters including average and maximum queueing sizes, idle and working times of resources. While there was no single scenario that did well on all performance measures, the results showed that when it comes to reducing average waiting time for patients, adding an extra chair or reserving one chair for walk-in patients promised to give the best results **Conclusion**: Time constraint, quality of data, and limited programming power represented three major constraints of the study. Despite these limitations, the model seems to predict fairly well the relative values of performance measures.
Keywords: operations management, simulation, oncology clinic

The role for th17 cells in the progression of the cutaneous t cell lymphoma (ctcl) and in maintenance of the normal skin homeostasis

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Cutaneous T cell lymphomas (CTCL) are the most common lymphomas afflicting the skin. Currently the etiology of the disease is not known, however a number of recent reports indicate a possible involvement of the novel T helper (TH) 17 cell subtype in the disease progression. To acquire better understanding of the TH17 biology in CTCL and in normal skin homeostasis, Florescence Activated Cell Sorting (FACS) analyses were carried out on T cells isolated from the normal and the CTCL-lesioned skin for the presence of the four TH subtypes (i.e., TH1, TH2, TH17 and T reg). Similar analysis was carried out on Peripheral Blood Mononuclear Cells (PBMC) from the normal and CTCL patient blood. Furthermore, CTCL lesions were further analyzed by the Real Time PCR (RT-PCR) to detect the expression of the TH17 signaling cascade proteins. Our results indicate that the TH17 cells are present in normal and CTCL skin. These cells can be expanded by treating the skin explant cultures with IL-15 alone or in combination

with IL-21, IL-23 and IL-2. Interestingly, in normal skin all of the combination treatments expanded TH17 and the novel merged TH1/TH17 T cells, while in CTCL skin we observed only the expansion of TH17 cells with IL15/IL-21 treatment and the TH1/TH17 cells with IL-15/IL-23 treatment. Furthermore we document that the subset of CTCL patients, but not normal individuals, exhibit the presence of the TH17 cells in their PBMC population. RT-PCR data confirms the FACS results and documents that a large subset of the CTCL patients expresses the critical components of the TH17 signaling cascade and thus are able to elaborate a TH17 immune response. Current work refocuses our attention on the presence of the TH17 and TH1/TH17 pathogenic cells in PBMC samples and skin of the CTCL afflicted individuals and opens the avenue for further studies of the IL-17 signaling in this disease.

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Keywords: Cutaneous T Cell Lymphoma (CTCL), IL-15, IL-21, IL-23, TH-17

The role of the subventricular zone in neurogenesis in Parkinson's Disease

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Background information: Parkinson's disease is a neurodegenerative disease of unknown etiology characterized by a progressive degeneration of dopaminergic neurons in the pars compacta of the substantia nigra. Patients are typically diagnosed with symptoms of motor dysfunction, rigidity, mood disturbances, etc – most of which appear after more than 70% of the striatal dopamine is already depleted. Current treatments are mainly neuroprotective for a limited number of years, consisting of a dopamine replacement strategy using levodopa. Since dopamine modulates ontogenetic neurogenesis and contributes to morphogenesis by governing the proliferation of neural stem cells, it is hypothesized that its depletion may affect neural precursors in the subventricular zone (SVZ) of the adult brain. **Purpose of the study**: The goal of this study was to analyze neurogenesis in the subventricular zone and the effect of dopaminergic neuronal loss on proliferation in the subventricular zone. **Methods**: Three wild type mice and three aphakia mice, aged 7 weeks, received injections of bromo-2-deoxyuridine (BrdU) intraperitoneally at 3 hour intervals. Then, the animals were perfused transcardially with saline and heparin, and then buffered paraformaldehyde. Brains were removed and cut at 40 μm-thickness on a freezing microtome in the coronal plane. Every 6th serial section was collected in phosphate-buffered solution and immunohistochemically stained with mouse anti-BrdU antibody; then exposed with biotinylated goat anti-mouse IgG and finally nickel DAB chromogen (in Tris buffer). Sections were rinsed and mounted on slides, air dried, Nissl stained, and coverslipped. Optical Fractionator, an unbiased stereology technique, was applied to estimate the total number of BrdU positive neurons in the SVZ through the Stereo Investigator software and a light microscope. **Results**: The average Nissl count for wild type mice was 110,097 ± 6675, slightly higher than the average aphakia cell count 105,314 ± 11,850 cells ($p>0.05$). BrdU profiles in the adult subventricular zone of wild type and aphakia mice were 20,650 ± 1323 and 22400 ± 3491, respectively. While the average BrdU profile was marginally higher in aphakias, statistical analysis did not show statistical significance ($p>0.05$). This result was consistent within all delineated zones in aphakia and control mice. Further, the ratio of BrdU to Nissl cells was evaluated – 0.211 for aphakia and 0.187 for wild type; while the average proportion was higher in aphakia, the results were also insignificant ($p>0.05$). With regards to total volume sampled, the wild type mice volume of 0.139 ± 0.00888 mm3, compared with 0.124 ± 0.0186 mm3 in aphakia animals, showed no statistical significance ($p>0.05$). **Conclusion**: Analysis of the SVZ suggested that there is no significant difference in cell proliferation and neurogenesis between aphakia and wild-type control mice. To further validate the conclusions of this study, it may be necessary to increase the number of animals tested.

Keywords: Neurogenesis, Aphakia, BrdU, Parkinson’s Disease, Subventricular Zone

Establishment of non-invasive direct pulmonary infection technique for murine study of cystic fibrosis nutritional therapy

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Background information: Cystic Fibrosis is a chronic inflammatory disease, characterized by progressive lung damage and failure, leading to premature death. CF patients are prone to bacterial infection; the exaggerated inflammatory response and the resulting oxidative stress cause the characteristic impairment in pulmonary function. Among the infective agents that cause damage in cystic fibrosis patients' lungs, Pseudomonas aeruginosa is one of the most common and most destructive. Animal models have been developed throughout the years with the goal of gaining a more complete understanding of P. aeruginosa infection and pathogenesis, and by extension, of cystic fibrosis as a whole. Recently, a novel method was developed in which bacteria-impregnated agar beads are administered orally into the trachea, through the vocal cords. This technique allows for the bilateral infection of the lungs without the need for surgical intervention, eliminating the potentially confounding inflammatory effects resulting from this injury and the healing thereafter. **Purpose of the study**: It was our intention to establish this less invasive model in our lab, for later use in a series of studies to determine the effects of a novel nutritional supplementation on the pathological course of chronic infection and inflammation in CF. **Methods**: Two time courses were studied, each with two groups of animals (infected and control). The mice were instilled with either bacteria-impregnated beads (5 x 105 CFU) or sterile beads, and then evaluated and weighed for 3 or 7 days. Bronchoalveolar lavage was performed at the end of the time course in order to recover inflammatory cells from the lungs. These cells were then counted to determine the total leukocyte number per mL as well as the proportions of specific cell types (macrophages, polymorphonuclear cells, lymphocytes). **Results**: Our results showed few significant differences between the groups in terms of weight change over time and total and differential leukocyte numbers. It was suspected that several of the animals were not successfully infected, and there was difficulty as well in recovering adequate numbers of leukocytes for analysis. These difficulties may be due in part to the technician's expertise with the model, but also to its inherent challenges. Possible solutions include the use of novel infection-monitoring techniques, such as PET or bioluminescence, in order to confirm and quantify infection, as well as the use of certain biomarkers to serve as proxy indicators of specific cell infiltration. **Conclusion**: The above additions warrant investigation as they could prove pivotal in the consistent success of this model, and consequently in its use in the development of effective therapies for Cystic Fibrosis patients.
Keywords: Cystic, Fibrosis, Murine, Infection, Nutrition

Optimum stimulus characteristics for speech perception interventions

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Similarities exist between adults learning a second language and children with speech sound disorders. Specifically, both groups have inaccurate phonological representations of the speech sounds they are attempting to learn, leading to incorrect production of these new sounds. Speech perception training has been shown to be effective in improving phonological representations in both adult second language learners and children with speech sound disorders. However, there have been no studies as of yet describing a systematic procedure for creating a speech perception training program. Such a systematic procedure is necessary in order to determine the stimulus characteristics, such as variability in voices and speaking rate that are optimally related to an effective speech perception training program. This study examined the role of multiple voices versus one voice with prototypical stimuli in training individuals to perceive a vowel contrast used in French, but not used in the native language of the participants. Participants were nine monolingual English speakers, aged 16 to 52 years. Participants first completed a pre-test to obtain a baseline of their ability to perceive the difference between two French vowels. They were then randomly assigned to a control condition or one of two training conditions involving a two-alternative forced-choice word identification task. Participants received immediate feedback during these training sessions. The training sessions were followed by a post-test identical to the pre-test, and results were compared to the baseline measure. It was hypothesized that those in the multiple voice condition would show greater effects of training than those in the single voice and control conditions. Preliminary results provided support for this hypothesis, as those in the multiple voice condition performed better on the perception task following training than those in the single voice and control conditions.

Although the results revealed a trend in favour of speech perception training with multiple talkers rather than with a single talker, further data must be collected to confirm this conclusion.
Keywords: speech perception training, speech sound disorders, second language, learning, adults

The role of the subventricular zone in Huntington's Disease

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Background Information: Huntington's Disease is a genetically inherited neurodegenerative condition characterized by a progressive loss of neurons in the striatum and the cerebral cortex. It is caused by a trinucleotide repeat expansion in the Huntington gene (Htt) which produces an altered form of the Huntington protein (mHtt) resulting in neuronal death. The most common presenting symptoms in adults are chorea (jerky, rapid, uncontrollable movement), memory deficits, and additional manifestations of motor dysfunction such as parkinsonism and dystonia. Striatal neuronal loss results in progressive worsening of the movement disorder, difficulty swallowing, mood disturbance and eventual death. Current treatments are mainly neuroprotective since there is no effective method of replacing lost neurons. **Purpose of the Study**: The goal of this study was to determine whether new neurons are produced in the subventricular zone, which under normal circumstances produces neurons for the olfactory bulb and to some extent for the striatum, in response to neuronal loss in the Huntington brain. **Methods**: Fourteen month old YAC128 and control animals were injected with BrdU 4 times over a 48 hour period and were perfused 12 hours after the final injection. Immunohistochemistry staining was done by incubating sections in mouse anti-BrdU antibody overnight at 4 °C and then leaving the sections in goat anti-mouse IgG antibody for 1 hour at room temperature. Sections were then mounted onto slides, air dried, Nissl stained with cresyl violet and coverslipped. The subventricular zones of the two groups of mice were analyzed using unbiased stereology to obtain an accurate estimation of the total number of proliferating cells. **Results**: The estimated total averages of Nissl cells, an indicator of total cell number since all cell are Nissl positive, were 53013 ± 2593 and 56671 ± 3661 for the wild type and YAC128 animals respectively. This was not statistically significant (p=0.3829). The estimated total average of proliferating cells, i.e., those cells stained with BrdU, in the wildtype and YAC128 animals was 17,100 ± 2951 and 14,745 ±1105 respectively. Although cell proliferation appeared slightly decreased in the YAC128 animals analysis showed that this difference in BrdU labeled cells was not statistically significant (p=0.4215). Average total volumes in the two groups were 84641575 ± 3008666 mm3 and 91377825 ± 6166240 mm3 respectively, however this too was not statistically significant (p=0.3002). **Conclusion**: The results showed no significant difference in cell proliferation and brain volume between the two groups of mice. Further experimentation with younger animals and increased mice in each group may be necessary to obtain conclusive results.
Keywords: Huntington's Disease, Subventricular Zone, Neurogenesis, YAC128 Mouse

Significance of extreme high d-dimer levels in patients with clinically suspected venous thromboembolism

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Introduction: Positive d-dimer values are considered to be non-specific for the diagnosis of venous thromboembolism (VTE). However, the potential relevance of extreme high positive d-dimer values is unknown. **Purpose of study**: The objective of our study was to investigate the significance of extreme high d-dimer levels (>2500ng/ml) among patients presenting to the emergency department (ED) with clinically suspected VTE. **Methods**: We performed a retrospective chart review of patients who met all of the following inclusion criteria: 1) outpatient who presented to our hospital's ED from 2002-2007; 2) patient identified by an attending physician as having clinically suspected pulmonary embolism (PE) or deep vein thrombosis (DVT); 3) patient had a d-dimer blood test during the ED visit with result >2500ng/ml; 4) patient underwent imaging tests to objectively rule in or rule out PE and/or DVT. Data were collected on demographic information, history of VTE and thrombophilia, co-morbid conditions and VTE risk factors (including recent surgery, trauma, cardiac disease, pregnancy/post-partum, use of oral contraceptives, smoking, cancer), results of imaging tests for VTE, final diagnosis and outcomes after the ED visit including hospitalization and death. **Results**: Of 164 patients identified to have d-dimer >2500 ng/ml, 123 met all eligibility criteria and were included in the study. The mean age was 67 years and 51% were female. D-dimer

levels in the participants ranged from 2500 to 4000 ng/ml, with a mean of 3648 ng/ml. Older patients, male patients and those with active cancer tended to have higher d-dimer levels. Overall, 54% of patients were diagnosed with VTE. The prevalence of VTE increased as the d-dimer level increased, such that between 3500-4000 ng/ml, 58% percent of patients had VTE. In patients with DVTs, proximal clots (84%) were more frequent than distal clots (16%). Patients diagnosed with active cancer had a higher d-dimer level, and of those, 67% were diagnosed with VTE. Patients diagnosed with VTE had poorer outcomes than those without VTE. 61% of patients with VTE were hospitalized versus 42% of patients without VTE, and 27% of patients with VTE died compared to 19% without VTE. Among patients in whom VTE was ruled out, the three most common alternate diagnoses were pleural effusion, cancer, and congestive heart failure. **Conclusion**: More than 50% of patients with clinically suspected DVT and extreme high d-dimer levels have VTE, which is much higher than the 10-20% prevalence of VTE among unselected patients with clinically suspected VTE reported in the literature. Within our population, the prevalence of VTE increased with increasing d-dimer levels, even in patients with multiple co-morbidities. Further analysis will determine which patient characteristics are associated with greatest risk for VTE among patients with extreme high d-dimer levels. Our findings challenge the assertion that positive d-dimer levels are not useful in the diagnostic process for VTE.

Keywords: venous thromboembolism, pulmonary embolism, deep vein thrombosis, high d-dimer, diagnosis.

Attitudes of health care professionals towards integration of complementary and alternative medicine into professional education and clinical practice

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Background: Complementary and alternative medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." According to the 2003 Canadian Community Health Survey, 20% of Canadians over the age of 12 used some type of CAM in the preceding year. However, health care professionals (HCPs) often do not have sufficient knowledge to discuss CAM use with their patients. Thus, formal education on CAM may be warranted. Further, up to 98% of nurses support the use of CAM, and up to 83% of physicians perceive CAM as useful. Integrating CAM into the hospital centers might therefore be desirable. **Purpose of the study**: This pilot study aimed to describe and compare attitudes of HCPs toward integrating CAM into their professional curricula, their institution, and their own clinical practice. **Methods**: Staff physicians, nurses and medical residents working at St. Mary's Hospital Center in Montreal were surveyed (June to August, 2007) using an anonymous self-administered questionnaire. Five CAM categories were defined according to NCCAM definitions. These categories were: whole medical systems, mind-body interventions, manipulative methods, biologically-based medicine, and energy therapies. The following was assessed for each category of CAM: the desire to see CAM taught as four different modalities, the desire to see CAM available at the HCPs' institution, and the desire to practice CAM oneself. Descriptive statistics were used to characterize the study sample; non-parametric tests were used to compare attitudes according to profession. **Results**: 126 HCPs completed the survey, including 39 (31%) staff physicians, 58 (46%) nurses and 29 (23%) residents. Interest to include CAM courses in the medical and nursing curricula was high. Interest levels for the 5 CAM categories ranged from 67% to 91% for staff physicians, 73% to 95% for nurses, and 71% to 90% for medical residents. 93% and 86% of HCPs wanted CAM taught as electives and continuing medical education, respectively; 52% wanted CAM taught as core courses and 37% as clinical rotations. More nurses (64%) and medical residents (50%) wanted to integrate CAM into their own clinical practices compared to staff physicians (16%) ($p<0.0001$). Of the HCPs who wanted a clinical rotation in CAM, 70% reported a desire to practice CAM themselves, whereas of those who did not want a clinical rotation in CAM, only 39% reported a desire to practice CAM themselves ($p=0.005$). More nurses (93%) than residents (79%) and staff physicians (68%) reported a desire to see CAM available at their institution ($p=0.004$). **Conclusion**: A majority of HCPs reported interest for including CAM courses in the medical and nursing curricula, and seeing CAM available at their institution. Nurses and medical residents displayed more interest in performing CAM therapies as part of their clinical practice compared to staff physicians.

Keywords: Physician, nurse, attitude, complementary, alternative.

Shape processing in human vision: binocular properties of shape-frequency and shape-amplitude after-effects

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Background information: Recently, Dr. Kingdom's lab in the Department of Ophthalmology at the Royal-Victoria Hospital has started to use a new tool for studying contour shape coding in human vision, known as the 'shape-frequency and shape-amplitude after-effect'. The SFAE and SAAE refer respectively to the perceived shifts in the shape-frequency and shape-amplitude of a sinusoidal test contour following adaptation to a contour with a different frequency or amplitude. The shift is always in a direction away from that of the adapting stimulus and is believed to reflect underlying changes in the distribution of neural responses to curvature. By manipulating the properties of the adapting and test contours, and by measuring the affect on the size of the after-effect, we can learn more about how visual neurons code curvature. **Purpose of study**: To gain a better understanding of the human visual system and of eye disorders by looking at (1) whether the SFAE and SAAE are encoded by a monocular or binocular mechanism, (2) whether stereoscopic depth influences our perception of them and (3) what the effect a parallel surround texture has on a contour. **Methods**: The stimuli, a pair of sine waves placed at equal distance, above and below a central fixation marker, were created using a VSG2/5 video-graphics card, presented on a calibrated monitor and viewed through a stereoscope. Each session began with an initial adaptation period of 90s after which a repeated test of 0.5s duration was shown, interspersed with top-up adaptation periods of 2.5s. Subjects, keeping their eyes on the fixation marker, were asked to judge whether the upper or bottom contour had a higher frequency/amplitude, indicating their choice via a button press. The computer then adjusted the ratio of test shape-frequencies/amplitudes, in order to move towards the point of subjective equality (PSE) from which the size of the after-effects was calculated. **Results**: (1) The size of the after-effects measured in the interocular condition (adaptation and test stimuli presented to different eyes) was comparable to that obtained in the intraocular condition (stimuli presented to the same eye).
(2) The magnitude of the SFAE and SAAE when the adapting and test stimuli were presented in different depth planes was similar to when the stimuli were in the same depth plane.
(3) The size of both after-effects was significantly reduced when a surround texture was located in the same depth plane as the contour compared to when they were in different depth planes and when there was only a single adapting contour. **Conclusion**s: (1) Simple shape encoding occurs via a binocular mechani (2) stereoscopic depth does not affect our perception of simple shapes and (3) a parallel surround texture has an inhibitory effect on a contour when they are placed in the same depth plane
Keywords: Shape-frequency / Shape-amplitude after-effect; Adaptation; Binocular contour-shape processing; Stereoscopic depth; Parallel surround texture

The relative spatial and temporal contributions to biological motion processing

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Background information: A Point light walker is an ensemble of dynamic point lights where each “point light” represents the joint of an actor (Johansson 1973). **Purpose of the Study**: Biological motion perception refers to our ability to perceive and understand the movements of other people. The aim of this study was to measure the relative spatial (form) and temporal (motion) contributions to biological motion perception in both central and peripheral vision using point light walker stimuli. By testing the relative sensitivities to spatial and temporal distortions, the information sources most relied on by central and peripheral vision could be established. **Methods**: Following Thompson, Troje, Hansen and Hess (2007), two walkers were presented for two seconds consecutively. After stimulus presentation, the subject then chose the walker closest to the ideal form using one of two keys on the keyboard. A staircase function of three down one up was used to calculate the threshold value for the run. **Results**: In the spatial conditions designed to evaluate form information, it was found that central vision could detect much finer spatial distortions than the periphery at the lower pedestal distortion levels as evidenced by lower distortion thresholds. However as the pedestal distortion level increased, the discrimination thresholds for central and peripheral vision seemed to converge. In the temporal conditions designed to evaluate motion information, subjects found identifying a walker with intact form but distorted motion much easier than a walker with only motion. With the extra form information, in the subjects’ central vision, the performance of form and motion walker was two-fold

easier than that of the pure motion walker. However, in the periphery, this two-fold increase was not seen. **Conclusion**: Both form and temporal manipulations affected fovea and peripheral performance on the biological motion task. Central vision was more sensitive than the periphery to the incremental distortion of spatial information whereas peripheral vision was just as sensitive as central vision to the incremental distortion of motion information.
Keywords: Biological Motion, Spatial Distortions, Temporal Distortions, Peripheral Vision, Central Vision

Contour shape processing independence from motion direction

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The aim of the project is to determine if the mechanisms in the visual system that are involved in processing the shape of a contour (such as a line or edge) are selective for motion direction (e.g. selective for contours moving, for example, leftwards versus rightwards). The experiment employed the idea of after-effect, where human subjects "adapted" to two sinusoidal (wiggles) contours of different frequencies (number of wiggles) or amplitudes (height of wiggles), and then were presented two sinusoidal contours of same frequency or amplitude. Although physically identical, the two contours were perceived as different due to the prior adaptation. Through a series of steps, a computer calculated the magnitude of these after-effects. In order to test for motion selectivity, we compared the magnitude of the after-effects between the condition where the "adaptor" and "test" contours moved in the same or opposite direction. We tested global motion (the whole sinusoidal contour moved left or right), and local motion (the sinusoidal contour was divided into little segments through which alternating black and white bands drifted). Our results demonstrated that the magnitude of the after-effects were relatively similar if the adaptor and test moved in the same or opposite direction, both for global and local motion. A possible explanation is perceptual invariance, which implies that an object can be recognized even though it moves or is placed in different depths.

Assessment of venous thromboembolism treatment in hospitalized cancer patients

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Introduction: Venous thomboembolism (VTE) is a serious and potentially fatal condition in cancer patients. The American College of Chest Physicians (ACCP) have acknowledged this, and in their most recent published guidelines (2004), have recommended that patients with cancer and VTE be treated with subcutaneous low-molecular weight herparin instead of an oral vitamin K inhibitor, such as warfarin. Despite this advisement, it seems that the implementation of the guidelines may be inconsistent and inadequate, with many physicians continuing to treat VTE patients in the same manner, regardless of whether they have malignancies or not. **Purpose of study**: The main objective of this study is to assess physicians' compliance with the ACCP guideline (2004) recommendations for the treatment of VTE in hospitalized cancer patients and to identify the obstacles that interfere with the successful implementation. **Methods**: A retrospective cohort study was conducted in which a medical chart review was preformed on all hospitalized patients with cancer and an objectively diagnosed VTE so as to examine the prevention and treatment strategies for VTE. **Results**: In all, 57 patients were included in the cohort. For VTE prophylaxis, 57.9% of the patient did not receive prophylaxis, and of those who were prophylaxed, 50% of them received ACCP-recommended prophylaxis therapy. Prior history of VTE was associated with ACCP- recommended prophylaxis therapy. With regard to VTE therapy (initial and long-term), 28.1% of patients received ACCP-recommended therapy. None of patients with color-rectal cancer received ACCP-recommended therapy, but among cancer patients receiving hormonal chemotherapy, 40% received treatment that was ACCP-recommended. **Conclusion**: Physicians treating cancer patients with VTE are implementing ACCP guidelines but adherence is not complete. Evaluation of VTE risk factors (such as prior history of VTE) is appropriately being considered in VTE prophylaxis and treatment, but there are still many missed opportunities for appropriate treatment. Fear of bleeding complications as a result of anticoagulant treatment may be one obstacle that prevents successful guideline implementation.
Keywords: Venous thomboembolism (VTE), subcutaneous low-molecular weight herparin (LMWH), warfarin, cancer, VTE prophylaxis.

Lumbar pedicle screw insertion with preoperative ct based navigation: review of 135 consecutive cases

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Background information: Traditionally, pedicle screws in the lumbar spine were inserted using anatomical landmarks. For planning the screw trajectory, surgeons use 2-D images such as simple X-Rays, CT and MRI scans. To improve intraoperative screw accuracy, surgeons use intra-operative X-Rays, which have shown a rate of misplaced screws varying between 14% and 55%, measured on postoperative CT scans. Using preoperative CT-based navigation, the literature reports a rate of misplaced screws varying between 4% to 7%, measured by postoperative CT scans. None of those reports rated the screw length error or reviewed simultaneously the detailed clinical results. **Purpose of the study**: In this study, we described both the short-term and long-term technical and clinical results of a large population having had a lumbar fusion. Our main goal was to determine the results of lumbar fusions planned with CT based navigation. **Methods**: This series included 44 men and 91 women (mean age 61 years, range 24-90 years). All screws were preoperatively planned for diameter, length and direction. Instrumentation included the lumbar spine only (49), S1 (80) or the thoracic spine (6) during a lumbar fusion surgery. The senior author inserted 840 screws and all of them were assessed with post-operative CT scans. Osseous union was assessed using dynamic plain films. Screw quality and listhesis was assessed on post-operative CT-scan sagittal reconstructions. Pain was surveyed using a self-rated scale /10, a visual analogue scale, and Oswestry and SF-36 questionnaires. **Results**: Misplacement of screws in the pedicle was found in 5.7% of screws, (2.3% lateralty, 1.7% inferiorly, 1.1% superiorly, 0.7% medially). There were no major errors (>4.1mm); the three intermediate errors (0.4%) were all lateral (2.1 to 4mm). We found 45 minor errors (5.4%) (0.1 to 2mm). Postoperative segmental degenerations were found most frequently in fusions ending at L2 superiorly and with iliac screws inferiorly. Above level degenerations were found in 30 patients (26/135; 19%) 15 months postoperatively on average. Self-rated back and leg pain was improved by 48% and 72% respectively one year postoperatively, and the improvement in pain was stable over time.
Conclusion: CT based preoperative navigation was shown to be safe and relatively accurate in our series. Accurate screw placement was associated with a good clinical outcome but did not prevent above level degenerations. This is reported as a major drawback for long fusions.
Keywords: lumbar spine, navigation • pedicle, screw

What influences the perceived impact of email alerts? Analysis of responses from a national study

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Background information: Email alerts are one type of computer-mediated communication available to practicing physicians to assist with knowledge translation of results from clinical research. Research involving knowledge exchange needs a valid measure of the impact of email alerts, and an acceptable method of deploying such a measure to health professionals. In 2006, Drs. Grad and Pluye were funded by the Canadian Institutes of Health Research to conduct a naturalistic mixed-methods study to validate a new method of gauging the impact of email alerts. Preliminary analyses of more than 29,000 POEM ratings submitted by 1,364 doctors revealed that:
• 16% of all ratings are statements of "No Impact" on the doctor,
• 14% of all ratings are statements that "My Practice Will Be Improved".
Purpose of study: To systematically examine the content of the InfoPOEMs in order to determine what elements are associated with a perceived positive impact on the physician's knowledge and practice. **Method**: We defined ten PECODR elements (table 1), and I extracted relevant sentences, segments and words, as well as data on number of characters, setting and level of evidence out of each InfoPOEM into an Excel® spreadsheed. Using 65,535 ratings collected from 1,008 family practitioners, we classified 109 InfoPOEM that had been evaluated by at least on physician into two categories, the preferred InfoPOEMs, those having high positive ratings, and those having at least one negative and/or neutral assessment by at least 40% of the rating physicians. We first compared preferred InfoPOEMs versus unfavorable ones with logistic regression; we then focused on how content of an InfoPOEM could affect impact perceived by physicians. **Results**: Level of Evidence (LOE), Number of Characters (NOC), Complexity, Number of Results (NOR) and Study Design (SD) have confidence intervals overlapping the null value (Odds Ratio of 1.0). We therefore concluded that these variables did not seem to be significantly predictive of a negative perceived impact. The only variable of study setting that approached statistical significance in the regression analysis was studies using inpatients. The odds ratio was 3.7 with only a slight overlap with the null value in the lower confidence interval (95% CI 0.85-16.1). This finding suggests that inpatient studies may increase the likelihood that physicians will perceive the impact of the POEM as negative or neutral. **Conclusion**: Using our initial analysis, we were able to conclude that studies with an inpatient setting increase the likelihood that physicians will perceive the impact of the POEM as negative or neutral.
Keywords: InfoPOEM, Family medicine

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ERRATUM

In the last issue of the MJM, Volume 10, Number 2, Victoria Au's abstract should have been included among scientific abstracts from the CSLSR conference. We include her abstract below. The MJM apologizes for any inconvenience this error may have caused.

Characterizing the functional domains of baculovirus Late Expression Factor 3 (LEF-3)

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The *Baculoviridae* is a family of arthropod-specific viruses found in over 600 insect species. Baculovirus species have very specific host ranges and are unable to replicate in mammalian cells, making them ideal for use as biopesticides and vectors for gene therapy. AcMNPV is the best-studied member of the *Baculoviridae* family and most of the genes identified in this virus serve as a basis for comparison to other baculoviruses. Six proteins are essential for AcMNPV DNA replication: LEF-1, LEF-2, LEF-3, DNA Polymerase, P143, and IE-1. LEF-3 (407 aa, 45 kDa) is a single-stranded DNA binding protein that functions as a homotrimer. LEF-3 also transports P143, a helicase, to the nucleus. We predict that LEF-3 has several functional domains responsible for: ssDNA binding, interaction with P143, and interaction with host importin proteins for nuclear localization. Site directed mutagenesis revealed that the N terminal region (amino acids 5 to 56) are responsible for LEF-3 nuclear localization, while a region including 125 amino acids at the N-terminus is required for interaction with P143. To identify amino acids within the 5 to 56 region essential for nuclear transport, conserved amino acids were targeted for mutagenesis. The intracellular localization of mutated proteins expressed by plasmid-transfected cells was examined using fluorescence microscopy and biochemical fractionation. A similar approach will be used to identify the regions responsible for P143 interaction and ssDNA binding. Although the first fifty amino acids of AcMNPV LEF-3 contain characteristics similar to classic NLSs, the results of mutating 14 conserved amino acids or from deleting various regions within the 5 to 56 region of LEF-3 did not demonstrate any clear effect on nuclear localization. Therefore, the essential components of the domain remain to be determined and the transport of LEF-3 into the nucleus may be mediated by a novel NLS.

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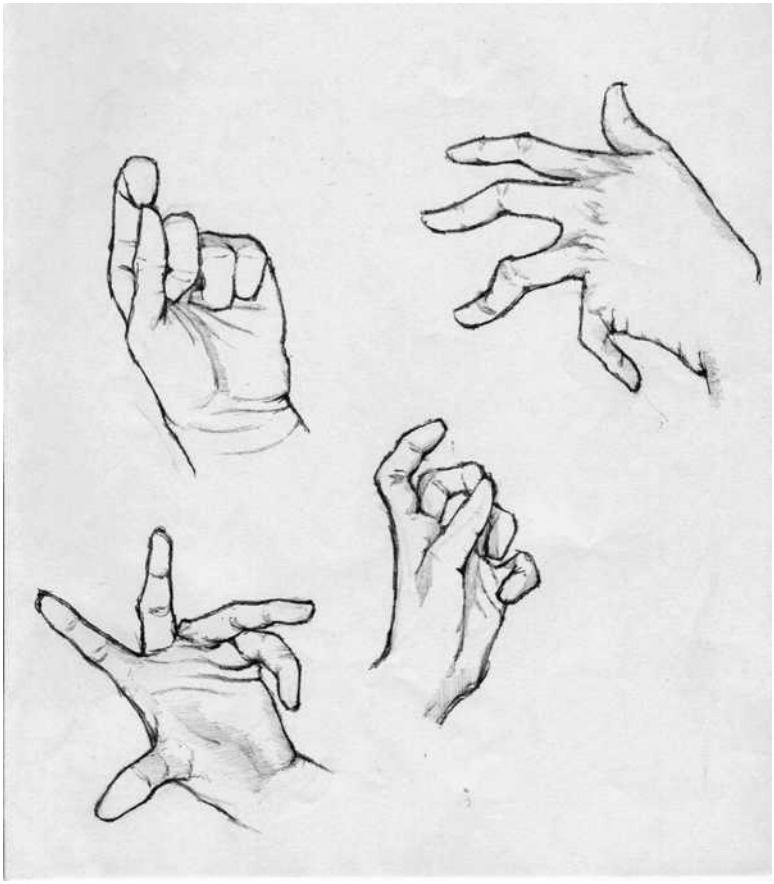

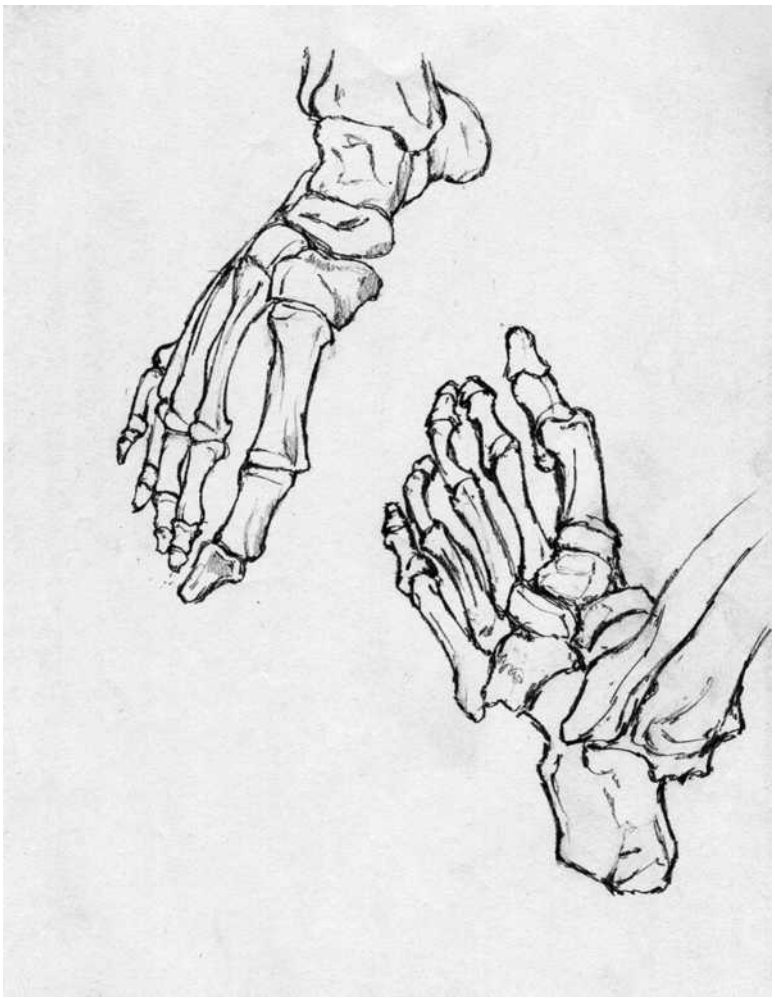

Title: **Homo sapiens 1 & 2**
Medium: **Pencil**

Nam Dinh Doan is a second-year medical student at McGill University (Class of 2010). He enjoys drawing and writing, and takes an interest in films. The above pictures were drawn in 2004 at the Biology Learning Center at John Abbott College, Montreal. Objects drawn were the property of John Abbott College

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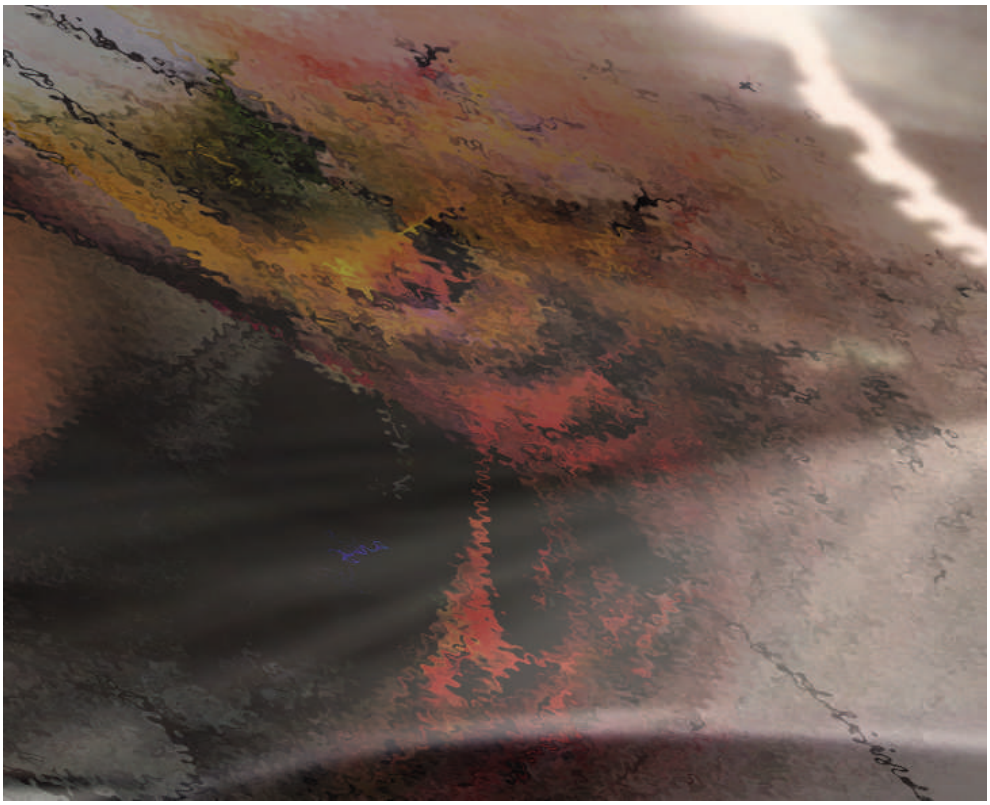

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