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The one constant in medicine is constant change. As students, we appreciate the evolving nature of our understanding of diseases, their pathophysiologies and manifestations, their treatment modalities, and the lives they affect. The crucial role which clinicians play in this evolution is often underestimated and poorly understood. The clinician-scientist is, ultimately, the investigator who poses the relevant questions acquired from clinical experience, and who links the theories of the abstract realm with solutions of the concrete and tangible world. Thus, translational research, as the cliché goes, from the bedside to the bench, and evidently back again, is of utmost importance and interest to clinicians and medical students alike (1).

THE CLINICIAN-SCIENTIST

While clinician-scientists have some characteristics that set them apart from other researchers, their task is inherently different. With one foot in a clinical setting, and the other in a research setting, the clinician-scientist occupies a unique niche which brings about advantages, yet limitations. On the one hand, clinicians have irreplaceable insight into the patient setting (2). Their motivations for research are often aimed at finding solutions to problems faced in everyday life (3). In this sense, they bridge the theories of basic science, and applications in the clinical settings. In addition, from their medical training and practice, they are used to collaborating, working in large teams, and have a wide network of contacts. On the other hand, clinicians face great challenges- they have less time for training, writing grants and team management (2, 4). Research translates into time, resources, and expertise taken away from patient care. Yet, what a career! In which other field can one derive this dual satisfaction, one that stems both from the warm and personal interactions of medicine, and the intellectual process of asking and solving a question?

INTERACTION OF CLINICAL PRACTICE AND SCIENCE: THE PLACEBO EFFECT

The placebo effect, the theme of this issue's Focus, is one example of a domain that has greatly benefited from collaborations between clinicians and scientists. For the first time in the history of the MJM, articles in this section were peer-reviewed by specialists in the field, through the organizing efforts of Dr. Amir Raz and Dr. Paul Clarke and our Focus Editor, Samuel Lapalme-Remis (McGill University). We are proud to feature articles by Dr. Kilhstrom (University of California Berkeley), Dr. Lichtenberg (Hadash Medical School, Israel), Dr. Loftus (University of Washington), Dr. Fries (Stanford University School of Medicine) and Dr. Kirsch (University of Hull, UK).

THE MJM: OVER 10 YEARS OF CONTRIBUTION

The MJM's core mission, beyond encouraging student research, is to foster a scientific career and approach within future clinicians. The great advantage in exposing and inspiring students at an early stage is the training acquired. Students witness the mammoth efforts and, at times, the serendipity involved in achieving a single outcome. At the same time, students receive criticisms and realize where research was unsuccessful. We see where research results can be misleading; after trying to spin the results of our own research to their most marketable form, we learn how to take someone else's paper with a grain of salt. Although, realistically, research performed in medical school is often not groundbreaking, the lessons learned remain. Studies have shown that students undertaking research experience during medical school are more likely to pursue an academic career (5, 6). With their interests sparked and curiosity piqued, they desire to delve deeper and inquire.

MEDLINE AND BEYOND

As the MJM moves forward in the early 21st century, it retains its central mission and mandate of promoting student research internationally and encouraging and inspiring students to pursue a career in research. The MJM is most proud to announce that we are now indexed in both PubMed/Medline and EMBASE, both invaluable resources for researchers and clinician-scientists internationally, and the perfect medium to showcase the efforts and successes of students. Currently, volumes 9 through 11 are indexed in PubMed/Medline and we endeavor to work in a retrograde fashion until the very first volume of the MJM. Indexing in Medline is a giant step for our student-based initiative. We are thrilled and excited to be acknowledged by the National Library of Medicine and hope that we continue to impress and publish solid research by students. The MJM is proud of its student contributors and is thankful for the support it has received from researchers globally.

With indexing in the PubMed/Medline database, the MJM enters a new phase. We would like express our gratitude to Dr. Phil Gold, a clinician-scientist recognized for leadership in the field of Oncology and Immunology, for his help and advice. He is our Faculty Advisor and a supporter of the MJM since the earliest

years.

We dedicate this issue to all the previous MJM editorial teams whose efforts contributed to today's publication, and to all medical students around the world, who are burgeoning in their field of research. We hope that you will be inspired to continue broadening your academic horizons.

Regards,

AYZ, AS, YG

REFERENCES

1. Atala, A. The clinician-scientist and medical advances. Journal of Urology. 2008; 180(2): 431-432.
2. Ley TJ, Rosenberg LE. JAMA. The physician-scientist career pipeline in 2005: build it, and they will come. 2005;294(11):1343-51.
3. Armstrong PW. A time for transformative leadership in academic health sciences. Clin Invest Med. 2007;30(3).
4. Harris JP, Ariessohn ML. Economic, family, and length-of-training issues that influence the selection of a clinician-scientist career path in otolaryngology. Otolaryngol Head Neck Surg. 2008;139(1):100-4.
5. Neacy K, Stern SA, Kim HM, Dronen SC. Resident perception of academic skills training and impact on academic career choice. Acad Emerg Med. 2000;7(12):1408-15.
6. Solomon SS, Tom SC, Pichert J, Wasserman D, Powers AC. Impact of medical student research in the development of physician-scientists. J Investig Med. 2003;51(3):149-56.
7. Fang D, Meyer RE. Effect of two Howard Hughes Medical Institute research training programs for medical students on the likelihood of pursuing research careers. Acad Med. 2003;78(12):1271-80.

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. Ada's research interests include genetics, congenital heart disease and atherosclerosis. 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

How many will it take?

Dear editors,

"He who kills himself is running after an image that he built of himself. One never kills himself only to exist.."

-André Malraux
French writer (1901-1976)

Last January, Quebec's National Public Health Institute published a portrait of the suicide status in the province. The media coverage highlighted the main conclusion that the overall annual suicide rates were decreasing and that in the urban part of the province, they were now quite similar to those in France or Switzerland. However, very little has been said about the situation of some specific communities, like the Innu people living in Nunavik, the territory at the northern end of the province of Quebec. In fact these people are the ones with the highest rates of suicide in the world.

In the year 2000, the worldwide suicide rate was estimated at 14.5/100,000 inhabitants (1). In Quebec, for the 2000-2004 period it was 17.3/100,000 inhabitants while Nunavik's rate was of 117.3/100,000 inhabitants, a rate almost 10 times greater than the one in Montreal (2). The majority of the Innus committing suicides are young men aged between 15 and 24 years old (3). For instance, out of 14 villages, there is one with only 350 inhabitants and in which as many as three people, or close to 1%, committed suicide in 2004. Between 2002 and 2006, they were eight of them in that village alone. That situation led Upaluk Poppel, Representative of the Inuit Circumpolar Youth Council, to comment: «If the populations of 'mainland' Canada, Denmark and the United States had suicides rates comparable to those of their Inuit populations, national emergencies would be declared. »

The problem first emerged 25 years ago. To inform the international community about what was happening to the Innu people, some international organizations like the Movement for Tribal People, also named Survival, published some reports to expose the local government's inaction. Things have not really improved since - they are, in fact, getting worse. Suicide is now the cause of almost 20% of the deaths among the Innus. A 2004 survey showed that 35% of people older than 15 answered that they already thought about committing suicide compared to 23.9% in a similar 1992 survey, an 11 points increase. More than one Innu out of five admitted having already attempted suicide (20.8% compared to 12.5% in 1992) (4). Even though the situation is quite alarming, very few studies about this are found in the literature (3).

All kinds of reasons have been suggested to explain the situation (3): the historical wound, the changes in the way of living, the loss of cultural identity, the lack of acknowledgment of their culture, the differences between what the young ones see on the internet or on television and what they are living in the Innu context, and other health indicators (such as the ones in the following box). None of these reasons alone can explain the situation. A suicide in Nunavik is at least as complex as it is anywhere else in the world and to believe that their suicide rates have always been high is totally wrong. In 1990, in a short review, Thorslund (5) notes a

Health Indicators:

Age distribution: 35.1% of the Nunavik people are less than 15 years old compared to 16.2% for the Province of Quebec (6)

Life expectancy: Men are expected to live 60.1 years (7) and women are expected to live 67.7 years (8) (men 76.7 and women 82.1 in Quebec)

Highest level of education: 55% of Nunavik adults Inuit have not completed their high school studies compared to 31.3% for the province (9).

Cost of life: Items are 50 to 55% more expensive in Kuujjuaq than they are in Montreal and 60 to 70 % more expensive in Saluit, the furthest north city of Quebec (10).

Average Income: The average income in Nunavik is $19,054; the median income is $14,311 (respectively $27,125 and $20,665 in the province).

Housing Condition: In 2006, 49% of Nunavik households were overcrowded with 12 to 15 persons living in a house (11). In fact, 25.5% of families were waiting for a new one. In June 2005, the Canadian government, the Quebec government and the Makivik society concluded a five-year program to built 275 new houses. It represents 11% of the needs. With the actual fertility rate, the situation will get worst if no additional money is invested (12).

Violence exposure: More than half of the children in Nunavik live in a household where at least one person has violence and alcohol consumption problems. Rape rates are 37 times higher in Nunavik than in the rest of the province (12).

Drugs consumption: In 2004, a survey objective that 60% of the population admitted taking drugs. This is four times higher than anywhere else in Canada (13).

Alcohol comsumption: More than a quarter of alcohol consumers admit drinking 5 or more drinks on a single occasion on a weekly basis. To try to solve the alcoholism problem (14), in many Nunavik villages, local regulation said that 24 beers or four bottles of wine are the maximum a citizen can buy for one month. Even though the existence of this law, smuggled alcohol allows people to drink more than what is expected. For example, a single illegal bottle of wine can be sold for as much as 300$ (14). This illegal traffic has an important social impact.

Human Development Index: The United Nations placed Canada number 4 among 192 nations in 2006. In 2001, the same formula was applied to Nunavik which ranked 76 (15).

15-fold increase in the suicide rate between 1944 and 1968. It confirms this is a recent problem and therefore it cannot be considered as “cultural” or “traditional”.

As seen in the health’s indicators box, there are a lot of social problems in Nunavik and many of them directly affect children. Johnny Oovaut, the mayor of the village Quataq, recently deplored the fact that some inhabitants prefer buying smuggled alcohol then feeding their children (15). His colleague, Muncy Novalinga, mayor of Puvirnituq, a village where five suicides and one murder happened during the six first months of 2008, added that when boxes of illegal alcohol arrive in his town, many people drink in the streets and those become unsafe for the children to play (15). In 2007, the Quebec’s Commission des Droits de la Personne et des Droits de la Jeunesse reported that the Nunavik children’s fundamental rights were violated: the right to integrity, the right to dignity, the right to protection, to security and to parental guidance (11). How can we expect the suicide situation to get better if the children’s hopes for the future are already affected by the violation of their rights?

On the positive side, the Quebec Innu population is very young; two thirds of them are under the age of 29. Much can be done but there is no time for racism and narrow thoughts. Some of the solutions are presented by the Nunavik people themselves: finding a solution for the housing problem, promoting detoxification programs, facilitating social, sportive, cultural and traditional activities for the young ones, providing meeting centers for the teenagers and promoting education among the community (4). However, a true governmental implication is necessary to allow those solutions to be initiated. This will not happen unless social pressures are applied. The Innu people alone do not have the political power to make it happen because of their geographic isolation and their small number. We have to help the government remember that these people exist and that they need help.

We are aware that the Innu suicide problem is complex and we do not think that our summary is complete. However, we believe that informing the community is an important step and that it must be done for action to be taken before it will be too late for many other Innus.

Sincerely,
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REFERENCES :

1. Krug, E.G., L.L. Dahlberg, J.A. Mercy, A.B. Zwi and R.Lozano, World report on violence and health. Geneva, SWI : World Health Organization. 2002
2. Institut National de la Santé Publique du Québec. Cited March 29th 2008. http://www.inspq.qc.ca/Santescope/.
3. Boothroyd LJ, Kirmayer LJ, Spreng S, Malus M, Hodgins S. Completed suicides among the Inuit of nothern Quebec, 1982-1996 : a case control-study. CMAJ 2001;165(1) :749-55.
4. Quanuippitaa. Institut National de la Santé Publique du Québec. Cited April 3rd, 2008. http://www.inspq.qc.ca/pdf/publications/658_esi_sociodemo.pdf.
5. Thorslund J. Inuit suicides in Greenland. Artic Med Res 1990;49:25-34.
6. Institut National de la Santé Publique du Québec. Cited April 3rd, 2008. http://www.inspq.qc.ca/Santescope/element.asp?NoEle=698
7. Institut National de la Santé Publique du Québec. Cited April 3rd, 2008. http://www.inspq.qc.ca/Santescope/element.asp?NoEle=709
8. Institut National de la Santé Publique du Québec. Cited April 3rd, 2008. http://www.inspq.qc.ca/Santescope/element.asp?NoEle=710
9. Institut National de la Santé Publique du Québec. Cited April 3rd, 2008. http://www.inspq.qc.ca/Santescope/element.asp?NoEle=703
10. Santé Canada. Cited April 3rd, 2008. http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2000/2000_20bk2_f.html
11. Commission des droits de la personne et des droits de la Jeunesse, Enquête portant sur les services de protection de la jeunesse dans la baie d’Ungava et la baie d’Hudson, Nunavik : Rapport, conclusions d’enquête et recommandations, Avril 2007
12. Statistique Canada. Cited April 3rd, 2008. http://www12.statcan.ca/francais/census06/analysis/aboriginal/crowded.cfm
13. Quanuippitaa. Institut National de la Santé Publique du Québec. Cited April 14th, 2008. http://www.inspq.qc.ca/pdf/publications/resumes_nunavik/francais/ConsommationAlcoolDroguesEtUtilisationDesJeuxDeHasard.pdf
14. Presse Canadienne, Contrebande d'alcool: des dirigeants du Nunavik demandent l'aide de Québec, Published June 8th, 2008, cited June 15th, 2008. (http://www.matin.qc.ca/articles/20080608175350/contrebande_dalcool_des_dirigeants_nunavik_demandent_laide_quebec.html)
15. Ann Silversides. The North ‘like Darfur’, Canadian Medical Association, October 23, 2007

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ORIGINAL ARTICLE

Tannin extracted from Sumac inhibits vascular smooth muscle cell migration

Hanieh Zargham, Ramin Zargham*

ABSTRACT: Background – Vascular smooth muscle cell (VSMC) migration is integral in the pathogenesis of atherosclerosis. Sumac (Rhus coriaria) berries are believed to have atheroprotective effects. Therefore, Sumac, which is a rich source of tannin antioxidants, was tested for its capacity to inhibit VSMC migratory activity. Materials & Methods – Tannin was extracted and purified from ground Sumac. Cultured rat carotid VSMCs were treated with different concentrations of tannin. After 10 days of tannin treatment, VSMC migratory activity in response to platelet-derived growth factor-BB was measured by transmembrane migration assay. An equal number of VSMCs was loaded on top of the inserts and at the bottom of the wells. After fixation and staining, cells migrating through the inserts and cells seeded at the bottom of the wells were counted. Results – A significant reduction (62%) of VSMC migration was evident in tannin-treated cells. To rule out any possible toxicity and cell death, cells at the bottom of the wells were also counted. No difference between the tannin-treated group and the controls was observed in the number of cells seeded at the bottom of the wells.Conclusion – Our data suggest that tannin extracted from Sumac possesses potent antimigratory activity. Sumac may have potential for the prevention or treatment of atherosclerosis and its clinical manifestations. Further experiments, especially in vivo, are required to examine the atheroprotective effect of Sumac.

KEYWORDS: vascular smooth muscle cell, migration, atherosclerosis, Sumac, tannin

INTRODUCTION

Atherosclerotic vascular disease is swiftly becoming the leading cause of morbidity and mortality worldwide. In the United States alone, approximately 13.2 million individuals suffer from documented coronary artery disease (1). Atherosclerosis of the coronary arteries evokes the most serious clinical manifestations of this disease, including unstable angina, acute myocardial infarction, and sudden death (2). Atherosclerosis is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel walls (3). The release of cytokines and growth factors from activated platelets and macrophages at the lesion site culminates in the heightened migratory activity of vascular smooth muscle cells (VSMCs). It is thought that VSMCs derived from the tunica media migrate towards the atherosclerotic lesion, proliferate and synthesize extracellular matrix, thereby contributing to atheroma growth. Platelet-derived growth factor (PDGF), secreted by activated platelets and lesion macrophages, is the most potent stimulus of VSMC attraction to the intima. It induces rapid downregulation of smooth muscle-selective markers in cultured VSMCs and stimulates VSMC migration in arterial injury models (4, 5). Any strategy to inhibit VSMC migration would benefit the treatment of atherosclerosis. Although many studies have focused on the blockade of VSMC migration, no effective therapy has yet been established.

Recently, natural products and foods such as red wine polyphenols have been shown to inhibit VSMC migration (6). In Persian traditional medicine, Sumac

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(Rhus coriaria) is believed to have atheroprotective effects and is consumed in some Persian dishes. This spice comes from the berries of a wild bush that grows in all Mediterranean areas. Previous studies have suggested that methanolic extracts of Rhus coriaria L. fruits may be a source of natural antioxidants (7, 8).

Sumac is a rich source of hydrolysable tannins (9). Tannins have been shown in vitro and in vivo to exhibit anticarcinogenic properties, such as the induction of cell cycle arrest and apoptosis as well as the inhibition of tumor formation and growth in animals (10). Therefore, we tested tannin extracted from Sumac for its capacity to suppress VSMC migratory activity.

The present study presents a methodological approach to determining whether tannin extracted from Sumac inhibits VSMC migration without causing cell death.

MATERIALS AND METHODS

Tannin extraction from Sumac

Two grams of dry Sumac (Aliments Akhavan, Montreal, Quebec) were ground using a mortar and pestle. To dissolve tannin in solvent, the ground Sumac was transferred to 50 mL Falcon tubes and 20 mL of acetone and water (7:3 ratio) was added. The collected tannin extracts were sonicated for 30 min at 4oC to break down additional materials associated with tannin. To pellet the additives and salts, the sonicated tannin extracts were centrifuged for 10 min at 2,500 rpm. The supernatants were removed from the pellets and tannin was separated from acetone in a Rota-evaporator. The extracted tannin was filtered and stored at 4oC until used. Extraction was repeated 2 more times. The pH of the extracted tannin was adjusted to 7.2 by titrating the tannin extract with 1M NaOH.

Isolation of rat carotid VSMCs and treatment with tannin

The carotid arteries of male Sprague-Dawley rats (Charles River Laboratories, St. Constant, Quebec) were excised to isolate VSMCs, as described previously (11). Animal housing and experimentation in accordance with Canadian Council on Animal Care and NIH guidelines were approved by the local animal care committee.

The optimal tannin concentration was defined in terms of VSMC survival. VSMCs were seeded in 10 cm culture dishes, treated with different tannin concentrations contained in Dulbecco's Modified Eagle Medium (DMEM) for 10 days. The different tannin concentrations were 5%, 1%, 0.5%, and 0.1% ml of tannin extract per ml of DMEM. Cultured VSMCs in tannin-free media were used as control.

Transmembrane migration assay

Cell migration was measured in a Transwell migration apparatus (Becton Dickinson Labware, Franklin Lakes, NJ) with 8-μm pore-size, fibronectin-coated membranes. From a concentration of 100,000 per ml of rat carotid VSMCs, 200 μL were loaded in the upper chamber whereas 630 μL of cells were loaded in the lower chamber. The cultures were incubated for 2 h at 37°C. PDGF-BB (20 ng/mL) (purchased from Sigma, Montreal, Quebec) was added to the bottom wells. After 14 h, the cells remaining on the upper membrane (that had not migrated through the filter) were removed with a cotton swab. The membranes were subsequently washed with phosphate buffered saline (PBS) and cells adhered under the membrane were fixed with 2% glutaraldehyde and stained with crystal violet as previously described [12]. The data are reported as the number of VSMCs in 4 random fields/filter. Each experiment was done in triplicate.

Statistical analysis

The results are expressed as means ± S.D. The difference between groups was evaluated by 1-way ANOVA and student's t-test by 2 independent investigators in a blinded fashion. Statistical significance was accepted at $P < 0.05$.

RESULTS

Tannin (extracted from Sumac)-treated VSMCs exhibit lower migratory activity in response to PDGF-BB

VSMCs were treated with different concentrations of tannin for 10 days. Tannin extracts were diluted in DMEM to obtain different tannin concentrations that were added to VSMC cultures to assess survival. These concentrations (5%, 1%, 0.5%, and 0.1%) were randomly chosen. Both 5% and 1% tannin extracts evoked considerable cell loss (the majority of cells were shrunk and fragmented with many dead cells floating) and were considered to be toxic. The optimal dilutions, 0.5% and 0.1% tannin extracts, did not elicit significant cell loss compared to cells without tannin treatment. (The cells were well stretched and appeared healthy and attached to the dish)

After 10 days of tannin treatment, VSMCs were loaded at the top of Transwell transmembrane inserts and at the bottom of the wells. PDGF-BB (20 ng/mL) was added to the bottom of the wells to stimulate VSMC migration through pores of the inserts. Migrated cells were counted under light microscope 14h after addition of PDGF-BB. The 0.1% tannin extract group did not yield any difference. The average migration (based on light microscopy) was 55 cells in the absence of tannin (with standard deviation of 3.4), 54 cells in the

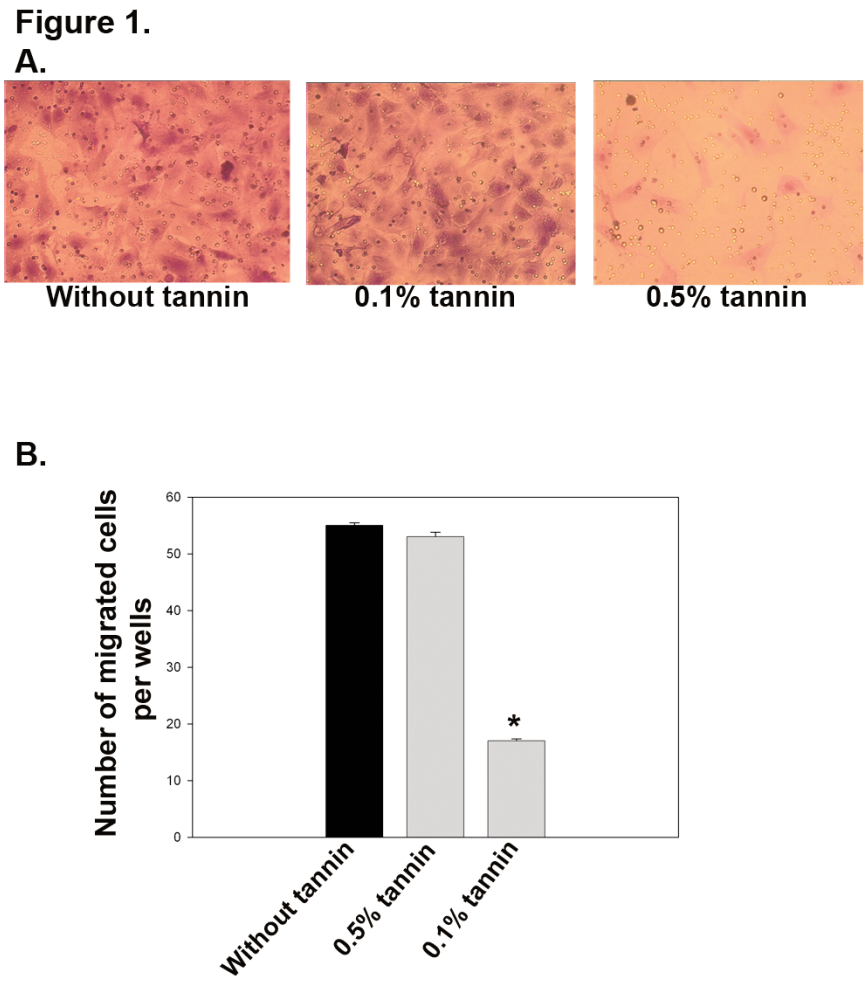

Figure 1: Migration of rat carotid VSMCs after 10d of tannin treatment. Migration was stimulated by the addition of PDGF-BB (20 ng/mL) to the lower chamber. VSMCs were allowed to migrate for 14 h. Representative images of crystal violet-stained cells that migrated to the lower surface of the membrane are shown for tannin-treated (0.5% and 0.1%) vs untreated VSMCs (A). Cell counts on the lower face of the membrane reveal reduced motility of VSMCs treated with 0.1% tannin extract (B). The data are expressed as means +SD of each experiment performed in triplicate. *P<0.005 vs. untreated cells. n=4 wells per treatment group (4 fields/well).

presence of 0.1% tannin extract (with standard deviation of 4.5), and 17 in the presence of 0.5% tannin extract (with standard deviation of 1.9). Repeated experiments showed a similar pattern. These data are shown in Figure 1. The results demonstrate that the addition of optimal dose of tannin extract inhibited VSMC migration by 62%.

No difference in cell viability between tannin-treated and control cells

It was possible that the reduced number of migrated cells was due to toxicity of the product. To rule out any possible toxicity and cell death, cells at the bottom of the wells were also counted. No difference between the tannin-treated and untreated groups was found in the number of cells seeded at the bottom of the wells, confirming that the observed reduction in the number of migrated cells was not due to cell loss.

DISCUSSION

Numerous studies have reported that VSMC accumulation plays a major role in the pathogenesis of occlusive vascular diseases (12,13). The results of recent studies suggest that antioxidants can cure or prevent atherosclerosis (14,15). Tannin and its derivatives are strong antioxidants and it is known that antioxidants can inhibit mechanisms leading to VSMC migration (16, 17).

In the present work, we investigated Sumac, a rich source of tannin (9), and its ability to inhibit VSMC migration. Pure tannin extracted from Sumac by analytical chemistry reduced VSMC migration at an optimal dosage. We found that at an optimal dose, pure tannin extracted from Sumac reduced VSMC migration by 62%.

Red wine is also a source of tannin. It has been reported that the consumption of red wine, which owes its antioxidant properties to tannin, imparts benefits in

the prevention of early atherosclerosis (18). Several epidemiological studies have shown a negative association between moderate wine consumption with the risk of cardiovascular events (19). A recent study has demonstrated that red wine polyphenols inhibit VSMC migration (6). However, there is a difference between the tannins present in Sumac and those in wine. Tannins are divided into 2 major classes: hydrolysable and condensed. Condensed tannins are not susceptible to cleavage by hydrolysis, are larger than hydrolysable tannins and their large size precludes absorption, suggesting that they are unlikely to have many health effects (20). In contrast to the condensed tannin from red wine (20), tannin extracted from Sumac is hydrolysable (21) and therefore may be easier to digest and absorb. Also, while high alcohol consumption results in high blood pressure (hypertension) and has a positive correlation with esophageal cancer (22), no negative side effects have been reported for Sumac. Other studies of tannin derivatives, including the one by Ignarro et al. (23), have shown that pomegranate juice can increase nitric oxide, thereby reducing the process of atherosclerosis. Interestingly, tannin from pomegranate juice is also hydrolysable. These results imply that Sumac, through it hydrolysable tannins, presents a preventative modality for the development of atherosclerosis. Further investigation is needed, to establish the in vivo significance of our in vitro findings.

One limitation of this study is the use of rat VSMCs instead of human VSMCs. Moreover, it would have been worthwhile to investigate and compare the effect of other tannin sources including red wine and pomegranate juice.

In summary, this is the first report demonstrating that tannin extract from Sumac has an inhibitory role on the migration of VSMC and thus suggests an atheroprotective role for this chemical. However, in vivo investigations are warranted to examine Sumac-derived tannin compared to the tannin derived from other products.

ACKNOWLEDGMENTS

We thank Drs. Gaetan Thibault and Yvan Guindon for providing the lab facilities and materials and Tao Trinh for the technical assistance.

REFERENCES

(1) Thom T, Ha N, Rea W. Heart Disease and Stroke Statistics – 2006 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee Source. 2006. American Heart Association Web site.

(2) Kher N, Marsh JD. Pathobiology of atherosclerosis˜ a brief review. Semin Thromb Hemost 30: 665-72; 2004.

(3) Shah PK. Pathophysiology of plaque rupture and the concept of plaque stabilization. Cardiol Clin 21: 303-14; 2003.

(4) Axel DI, Riessen R, Athanasiadis A, Runge H, Koveker G, Karsch KR. Growth factor expression of human arterial smooth muscle cells and endothelial cells in a transfilter coculture system. J Mol Cell Cardiol 29: 2967-78; 1997.

(5) Jawien A, Bowen-Pope DF, Lindner V, Schwartz SM, Clowes AW. Platelet-derived growth factor promotes smooth muscle migration and intimal thickening in a rat model of balloon angioplasty. J Clin Invest 89: 507-11; 1992.

(6) Iijima K, Yoshizumi M, Hashimoto M, et al. Red wine polyphenols inhibit vascular smooth muscle cell migration through two distinct signaling pathways. Circulation 105: 2404-10; 2002.

(7) Candan F, Sökmen A. Effects of Rhus coriaria L (Anacardiaceae) on lipid peroxidation and free radical scavenging activity. Phytother Res 18: 84-6; 2004.

(8) Ozcan M. Antioxidant activities of rosemary, sage, and sumac extracts and their combinations on stability of natural peanut oil. J Med Food 6: 267-70; 2003.

(9) Kosar M, Bozan B, Temelli F, Baser KHC. Antioxidant activity and phenolic composition of sumac (Rhus coriaria L.) extracts. Food Chem 103: 952-9; 2006.

(10) Perchellet JP, Gali HU, Perchellet EM, Klish DS, Armbrust AD. Antitumor-promoting activities of tannic acid, ellagic acid, and several gallic acid derivatives in mouse skin. Basic Life Sci 59: 783-801; 1992.

(11) Zargham R, Thibault G. Alpha8beta1 integrin expression in the rat carotid artery: involvement in smooth muscle cell migration and neointima formation. Cardiovasc Res 65: 813-22; 2005.

(12) Rudijanto A. The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. Acta Med Indones 39: 86-93; 2007.

(13) Doran AC, Meller N, McNamara CA. Role of smooth muscle cells in the initiation and early progression of atherosclerosis. Arterioscler Thromb Vasc Biol 28: 812-9; 2008.

(14) Ma A, Qi S, Chen H. Antioxidant therapy for prevention of inflammation, ischemic reperfusion injuries and allograft rejection. Cardiovasc Hematol Agents Med Chem 6: 20-43; 2008.

(15) Siekmeier R, Steffen C, März W. Role of oxidants and antioxidants in atherosclerosis: results of in vitro and in vivo investigations. J Cardiovasc Pharmacol Ther 12: 265-82; 2007.

(16) Harimaya K, Tanaka K, Matsumoto Y, Sato H, Matsuda S, Iwamoto Y. Antioxidants inhibit TNFalpha-induced motility and invasion of human osteosarcoma cells: possible involvement of NFkappaB activation. Clin Exp Metastasis 18: 121-9; 2000.

(17) Yasunari K, Kohno M, Kano H, Yokokawa K, Minami M, Yoshikawa J. Antioxidants improve impaired insulin-mediated glucose uptake and prevent migration and proliferation of cultured rabbit coronary smooth muscle cells induced by high glucose. Circulation 99: 1370-8; 1999.

(18) Auger C, Rouanet JM, Vanderlinde R, Bornet A, Décordé K, Lequeux N, Cristol JP, Teissedre PL. Polyphenols-enriched Chardonnay white wine and sparkling Pinot Noir red wine identically prevent early atherosclerosis in hamsters. J Agric Food Chem 53: 9823-9; 2005.

(19) Rotondo S, Di Castelnuovo A, de Gaetano G. The relationship between wine consumption and cardiovascular risk: from epidemiological evidence to biological plausibility. Ital Heart J 2:1-8; 2001.

(20) Waterhouse AL. Wine phenolics. Ann N Y Acad Sci 957: 21-36; 2002.

(21) El-Sissi HI, Ishak MS, El-Wahid MS, el-Ansari MA. The gallotannins of Rhus coriaria and Mangifera indica. Planta Med 19: 342-51; 1971.

(22) Fan Y, Yuan JM, Wang R, Gao YT, Yu MC. Alcohol, tobacco, and diet in relation to esophageal cancer: the shanghai cohort

study. Nutr Cancer 60: 354-63; 2008.
(23) Ignarro LJ, Byrns RE, Sumi D, de Nigris F, Napoli C. Pomegranate juice protects nitric oxide against oxidative destruction and enhances the biological actions of nitric oxide. Nitric Oxide 15: 93-102; 2006.

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ORIGINAL ARTICLE

The Delay in Diagnosis of Tuberculosis in the Monteregie region of Quebec, Canada

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ABSTRACT: Introduction – Despite being more prevalent in developing countries, tuberculosis (TB) remains an important health problem in Canada. Long diagnosis delays of respiratory tuberculosis are associated with adverse consequences for the patient but also for the community. From a public health perspective, identification of factors associated with long delays of diagnosis could help reduce these delays. Objectives – 1)To describe diagnosis delays of respiratory tuberculosis in Monteregie 2)To identify the characteristics of patients and factors associated with longer diagnosis delays 3)To identify consequences of these delays Methods – The study is descriptive and transversal. Data were obtained from notifiable diseases files of the Public Health Department of the Health and Social Services Agency of Monteregie. The diagnosis delay was calculated using the first symptomatic date and the date of diagnosis. For continued variable analyses, Student t tests and an ANOVA test were done. For categorical variables, Pearson's chi squared test and a Mann-Whitney test were done. Results – The average delay of diagnosis for the 115 cases studied was 92.2 days (CI 80.6-103.8). Weight loss and/or non specific general malaise were associated with a longer diagnosis delay. No association was found between the diagnosis delay and possible consequences of longer delays. Discussion and conclusion: Most patients had a diagnosis delay longer than two months. A larger study that would divide the total diagnosis delay into a patient delay and a suspicion delay (health care system delay) could permit a better identification of factors that favour long delays.

KEYWORDS : Tuberculosis; delay of diagnosis; treatment delay; immigration; consequences of delay

INTRODUCTION

Tuberculosis epidemiology

The World Health Organisation (WHO) estimated that almost one third of the global population was infected by the tuberculosis bacillus in 2006.[1] Presently, approximately 2 million people die each year of the disease. The majority of cases occur in developing countries, but the problem is still important in Canada, despite a constant reduction of the disease incidence in the past 20 years. The increase of immigrants born in countries endemic for tuberculosis (TB) during the past decades and the more prevalent resistance to treatment in immigrants bring a new challenge to the anti-tuberculosis plan. [1]

In Canada, the majority of new tuberculosis cases occur in the first nation population and immigrants. [1] In Monteregie, approximately 20 cases are declared each year to the Public Health.[2] In 2006, 227 cases were reported in Quebec, from which 19 cases occurred in Monteregie. In Quebec, the incidence was of 3 cases per 100 000; in Monteregie, it was of 1.4 case per 100 000. [3]

Diagnosis

There are 4 principal methods to establish diagnosis:

1. Pulmonary x-rays: sensitivity of 70 to 80%. [1]

2. Zhiel-Neelsen smear: fast (less than 2 days), sensitivity with and without PCR of 95% and 60%, respectively. Allows the evaluation of contagiousness of the infected individual; the greater the number of bacillus in each microscopic field, the more contagious

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the individual is. [1, 4]

3. PCR: in clinical use since approximately 15 years, completed in 3 to 24 hours. Its sensitivity, around 80%, is higher than that of the smear but lower than that for the culture. [1]

4. Culture: The gold standard to establish the diagnosis. Sensitivity around 90% for 3 sputum cultures. However, it can take up to 6 weeks to obtain results. [1, 4]

Patients with a positive smear result and those with a pulmonary cavities on x-ray are more contagious than other patients. [4]

Screening for contacts – Public health intervention

In Quebec, active tuberculosis is a disease that must be mandatorily declared and treated. Because of the potential severity of the disease and the consequences, screening of close contacts of each respiratory tuberculosis case is performed, to detect the presence of disease or latent infection. This process requires human and material resources and generates anxiety in contacts being screened.

Delays of diagnosis

An important factor in the control of the disease is a rapid diagnosis and instauration of an appropriate treatment. A long delay is associated with a greater risk for the patient to develop a more advanced disease, to have more complications and a higher mortality. [5,6] Also, an increase in the delay causes a higher risk for the community because of the increased contagiousness of the case: the longest delays are associated with larger numbers of bacilli on the smears. [7,8] A systematic review by Storla and al. [9] on delays of diagnosis of tuberculosis described an average total delay of diagnosis of 72 ± 28 days.

These findings show that delays of diagnosis represent a major concern for public health and that a decrease in delays could reduce the consequences of tuberculosis. For this reason, it is important to identify factors associated with delays in diagnosis and treatment of TB to make recommendations and develop new methods or protocols to reduce these delays.

The total delay of diagnosis may be divided into different delays. First, there is a delay between the first symptom and the moment when the patient first makes contact with the health care system (patient delay). Next, a delay occurs between the first consultation with a doctor and the beginning of laboratory investigations for tuberculosis (suspicion delay). These two delays combined together represent the pre-test delay. Finally, a delay exists between the first sputum sampling and the confirmation of the diagnosis, either by PCR or by culture (test delay).

The principal factors associated with delays of diagnosis include seropositivity to HIV, chronic cough and/or chronic pulmonary disease, a negative smear result, advanced age, female sex, a low socio-economic status, substance abuse and an immigrant status. [9]

Considering this information, the goal of this study is to describe the delays in diagnosis and treatment of respiratory tuberculosis in Monteregie from 1998 to 2007, to identify factors associated to these delays and to document some of the possible consequences associated with a prolonged delay.

METHODS

Population studied

This cross sectional study includes contagious active tuberculosis cases declared to the Public Health Department (PHD) in Monteregie between January 1st 1998 and June 30th 2007. Because this study concerns contagious tuberculosis, only the pulmonary, laryngeal and miliary forms of the disease were included. The extra-pulmonary cases of tuberculosis that had no respiratory tract involvement were excluded. In order to avoid duplicating data related to a single patient, only the first episode of respiratory tuberculosis identified for each patient in Monteregie during the period studied was considered. The non-confirmed cases (clinical cases, not confirmed by a positive culture or PCR test for a tuberculosis agent) were also excluded to reduce the information bias associated with a wrong diagnosis.

Because the primary objective of the study is to describe the factors associated with delays of diagnosis and treatment of tuberculosis in Monteregie, incidentally found cases were excluded. These cases have a delay of diagnosis of 0 days (the disease start date being the same as the date of diagnosis) and could lead to an underestimation of the delay of diagnosis in symptomatic patients.

Variables studied

With the information available in the Tuberculosis Epidemiologic Questionnaire of the Public Health Department of the Health and Social Services Agency of Monteregie, three important dates in the diagnostic process of active tuberculosis have been identified: the start date of the disease (which corresponds to the first symptomatic day as recalled by the patient), the first sampling date and the date of diagnosis. The date of diagnosis is defined as the date that tuberculosis was diagnosed for the first time by the treating physician; if this date is unknown, the date of diagnosis was then determined by the date that treatment began or the date of the first positive test result (smear, culture). With these dates, three delays can be evaluated: the pre-test delay, the test delay, and the delay of diagnosis (Table

1). The data sources available do not identify the date of the first consultation, making it impossible to determine the patient delay and the delay of suspicion. The delay of diagnosis was mostly chosen because it includes the other two that are strongly correlated with it (mostly the pre-test delay) and because the test delay only represents a small fraction of the delay of diagnosis.

With the available information in the diseases files, the presence of an association between the following factors and the duration of the delay of diagnosis was studied (Table 2): year of diagnosis, the exposition of the Health and Social Services Center (HSSC) consulted by the patient to tuberculosis, sex, age, native country (endemic or not) and the number of years since the arrival in Canada in the cases of immigrants, the presenting symptoms, the medical history and the results of diagnostic tests (pulmonary x-rays, smears and PCR).

A second objective of the study is to evaluate the possible consequences of diagnosis and treatment delays of tuberculosis. The four factors analysed to evaluate consequences of the delay are : presence or not

Table 1: Variable Definitions

Delay of diagnosis	Number of days between the beginning of the disease date and the diagnostic date, inclusively
Pre-test delay	Number of days between the beginning of the disease date and the first sputum sampling date, inclusively
Test delay	Number of days between the first sputum sampling date and the diagnostic date, inclusively
Patient delay	Number of days between the beginning of the disease date and the first consultation date
Suspicion delay	Number of days between the first contact with the health care system date and the first sputum sampling date
HSSC with a high exposition to tuberculosis	A HSSC in Monteregie with an average of at least 3 cases of tuberculosis each year between 2004 and 2006, according to the statistics from the Public Health Department of Monteregie [10,11,12].
Endemic native country	A country with an estimated incidence of positive smear tuberculosis of at least 30 cases / 100 000 between 2003 and 2005, according to the Global Health Atlas of the WHO [13]
Number of years since arrival in Canada	Number of years between the diagnosis and the arrival in Canada (for immigrants)
Presenting symptoms	Symptoms included in the questionnaire : fever, nocturnal sweats, weigh loss and/or non specific general malaise, cough, expectorations, haemoptysis, thoracic or pleuritic pain
Duration of hospitalisation	Number of days between the admission date and the end of hospitalisation, inclusively
Number of contacts	Number of persons identified as being close contacts of the index case of tuberculosis during the standardized inquiry by the PHD
Proportion of contacts with positive TST	Proportion of index case close contacts that had a TST result of 5 mm or more in one of the two tests
Attribuable deaths	Death directly caused by or favoured by tuberculosis

Table 2: Delays of diagnosis in relation to the different variables studied.

Socio-demographic variables	Number (%)[a]	Aver. delay of diagnosis (in days)	CI 95%	p value
Sex	115			
Men	72 (62.6)	90.8	74.5-107.1	0.774[c]
Women	43 (37.4)	94.4		
Age	115			
0-19years	8 (7.0)	71.6	24.1-119.2	0.752[d]
20-39 years	25 (21.7)	87.8	68.9-106.6	
40-64 years	35 (30.4)	93.9	72.0-115.7	
>64 years	47 (40.9)	96.7	77.0-116.4	
HSSC	115			
Low exposition	52 (45.2)	94.5	74.9-114.1	0.719[c]
High exposition	63 (54.8)	90.2	76.4-104.0	
Native Country	114			
Canada	62 (54.4)	105.1	87.7-122.5	
Endemic country	36 (31.6)	80.4	64.2-96.6	0.066[c,e]
Other	16 (14.0)	73.9	46.1-101.1	0.102 [c,f]
# of years since arrival in Canada[b]	51			
0-5 years	27 (52.9)	81.7	62.9-100.5	0.599[c]
>5 years	24 (47.1)	74.0	52.3-95.7	
Presenting Symptoms				
Fever & or nocturnal sweat	115			
Yes	66 (57.4)	99.1	82.9-115.3	0.175[c]
No	49 (42.6)	82.8	66.6-99.0	
Weight loss & or non-specific gen. malaise	115			
Yes	76 (66.1)	102.4	88.2-116.6	0.016[c]
No	39 (33.9)	72.3	53.4-91.2	
Cough &/or expectoration	115			
Yes	91 (79.1)	95.1	82.0-108.2	0.335[c]
No	24 (20.9)	81.0	56.3-105.7	
Haemoptysis	97			
Yes	20 (20.6)	109.0	78.0-140.0	0.122[b]
No	77 (79.4)	85.1	72.1-98.1	
Antecedents				
Smoking	61			
Yes	19 (31.1)	88.7	64.0-113.4	0.599[c]
No	42 (68.9)	98.9	75.9-121.9	
Known contact w TB pxt	94			
Yes	40 (42.6)	88.8	68.4-109.2	0.865[c]
No	54 (57.4)	91.1	75.0-107.2	
HIV sero(+)ve & or immunosupp.	71			
Yes	7 (9.9)	112.3	51.4-173.2	0.295[c]
No	64 (90.1)	85.5	70.4-100.6	
Stay in an endemic country	105			
Yes	40 (38.1)	82.9	64.9-100.9	0.356[c]
No	65 (61.9)	94.1	79.2-109.0	
Paraclinic Tests				
Chest Xray result	115			
Norm or Abnorm	88 (76.5)	91.0	77.9-104.1	0.729[c]
Abnorm Cavitary	27 (23.5)	95.9	70.8-121.0	
Smear	111			
Positive	67 (60.4)	93.7	79.7-107.7	0.711[c]
Negative	44 (39.6)	89.3	69.7-108.9	
PCR	115			
+ or -	77 (67.0)	89.3	76.4-102.2	0.498c
No PCR done	38 (33.0)	97.9	74.2-121.6	

[a] Proportion expressed in percentage of the total of valid cases for each variable; [b] For immigrants only; [c] Student t test; [d] ANOVA test; [e] Comparison of the average delays of diagnosis between Canadian born patients and foreign-born patients of endemic countries; [f] Comparison of the average delays of diagnosis between Canadian born patients and foreign-born patients of non-endemic countries (beside Canada)

of hospitalisation of the patient and its duration if present, total number of contacts, proportion of contacts with a positive TST and the number of deaths attributed to tuberculosis (caused entirely or partially by tuberculosis).

Measurement instrument and data collection

Data collection was realised with a data gathering tool elaborated from the available information in the notifiable diseases files of the patients (Appendix 4). The information used in this study was obtained from the Tuberculosis Epidemiologic Questionnaire (Appendixes 5,6) which is an integral part of the standardized inquiry of the PHD and is filled out for all cases of tuberculosis reported in Monteregie. This document is kept in the archives of the transmissible diseases program of the PHD of Monteregie.

To confirm the validity of the data gathering tool elaborated and to reduce the inter-observer variability, it was pre-tested on 15 cases chosen randomly, after which minor modifications were done and a consensus on the way to collect data was established. The cases used for the pre-test were not eliminated from the study because the data gathering tool is used to review files, not to survey patients (results are therefore not influenced by question formulation).

When imprecise dates were reported in the patient files, for example "beginning of the month", "middle of month" or "end of month" it was decided to transcribe them as the 1st, the 15th or the 30th (28th for February) of the month, respectively. Data not found in the questionnaires were transcribed as "unknown".

The information obtained with the data gathering tool was then transferred in a data bank using the program "Statistical Package for Social Sciences (SPSS) version 15.0. (SPSS Inc, Chicago)" A complete verification of the data bank was done to minimise transcription errors.

Analysis

To establish the statistical signification of the results obtained, a Student t test was done for the analysis of continuous variables, such as factors associated with delays of diagnosis. An ANOVA test was used for the evaluation of the delay in diagnosis as a function of patient age. A Mann-Whitney test was used to analyse the number of close contacts as a function of the delay in diagnosis, because the values taken by the first variable deviated largely from a standard distribution. A Pearson Chi-squared test was used to analyse nominative variables. For each statistical test done, the signification threshold was fixed at 0.05.

Ethical aspects

This study was done under the supervision the Public Health Department of Monteregie and its objective is part of the public health mandate. The confidentiality of the cases studied was preserved with many precautions, including non nominative data collection.

RESULTS

A total of 206 cases of TB were declared to the PHD of Monteregie between January 1st 1998 and June 30th 2007. From this number, 65 were non-respiratory TB and 7 respiratory cases were clinical ones not confirmed by culture or PCR. There were 134 cases of active tuberculosis validated. From this number, 11 were incidentally found and were excluded for the study. Eight others were excluded during data collection: 4 files were not found at the time of data collection, a fifth case was excluded because the file was incomplete, another was excluded because the delay of diagnosis could not be determined (the first symptomatic date was not identified) and the last two cases were in fact recurrences in patients with a previous episode of TB already declared to the PHD of Monteregie. The population studied represents a total of 115 cases.

Description of the population studied

All of the cases presented at least one pulmonary TB component. For the immigrants, the median number of years between arrival in Canada and the diagnosis was 5 years. Table 2 presents the principal characteristics of the cases studied. The population is composed of a larger number of men compared to women, of people mostly aged more than 40 years and of people mostly native from Canada.

Delays of diagnosis

The different delays analysed in this study are presented in table 3. The average delay of diagnosis is 92.2 days and the median delay is 83.0 days.

Factors associated with the delay of diagnosis

Many factors were analysed to evaluate the presence of association with the length of the delay of diagnosis. None of the sociodemographic variables studied (sex, age, HSSC and native country) were statistically significantly associated with differences in the delay of diagnosis. Individuals native from endemic countries for tuberculosis seemed to have a shorter delay of diagnosis than those born in Canada; the p value found for this relation is near but not below the 0.05 threshold.

Only one presenting symptom studied was statistically associated with a delay of diagnosis: weight loss and/or non specific general malaise was associated with a longer delay of diagnosis (102.4 days) than if that symptom is absent at presentation (72.3 days).

Possible consequences of delays of diagnosis

To evaluate the presence of an association between possible consequences of delays of diagnosis studied and the delay of diagnosis, delays were classified as long or short. The results of the study show that a delay of diagnosis of 100 days coincided with the 64th percentile. It was arbitrarily decided that a delay of 100 days or more was a long delay and that a delay of less than 100 days was a short delay.

None of the possible consequences of delays of diagnosis (number of contacts, presence or absence of hospitalisation and number of days of hospitalisation) were related to the duration of the delays. The overall proportion of positive TCT results for close contacts of the index case was compared to an analysis that included only cases with patients native from an endemic country for TB. There was no significant difference in the results obtained.

DISCUSSION

This study describes for the first time delays in diagnosis and treatment of tuberculosis in Monteregie. During the period studied, the population of confirmed tuberculosis cases is nearly complete because laboratories declared all cases of the disease, tuberculosis being subject to mandatory declaration.

Discussion of results

The average delay of diagnosis was 92.2 days and is similar to results obtained in the systematic review by Storla et al. [9] (72 days ± 28 days).

Table 3: The different delays analysed in this study

Delays	Median delay (days)	Average delay (days)	CI 95%	Range (days)
Delay of diagnosis	83.0	92.2	80.6-103.8	(3, 344)
Pre-test delay	61.0	76.1	64.9-87.3	(0, 335)
Test delay	7.0	15.0	11.6-19.4	(-4, 133)

In the notifiable diseases files of patients, the date of first consultation was not available. It was impossible to divide the total delay of diagnosis into patient and suspicion delay as was often done in other studies. In some studies [14,15], it was found that the two delays were not influenced by the same factors and that a particular factor could influence the two delays in opposite ways. For example, being an immigrant can increase the patient delay but reduces the delay of suspicion; the final effect on delay of diagnosis is therefore difficult to predict.

For the relation between the delay of diagnosis and patient age, a tendency of increased delay was observed with older patients using four age sub-divisions (shown in Table 2). This observation is reported in other studies [9], where an advanced age is a risk factor for a longer delay of diagnosis. This relation was not statistically significant, but motivated a second analysis with only two age divisions: less than 40 years and 40 years or older. This second analysis in turn did not show a statistically significant result.

No significant relation was observed between the exposition of the Health and Social Services Center to tuberculosis and the delay of diagnosis. It was believed that the HSSC with a higher exposition to the disease would have shorter delays of diagnosis. However, an information bias exists since the HSSC identified for each patient is established with the patient address at the time he had the disease and is therefore not necessarily the one where the patient first consulted a doctor. Also, the number of cases of TB in all HSSC is small, the largest number of cases per HSSC being 10 per year. The difference between HSSC is likely minimal.

In this study, a shorter average delay of diagnosis (80.4 days) was observed for immigrants native from an endemic country (a country with an estimated incidence of positive smear tuberculosis of at least 30 cases / 100 000) than for patients born in Canada (105.1 days). The p value for this relation, at 0.066, is not below the 0.05

Table 4: The possible consequences studied in relation to delays of diagnosis
[a] Proportion expressed in percentage of the total of valid cases for each variable

	Short Delay	Long Delay	p value
Contacts			0.123
Number of cases concerned (%)[a]	64 (61.5)	40 (38.5)	
Average number of contacts (CI 95%)	15.1 (7.1-23.2)	13.7 (10.5-16.8)	
Median number of contacts	7.0	13.0	
Positive TST results among close contacts			0.703
Number of cases concerned (%)[a]	60 (60.6)	39 (39.4)	
Average proportion of +ve results among close contacts (CI 95%)	0.419 (0.329-0.509)	0.393 (0.303-0.483)	
Hospitalisation			0.107
# of pxts hospitalised (%)[a]	50 (68.5)	23 (31.5)	
# of pxts non hospitalised (%)[a]	21 (52.5)	19 (47.5)	
Average duration of hospitalisation (days) (CI 95%)	25.9 (18.8-33.0)	26.5 (8.9-44.1)	0.951
Outcome of the disease			0.776
Healing (%)[a]	56 (64.4)	31 (35.6)	
Death (%)[a]	9 (0.6)	6 (0.4)	

threshold. It is possible that the number of cases studied was not sufficient to establish a statistically significant association. This relation, if found to be true, could be explained by the fact that clinicians will include tuberculosis in their differential diagnosis more readily in an foreign born than in a Canada born patient because the disease is less prevalent in Canada. This hypothesis is supported by other studies [14,15,16] that show the health care system associated delay is shorter for foreign patients. A previous stay in an endemic country, which was also verified in each case, seemed to follow this trend.

A longer delay of diagnosis was observed in the presence of each presenting symptom. These relations were not statistically significant except for the weight loss and/or non specific general malaise (p value of 0.016.) This is not consistent with the current literature where certain symptoms are associated to longer delays (ex: cough) and other with shorter delays (ex: fever) [9,17]. These observations could be explained by the fact that a long delay of diagnosis favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.

Smoking, a known contact with a tuberculous patient, and a stay in an endemic country are not significantly associated with a shorter delay of diagnosis. It was believed that the presence of certain medical conditions would lead to shorter delays of diagnosis. First, smoking is associated to lung cancer. Tuberculosis and lung cancer share many symptoms: cough, haemoptysis, weight loss, etc. Clinicians who face a patient that smokes and presents some of these symptoms have to rule out lung cancer, requiring a more in-depth investigation. However, an information bias for smoking is probably present, because this information was not systematically indicated in all the questionnaires. The hypothesis of a shorter delay in patients with a known contact with another tuberculosis case or a stay in an endemic country came from the assumption that clinical suspicion would be higher in these patients. However, clinicians might not ask their patients these important questions.

Smear results and pulmonary x-ray results do not significantly influence the delay of diagnosis. A positive smear result or a cavitary pulmonary x-ray is logically associated with a faster diagnosis. However, the absence of such an observation in this study could be due to a long delay before consultation with a doctor or to a longer suspicion delay by the clinician, prolonging the delay of diagnosis. Use of PCR for investigating tuberculosis reduces the average delay of diagnosis in the cases studied, but the relation is not significant.

For the possible consequences of delays of diagnosis, the median number of contacts increases with the duration of the delay but the relation is not statistically significant. The number of contacts retrieved in the patient file depends on the extent of the inquiry made by the PHD and depends on the social environment (work, school, family, etc.) of the index case. The number of investigated contacts is possibly more dependant on social environment than on the duration of the contagious period. This hypothesis cannot be verified with the available data.

The proportion of infected contacts (established by a positive TST result) would logically be higher if the contagious period is prolonged, but the contact lists retrieved in patient files were often incomplete and a recall bias is therefore possible. A more structured contact list separating close contacts from other contacts could offer more interesting research data. Interestingly, division according to native country did not modify the relation observed.

Hospitalized patients often have a shorter delay of diagnosis, but the relation observed is not significant. This could be explained by the fact that hospitalization permits a faster management of the patient and favours a faster diagnosis. A study of a larger population is suggested to obtain a statistically significant relation.

There is no significant difference of treatment outcome (recuperation or death) between the long and short delay groups. Three cases were diagnosed post-mortem making the delay of diagnosis difficult to establish because the first symptom date is not known. The number of deaths caused or favoured by TB is limited. A larger study should be done to determine the association between delay of diagnosis and treatment outcome.

Principal limitations of study

Exclusion of clinical cases (not confirmed by culture or PCR results) reduces the number of cases studied. Also, these cases may have longer delays of diagnosis and the factors associated with them could be different. However, the number of these case is limited (only 7) and is not significant compared to the total number of cases studied (115).

Even if the data bank used included all the respiratory cases of tuberculosis declared in Monteregie between 1998 and June 2007, the statistical power of the study is low; the number of cases may be insufficient to obtain other statistically significant associations.

This study, being descriptive and transversal, cannot establish links of causality between the variables studied. It is only possible to identify the presence of an association between them.

The date when the disease began, needed to establish the delay of diagnosis, is determined by asking the

patient to identify the moment where he or she first noticed symptoms. This could result in a recall bias because the patient does not necessarily remember the precise date of symptom appearance. Also, it is difficult to determine if that symptom was really caused by TB.

Secondary utilisation of data in this study can result in a recall bias. For most variables, the fact that questions were asked in an inquiry context rather than for research purposes probably did not significantly influence the results. However, for certain questions, the lack of strict term definitions and questions asked with different wording can diminish the value of the information obtained.

External validity

The external validity of the study is good enough to extend the results obtained to the population of Monteregie for the next years, because all confirmed cases of pulmonary TB during the studied years were included. However, results cannot be extended to other regions, because sociodemographic characteristics of the population and healthcare organization may vary from those found in Monteregie.

CONCLUSION AND RECOMMENDATIONS

The average delay of diagnosis of TB in Monteregie between January 1st 1998 and June 30th 2007 is similar to delays described in the literature. [9] Weight loss and/or non specific general malaise are associated to a longer delay of diagnosis. No other factors associated to delays were statistically significant. No possible consequence analysed could be attributed to a longer delay. Limits of the study have to be considered; these include a population possibly too small to obtain statistically significant results for the analyses made.

Recommendations

1. This study, being descriptive and transversal, does not allow the identification of factors of causality between delays in diagnosis and factors associated to these delays or consequences of these delays. In addition, most results were not statistically significant, making it difficult to determine factors that could help in the early diagnosis of TB. However, since the delays in diagnosis of TB remain long, physicians should be informed on the importance of an early diagnosis and thus a high clinical suspicion of TB.

2. A systematic tool to trace contacts and gather follow-up information would be useful for future studies. A summary sheet organising patients according to the relative importance of their contact with the index case would give a better appreciation of the chain of contagiousness and allow more easy access to the relevant information.

3. The first consultation date could be added to public health TB questionnaires in order to differentiate patient delays from health care system delays. This information would allow a better determination of the relative importance of each type of delay, and a better identification of interventions to correct factors causing delays in diagnosis of TB.

ACKNOWLEDGMENTS

The original study was done by five third grade medical students of the Université de Sherbrooke, during their public health training of the medical internship in the Public Health Department of the Health and Social Services Agency of Monteregie.

They also thank everyone that contributed in a certain way to the accomplishment of this work: Mrs Caroline Gélinas, technician in psychosocial study; Mrs Ginette Lagarde, public health nurse; Dr Éric Levac, consulting physician of the transmissible diseases sector.

REFERENCES

1. Agence de la santé publique du Canada. Normes Canadiennes pour la lutte antituberculeuse 6e édition – 2007. http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-fra.php
2. Direction de la santé publique de la Monteregie, Bulletin Sentinelle, années 2003 à 2006. http://www.rrsss16.gouv.qc.ca/Menu_Gauche/4-Publications/2-Bulletins/Bulletins_de_la_Sante_publique/Sentinelle/sentinelle_theme.html
3. Agence de la santé publique du Canada. La tuberculose au Canada – 2006, prédiffusion. http://www.phac-aspc.gc.ca/publicat/2007/tbcanpre06/index-fra.html
4. Southwick FS. Pulmonary infections. In: Southwick FS, editor. Infectious Diseases in 30 days. United states of America, McGraw Hill; 2003. P 107-153
5. Zafran N, Heldal E, Pavlovic S, Vuckovic D, Boe J. Why do our patients die of active tuberculosis in the era of effective therapy? Tubercle and Lung Disease. 1994; 75(5): 329-333.
6. Enarson D. Failure of diagnosis as a factor in tuberculosis mortality CMAJ. 1978; 118 : 1520-1522.
7. Madebo T, Lindtjorn B. Delay in treatment of pulmonary Ttuberculosis : An analysis of symptom duration among Ethiopian patients. Medscape General Medicine. 1999: E6.
8. El-Sony A, Enarson D, Khamis A, Baraka O, Bjune G. Relations of grading of sputum smears with clinical features of tuberculosis in patients in routine practice in Sudan. Int J Tuberc Lung Dis. 2002; 6(2): 91-97.
9. Storla DG. Yimer S. Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008; 8(1) : 15-22.
10. Perron L, Levac E et al. Rapport annuel 2006 - Les maladies infectieuses en Montérégie, incluant les maladies à déclaration obligatoire (MADO). Agence de la santé et des services sociaux de la Montérégie, juin 2007. http://www.rrsss16.gouv.qc.ca/Menu_Gauche/4-Publications/3-Monographies_Orientations_Rapports/Maladies_transmissibles/dsp_pub_rap_mado_2006.pdf
11. Lina Perron, Louise de la Boissière et al. Les maladies infectieuses en Montérégie, incluant les maladies à déclaration obligatoire (MADO) – Rapport annuel 2005. Agence de la santé et des services sociaux de la Montérégie, juin 2006.

http://www.rrsss16.gouv.qc.ca/Menu_Gauche/4-Publications/3-Monographies_Orientations_Rapports/Maladies_transmissibles/dsp_pub_rap_mado_2005.pdf

12. Éric Levac, Julie Loslier et al. Maladies à declaration obligatoire d'origine infectieuse – Rapport annuel 2004. Agence de développement de réseaux locaux de services de santé et de services sociaux, avril 2005. http://www.rrsss16.gouv.qc.ca/Menu_Gauche/4-Publications/3Monographies_Orientations_Rapports/Maladies_transmissibles/dsp_pub_rap_mado_2004.pdf
13. World Health Organisation. Communicable diseases, Tuberculosis. http://www.who.int/globalatlas/dataQuery/default.asp
14. Fara MG, Rygh JH, Steen T.W, Selmer R, Heldal E, Bjune G. Patient and health care system delays in the start of tuberculosis treatment in Norway. BMC Infectious Diseases. 2006; 6(33).
15. Gagliooti C, Resi D, Moro ML. Delay in the treatment of pulmonary TB in a changing demographic scenario, International Journal of Tuberculosis and Lung Disease. 2006; 10(3): 305-309.
16. Rodger A, Jaffar S, Paynter S, Hayward A, Carless J, Maguire H. Delay in the Diagnosis of Pulmonary Tuberculosis., London, 1998-2000 : Analysis of surveillance data. BMJ. 2003; 326(7395): 909-910.
17. Sanz B, Blasco T. Variables associated with diagnostic delay in immigrant groups with tuberculosis in Madrid. International Journal of Tuberculosis and Lung Disease. 2007; 11(6): 639-646.

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ORIGINAL ARTICLE

The Correlation between Phalangeal Quantitative Ultrasonography and Dual Energy X-ray Absorptiometry in Women with Premature Ovarian Failure

Tandip S Mann*, Alison H McGregor, Rajesh Patel

ABSTRACT: Objectives – With the growing demand for bone densitometry services there is a need for simple, cost-effective and ideally mobile devices which can identify individuals who are at risk of osteoporotic fracture. When new devices are evaluated, it is useful to examine the correlation with the established 'gold standard' technique of dual x-ray absorptiometry (DXA). This study examined the correlation between quantitative ultrasound (QUS) measurements performed at the phalanges and conventional DXA measurements of the spine and hip in women with premature ovarian failure – a known risk factor for osteoporosis. Methods - Thirteen white Caucasian women suffering from premature ovarian failure and 19 age- and sex-matched controls were recruited into the study. DXA measurements were performed at the spine and hip, followed by quantitative ultrasonography at phalanges II-V of the non-dominant hand. Results – Significant correlations were observed between the bone transit time (BTT) value from the Bone Profiler and bone mineral density measured at the spine (r=0.66). The spine Z-scores also correlated with many of the ultrasound values (r=0.44 - 0.63). Significant inverse correlations were observed between BMI, weight and ultrasound parameters (r = -0.48 to -0.78). Conclusion – We have reported moderate but significant correlations between phalangeal QUS and DXA parameters. The strongest correlation was observed between BTT and spine BMD, as well as between the Z-scores from the two devices. QUS parameters also demonstrated an inverse correlation with weight and BMI.

KEYWORDS: Bone mineral density, osteoporosis, premature ovarian failure, DXA, quantitative ultrasound.

INTRODUCTION

In many developed countries, osteoporosis is now recognised as one of the most serious problems in public health [1-3]. For a 50-year-old white woman, the life-time risk of suffering a fragility fracture is estimated to be 30-40%, which compares with the figures for breast cancer and cardiovascular disease of 9-12% and 30-40% respectively [3]. The increased recognition of the impact of osteoporosis on the lives of elderly people and the consequent costs of healthcare has led to the development of a variety of new treatments for preventing fractures [4-7]. Scans to measure bone mineral density (BMD) using the technique of dual x-ray absorptiometry (DXA) are widely believed to be the most effective way of identifying patients at risk of fracture and targeting these treatments appropriately [8,9]. Conventionally, the hip and spine are regarded as the most important measurement sites because fractures at these sites have the greatest impact on quality of life, morbidity and mortality of patients.

An individual's BMD undergoes progressive changes throughout life. There is rapid skeletal growth until peak bone mass (PBM) is reached at around age 30 [10], after which there is minimal change until the menopause in women. Following menopause, there is an approximately linear loss of BMD with increasing

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age [11]. PBM occurs in the third decade of life, but an inadequate nutritional intake of calcium [12] can prevent optimum peak bone mass being achieved. Low levels of physical activity during puberty can also lend to suboptimal bone density in later life [13]. Certain medical conditions and therapies can also affect bone metabolism and thus adversely affect BMD [14]. Long-term corticosteroid use is one such example, causing changes to trabecular bone structure, as well as reducing BMD [15]. Other factors known to compromise BMD include a previous atraumatic fracture or maternal hip fracture, a previous report of X-ray osteopenia, a positive family history of osteoporosis [16], a body mass index (BMI) of less than 19kg/m2, smoking and suffering from rheumatoid arthritis [17]. Sex hormone deficiency, most notably oestrogen in females, is a well established contributor to the pathogenesis of osteoporosis [18]. Menopause results in oestrogen deficiency, which stimulates bone resorption [19] and is associated with substantial bone loss continuing into old age [20]. The mean age at menopause is around 51 years [21]. However, approximately 1% of women develop premature ovarian failure (POF) and go through an early menopause by the age of 40 [22]. Although POF patients commonly receive hormone replacement therapy (HRT), their BMD remains significantly lower than that of age-matched controls. POF thus remains one of the major risk factors for osteoporosis in women.

With such a variety of risk factors for a reduced BMD and osteoporosis, there is a need to identify patients who are at increased risk of sustaining fractures [23]. The Royal College of Physicians in the United Kingdom have issued guidelines for referring patients for bone densitometry investigations based on clinical risk factors [8]. Similar guidelines have also been published by the European Foundation of Osteoporosis and Bone Disease [3], the National Osteoporosis Foundation [24] and the International Society for Clinical Densitometry [25]. All of the aforementioned guidelines include early menopause as a recognised risk factor for osteoporosis and as a basis to refer patients for a bone density examination.

The most widely accepted method of performing BMD scans to establish a diagnosis of osteoporosis is the DXA technique. DXA involves scanning the lumbar spine and hip, measurement sites chosen because they are the most prone to osteoporotic fractures. However, DXA scanners are relatively expensive pieces of equipment and their availability is generally restricted to major hospitals. If the diagnostic benefits of bone densitometry are to be fully realised, smaller, cheaper devices are required. One possibility is the introduction of small DXA scanners designed to scan only the forearm. This technique is referred to as peripheral DXA (pDXA). Another peripheral technique is quantitative ultrasound (QUS). Measurements of broadband ultrasonic attenuation (BUA) in the calcaneus can discriminate elderly women with hip fractures and there is a consensus that QUS has a potentially valuable role to assess fracture risk. The attraction to QUS devices is that as well as being cheap and portable, they do not use ionising radiation.

Since fractures may be present or absent in patients with similar BMD, bone strength cannot depend exclusively on bone density, but also on bone architecture [26]. Use of ultrasound in fracture risk assessment is thus advantageous as it seems to provide structural information, e.g. data on trabecular orientation [27], and can also reflect the mechanical properties of bone [28] in addition to estimation of its density. The calcaneus is an easily accessible, weight-bearing site, rich in trabecular bone and has been the most extensively studied site with QUS devices [29]. QUS measurements at this site have shown the ability to detect changes associated with age and menopause [26,30]. Measurements have also demonstrated the ability to differentiate healthy subjects from those with fractures [30,31] and also identifying those who are at an increased risk of fracture [32,33]. However, calcaneal QUS measurements can be unreliable in patients with ankle oedema. Variations in temperature (both ambient and of the patient's limb) are also believed to have an adverse effect on measurements [34].

An alternative, non-weight-bearing site for the assessment of bone mass using QUS is at the phalanges. The phalanges are composed of predominantly cortical bone and the regions of interest are easily accessible. The DBM Sonic Bone Profiler (IGEA, Italy) has been designed to transmit a single ultrasound burst through the distal metaphyses of the proximal phalanges. Bone resorption results in enlargement of the medullary canal and other structural changes, decreasing the ultrasound velocity and altering the characteristics of the signal arriving at the receiver probe [35]. The hand is very sensitive to these changes and is thus ideal for such assessment [36]. Previous studies using the DBM Sonic device have reported good precision with a coefficient of variation of 0.34% [37]. There is also evidence suggesting that phalangeal QUS measurements may be more sensitive than calcaneal measurements in identifying trends due to ageing and menopause [38].

The purpose of the present study was to examine the correlation between QUS parameters as measured at the proximal phalanges using the DBM Sonic Bone Profiler and conventional DXA measurements of BMD at the spine and hip in Caucasian women with POF. The study

population was readily available to us from a local menopause clinic and hence women with POF were chosen as a specific group in which to assess the correlation. It was not the aim of the present study to determine the fracture discrimination capability of the DBM Sonic device.

METHODS

Study Population

Thirteen Caucasian women (mean age 35.7 yrs, range 30.5 – 40.6 yrs), suffering from POF, were recruited from the menopause clinic at Chelsea and Westminster Hospital (London, UK). The control group consisted of 19 age-matched healthy Caucasian women (mean age 32.9 yrs, range 20.4 – 40.1 yrs) and were recruited with advertisements placed around the hospital sites. The study was approved by the Charing Cross Hospital Research Ethics Committee and all participants gave written informed consent.

Health assessment was carried out using a detailed questionnaire which included questions relating to known risk factors for osteoporosis, detailed medical history of POF, and use of HRT. Women on HRT were not excluded from the study. However, those with known risk factors for osteoporosis were excluded. These included women with a previous atraumatic fracture, and those on therapies or with conditions known to affect BMD (including thyroid conditions, malabsorption and use of corticosteroids).

Dual X-ray Absorptiometery

BMD was measured with a Lunar Prodigy (GE Healthcare, Madison, WI) DXA scanner. Measurements were performed at the lumbar spine (L1-L4), hip (total and neck of femur). In addition to recording BMD at these sites, we also recorded the T-score (a measure of how a subjects BMD value compares to those of a normal young adult at PBM – defined in terms of the standard deviation of young normal subjects) and Z-score (a measure of how a subjects BMD compares to an age-matched population – defined in terms of the standard deviation of the age-matched population). BMD measurement of the spine could not be obtained in one subject due to a navel ring, which could not be removed.

QUS

QUS measurements were performed on all subjects using the DBM Sonic Bone Profiler (IGEA, Carpi, Italy). A calliper was used to position the two probes (transmitter and receiver) laterally on either side of the metaphysis of the proximal phalanx, with ultrasound gel to achieve coupling. An ultrasound signal of 1.2MHz frequency is transmitted through the finger and an amplitude-dependent speed of sound (AD-SoS) parameter is generated, which depends on both the amplitude and the velocity of the signal received. Finger thickness and AD-SoS measurements were obtained for digits II-V of the non-dominant hand. Mean AD-SoS across all four digits was also obtained. Further measurement parameters included the Ultrasound Bone Profile Index (UBPI), a number between 0 and 1 describing the fracture risk [51], and the Bone Transmission Time (BTT) - the interval between the first received signal and the received signal that is propagated through soft tissue only [39]. T-scores and Z-scores based on the AD-SoS values are also automatically generated.

Duplicate measurements were performed for each subject to estimate precision, which was expressed as the coefficient of variation (CV). The mean values of the two measurements for each parameter were recorded and used for analysis. Ambient room temperature was kept constant with an air conditioning system as previous reports have suggested that QUS measurements are temperature-dependent [40]. Daily quality control measurements to ensure consistency of calibration were performed with a phantom supplied by the manufacturer.

Statistical Analysis

Data analysis was performed using Microsoft Excel (Seattle, WA, USA). Student's t-test was used to compare differences in demographic variables and in QUS and DXA parameters between the two groups. P-values of less than 0.05 were considered to be statistically significant. Linear regression analysis was carried out to determine the correlation between QUS and DXA parameters in (i) patients only (n=13), (ii) control group only (n=19) (iii) all participating subjects (n=32). The following comparisons were made: Spine BMD v AD-SoS; Spine BMD v BTT; Spine BMD v QUS Z-score; Spine Z-score v AD-SoS; Spine Z-score v BTT; Spine Z-score v QUS Z-score. The same correlations were also determined for hip BMD and hip Z-scores. The correlation of QUS and DXA parameters with weight and BMI was also examined.

RESULTS

Duplicate QUS measurements with repositioning on all 32 patients were combined to give short-term precision (CV%) of 0.37%, 3.36% 1.67% for AD-SoS, UBPI and BTT respectively.

Table 1 gives a summary of the demographic data, BMD parameters and QUS parameters for the patient group and the controls. Student's t-test showed no significant differences in any of the demographic or measurement parameters between the two groups.

Linear regression analysis was used to establish the correlation between DXA and QUS parameters. None of the correlations between UBPI and the DXA parameters were significant. The correlation between remaining QUS parameters and spine BMD are shown in Table 2. A significant correlation (r=0.66) was observed in POF patients between spine BMD and BTT. This relationship remained significant (r=0.48) when all 32 subjects were included in the analysis (Figure 1). All QUS variables (AD-SoS, BTT and Z-score) showed significant correlations (r=0.47 to 0.60) with spine Z-scores (Table 2, Figures 2-4). The T-score is a linear function of AD-SoS (for QUS measurements) and BMD for (DXA measurements). T-score correlations therefore provide no additional information and were excluded from the analysis. QUS correlations with DXA measurements at the hip (total hip and femoral neck sites) were not significant (Table 2). Normalising the QUS parameters by age and BMI did not improve the strength of correlation between any of above comparisons.

As well as providing the mean AD-SoS values, the Bone Profiler displays data for the thickness and AD-SoS for each of the four phalanges measured. Correlations between the AD-SoS values for individual fingers and the DXA parameters were again moderate (r = 0.44 – 0.63) but only significant when compared to spine Z-scores (Table 3).

Further analysis was carried out to compare QUS parameters with weight and BMI. Our results show a

	All women n = 32	POF group n = 13	Control group n = 19
Age (years)	34.1 ± 5.1	35.7 ± 3.4	32.9 ± 5.8
Height (m)	1.66 ± 0.06	1.65 ± 0.08	1.67 ± 0.05
Weight (kg)	68.3 ± 12.3	68.5 ± 15.7	68.3 ± 9.9
BMI (kg/m2)	24.8 ± 4.6	25.2 ± 5.9	24.5 ± 3.7
QUS DBM Sonic			
AD-SoS (m/s)	2128 ± 74	2138 ± 85	2121 ± 67
UBPI	0.72 ± 0.14	0.74 ± 0.14	0.71 ± 0.14
BTT (μs)	1.54 ± 0.21	1.53 ± 0.21	1.54 ± 0.22
DXA Lunar			
Spine BMD (g/cm^2)	1.19 ± 0.11	1.19 ± 0.11	1.18 ± 0.11
Hip (total) BMD (g/cm^2)	1.00 ± 0.12	0.99 ± 0.11	1.00 ± 0.13
Hip (neck) BMD(g/cm2)	1.03 ± 0.13	1.02 ± 0.10	1.04 ± 0.15

Table 1: Demographic, QUS and DXA data for patient group, control group and all subjects (mean and standard deviation). Student's t-tests show p>0.1 for all parameters

		AD-SoS (m/s)	BTT (μs)	Z-score
Spine BMD (g/cm2)	POF group	0.12	0.66*	0.12
	Control group	0.34	0.37	0.34
	Pooled data	0.24	0.48*	0.24
Spine Z-scores	POF group	0.43	0.54	0.43
	Control group	0.60*	0.43	0.59*
	Pooled data	0.51*	0.47*	0.51*
Total Hip BMD (g/cm2)	POF group	0.08	0.52	0.08
	Control group	0.001	0.09	0.009
	Pooled data	0.04	0.22	0.03
Total Hip Z-scores	POF group	0.15	0.49	0.15
	Control group	0.12	0.12	0.13
	Pooled data	0.12	0.23	0.12

Table 2: Correlation (r-values) between three QUS parameters and spine BMD shown for all subjects (n=32), POF group (n =13) and control group (n = 18). Results are also shown for the correlation with Total Hip BMD and Z-score.*Statistically Significant (p<0.05)

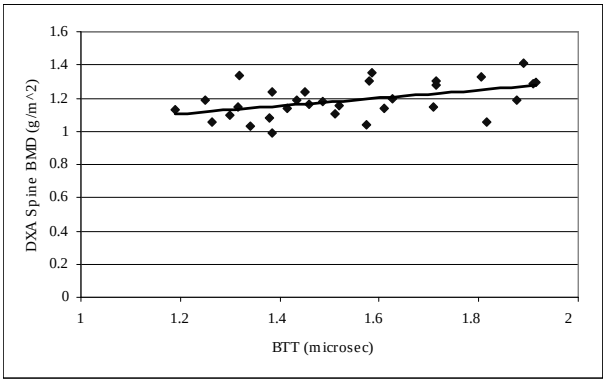

Figure 1: Graph showing the positive correlation between the QUS parameter BTT, and spine BMD for all subjects (n=31; r = 0.48; p = 0.007)

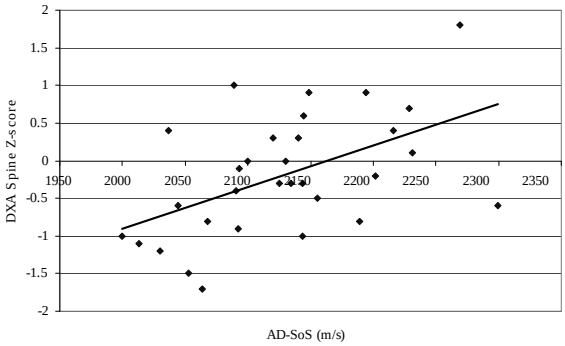

Figure 2: Graph showing the positive correlation between the QUS parameter AD-SoS, and spine Z-score for all subjects (n=31; r = 0.51; p = 0.003).

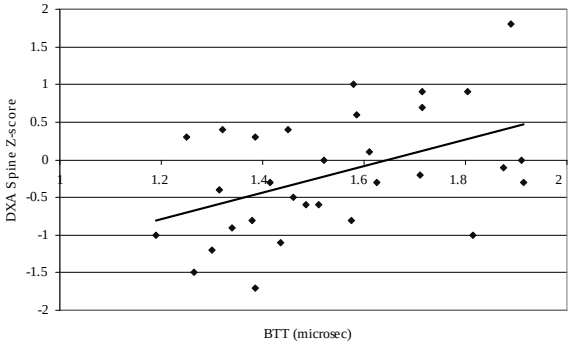

Figure 3: Graph showing the positive correlation between the QUS parameter BTT, and spine Z-score for all subjects (n=31; r = 0.47; p = 0.008)

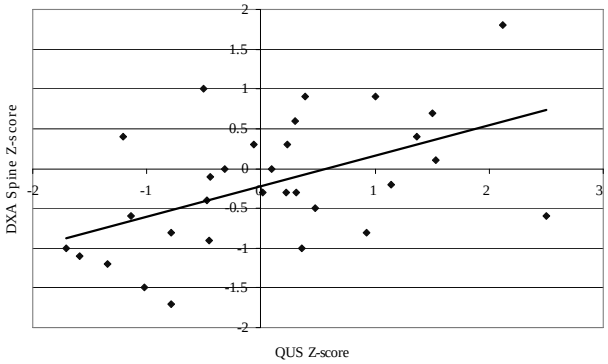

Figure 4: Graph showing the positive correlation between the QUS Z-score and spine Z-score for all subjects (n=31; r = 0.51; p = 0.003).

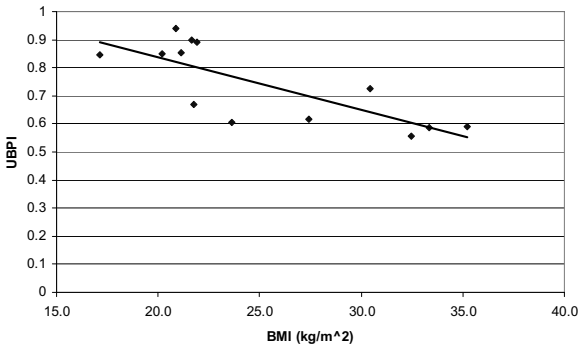

Figure 5: Graph showing the inverse correlation between BMI and the QUS parameter UBPI for the POF group (n=13; r = -0.78; p = 0.002)

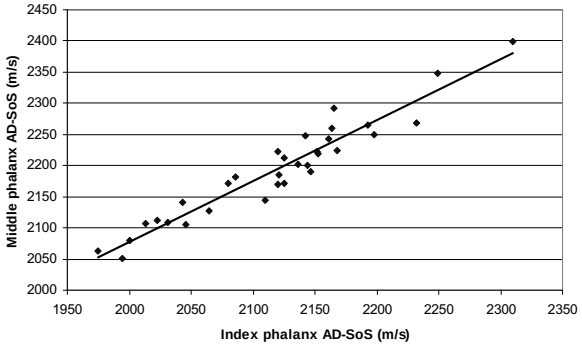

Figure 6: Graph showing the positive correlation between AD-SoS measurements obtained from the index (phalanx II) and the middle (phalanx III) fingers, for all subjects (n=32; r = -0.96; p < 0.0001).

Table 3: Correlation (r-values) between individual phalanx AD-SoS values and the spine Z-score measurements from the DXA for all subjects (n=31), POF group (n =13) and the control group (n = 18) *Statistically Significant (p<0.05)

		Phalanx II AD-SoS (m/s)	Phalanx III AD-SoS (m/s)	Phalanx IV AD-SoS (m/s)	Phalanx V AD-SoS (m/s)
Spine Z-score	POF group	0.38	0.30	0.53	0.44
	Control group	0.59*	0.63*	0.39	0.50*
	Pooled data	0.49*	0.47*	0.44*	0.47*

reasonably strong inverse correlation between all 3 QUS parameters (AD-SoS, UBPI and BTT) and BMI (Table 4). The strongest correlation was with UBPI in the POF patient group (r = -0.78) (Figure 5). Similar inverse correlations were observed (r = -0.48 to -0.76) between QUS parameters and subjects' weight. Similar values were also observed when comparing weight and BMI with AD-SoS values from individual fingers. The correlation between height and BMI was also established for DXA measurements at the spine and hip. Moderate but significant positive correlations were observed with spine and hip BMD (r = 0.37 – 0.62).

Finally, the correlation of AD-SoS values between the digits was established and found to be highly significant (p<0.0001). The strongest correlation (r=0.96) was observed between the index and middle fingers (Figure 6). Student's t-test demonstrated significant differences in AD-SoS and thickness values between fingers. These observations were similar in the patient group and in the controls. The AD-SoS values were greatest in phalanx III, followed by IV, II and V (p < 0.02).

DISCUSSION

Because of the growing demand for bone densitometry services, there is a need for cheap, safe and portable devices that can be used in a primary care setting to assess BMD and fracture risk. The ability of a device to independently assess fracture risk is best established through prospective fracture studies which can be expensive and time consuming. When evaluating new bone density scanners it is of interest to examine the correlation with DXA measurements at the spine and hip – the established 'gold standard' bone density measurements. In this study, we investigated the correlation between QUS parameters obtained using the DBM Sonic Bone Profiler and spine and hip

Table 4: Correlation (r values) between three QUS parameters and BMI; split by POF group (n =13), control group (n = 19) and the pooled data (n = 32). Correlations are also shown for weight. *Statistically Significant (p<0.05)

		AD-SoS (m/s)	Z-score	UBPI
BMI (kg/m2)	POF group	-0.69*	-0.69*	-0.78*
	Control group	-0.48*	-0.48*	-0.25
	Pooled data	-0.58*	-0.58*	-0.49*
Weight	POF group	-0.49	-0.50	-0.76*
	Control group	-0.48*	-0.48*	-0.25
	Pooled data	-0.48*	-0.48*	-0.57*

measurements acquired on a Lunar Prodigy system.

The precision analysis of our QUS measurements returned CV% values of 0.37 - 3.36% for the various parameters. The AD-SoS precision compare favourably with previously reported results [41,42]. The precision for the Prodigy DXA device has been previously quoted as 1.0% for the spine (L1-L4), 0.9% for hip (total) and 1.5% for femoral neck [43].

Linear regression analysis between DXA and QUS parameters showed a significant correlation of 0.66 (p=0.01) between the BTT value and spine BMD in women with POF, although this was not the case for other QUS parameters. BTT is a measure of the time delay between the two signals arriving at the receiver probe, with one having passed through bone and the other through the soft tissue phase. The significant correlation observed in our study could indicate that an improved bone structure at the phalanx correlates with higher bone density at the spine, and thus allows a more rapid transmission of the ultrasound signal through bone compared to soft tissue. Although much of the literature currently focuses on the AD-SoS values provided by the QUS device, Montagnani et al [44] have presented data highlighting the importance of BTT as the parameter most comparable to DXA and with the greatest ability to predict osteoporotic fractures.

Significant correlations of r=0.5 to 0.6 were observed between spine Z-scores and AD-SoS, as well as with BTT. QUS and DXA Z-scores showed a moderate correlation when the data from patients and controls was pooled (r=0.51). Although Z-scores are not used in the diagnosis of osteoporosis our results suggest that this relationship between Z-scores merits further investigation. If QUS Z-scores can predict DXA Z-scores, it may suggest a role for QUS measurements as a screening tool. It has previously been suggested that phalangeal QUS Z-scores may be a useful tool in the screening of bone disturbances in young patients with type I diabetes mellitus [45]. It is possible that phalangeal QUS may also have a role in other disease states affecting bone.

Regression analysis demonstrated that AD-SoS, UBPI and QUS Z-score parameters are all inversely related with both BMI and weight. Although the Bone Profiler accounts for soft tissue content, weak but significant correlations (r = -0.30 to -0.32) between AD-SoS and BMI have been reported previously [41,46]. Interestingly, BTT does not show a similar correlation but was the only QUS parameter to show a positive correlation with height in the POF group. A similarly significant correlation was seen between spine BMD and height (r = 0.56), which strengthens the argument for further research into the potential value of BTT as a predictor of spine BMD. Currently however, the association between QUS and BMI remains unclear with some showing evidence of a significant correlation [47,48], whilst other data remains inconclusive [49]. Alenfeld et al. [48] postulate QUS may depend on body weight and BMI as the soft tissue surrounding the phalanges influences both acoustical contact and velocity.

Repeated student's t-test analyses for the differences in mean thickness between phalanges II to V showed a significant, progressive increase in width from index to small fingers. However, the mean AD-SoS values were significantly greater in the middle finger, followed by the ring, index and small fingers, implying that the QUS AD-SoS parameter is indeed not simply a function of the distance between the probes, but can identify quantitative differences between the structures of the digits. The potential of QUS measurement to reflect bone structure, as well as bone density, has in fact been one of the driving forces for QUS densitometry. QUS measurements may have a role in assessing fracture risk in patients on corticosteroids for example [15], which are known to affect the structure of trabecular bone and have a detrimental effect 'over and beyond' that reflected in a DXA measurement of low bone mass alone [50].

Analysis of the collected data has shown significant correlations between a number of QUS and DXA device parameters, as well as upon comparison with demographics. Perhaps the most promising of these is the correlation of spinal BMD with BTT and, with an r2 value of 0.44 in the POF group, offers the best predictive ability of BMD compared to the other QUS parameters.

However, other studies have highlighted the use of alternative QUS parameters for the estimation of BMD. Alexandersen et al [26] demonstrated weak but significant correlations between AD-SoS and BMD at the spine and hip (femoral neck) (r = 0.21 for both sites), whereas Wuster et al [51] obtained higher correlations (r = 0.46 and r=0.36 spine and hip BMD, respectively). The lack of concordance with our study may lie in the differences between populations from Denmark, Scandinavia and the UK, respectively. Furthermore, the Bone Profiler is a device with a higher sensitivity to skeletal changes occurring in the early postmenopausal period (in the range 50-65), which encompasses the population used by Wuster et al [51] and thus providing the strongest correlations. The mean age in the Alexandersen study [26] was 69.9 years, at which age postmenopausal changes can still be identified. However, our study had a mean age for all subjects of 34.1 years, with one group having been through an early menopause and the other group acting as controls. Thus, differences in the population age and

inconsistencies of menopausal state of the subjects may account for the discrepancies. Other studies have also shown negative associations of QUS parameters with age [52]. However, the unique patient group we selected has not been assessed by others in this manner. This adds a confounding factor to our data making comparison difficult. An unlikely alternative explanation for the discrepancies between studies is user-dependence which was highlighted as significant factor affecting the accuracy of measurements in a study by Krieg et al [53] who carried out measurements using the DBM Sonic on over 7000 women.

One advantage of assessing the human phalanges is their sensitivity to early changes in bone mass [54], and work originally based on animal studies has supported the argument that phalangeal ultrasound can identify architectural characteristics of bone [35]. However, unlike the calcaneus, phalangeal bone is not subject to weight-bearing activity and thus provides weaker correlations compared to peripheral weight-bearing sites [54]. Furthermore, inaccurate positioning of the calliper on the phalanx can lead to errors, as the joint itself has greater trabecular bone content than the metaphysis [55] and can therefore contribute to operator errors. QUS values are also dependent on the temperature of the limb, which can be difficult to control in variable climatic conditions. However, in the present study room temperature was controlled using an air conditioning system. One further source of measurement error that has been reported is that the phalangeal joints are common sites for osteoarthritis [26], which could interfere with QUS measurements.

The stronger correlation of our results occurring between QUS and DXA at the spine, as opposed to at the hip, may partly be explained by the fact that trabecular rich vertebrae are more sensitive in identifying changes occurring with age or therapy compared to the hip.

As well as the relatively small sample size, there were further limitations to our study. HRT is known to significantly reduce the impact of the menopause on bone loss [56] but its duration of use in the present study (4 months to 7 yrs) varied widely between patients. Uygur et al [22] have suggested that current HRT regimes, designed for women undergoing natural menopause, may be inappropriate for some women with POF and thus cause further variations in the effects of HRT in POF groups. The use of HRT may have different effects on QUS and DXA parameters.

The potential benefits for phalangeal QUS to be adopted as a screening device could extend beyond its correlation with DXA. Other studies have shown the ability of the phalangeal QUS device to identify changes associated with age and with the menopause, but also to predict fracture risk [56-59]. Its relatively low CV% values can also allow frequent monitoring of bone health. Although QUS cannot provide a direct measurement of BMD itself, its potential for detecting structural changes may be more beneficial than established areal BMD measurements.

Our study suggests that there may be a need to move away from focusing on the AD-SoS parameter in place of the BTT, and even a greater role for Z-scores. BTT has shown stronger correlation with DXA values and stronger predictive r2 ability compared to other QUS parameters. Whilst some authors have described a combination of clinical risk factors and QUS values in the form of a ‘nomogram’ as the ideal method of screening for increased fracture risk [60], others believe the complex soft tissue–bone–ultrasound interactions and the resultant waveform they produce should be analysed [51]. In either case, the aim is to identify patients at risk of fracture before the fracture occurs. Possible further roles for phalangeal QUS may include measurements in children on long-term corticosteroids. All this is only possible through studies such as this being able to identify and harness the great expectations with which these devices were introduced, and allow early preventative interventions to be taken in high-risk groups.

CONCLUSION

We have reported moderate but significant correlations between phalangeal QUS and DXA parameters. The strongest correlation was observed between BTT and spine BMD, as well as between the Z-scores from the two devices. QUS parameters also demonstrated an inverse correlation with weight and BMI. These correlations were seen within the POF group, control group and when data for all patients was pooled. Our data support further studies to evaluate the ability of phalangeal QUS measurements to independently assess fracture risk in patients with and without different risk factors. Such studies will help establish whether phalangeal QUS can be used as a screening tool in the primary care setting. Currently, the best measurement sites for QUS and the ideal parameters with which to form guidelines still have to be established.

ACKNOWLEDGMENTS

We would like to thank Dr Nick Panay at the Chelsea and Westminster hospital (London UK) for help with recruitment of patients with POF.

REFERENCES

1. Cooper C, Campion G, Melton LJ Hip fractures in the elderly; a

world-wide projection. Osteoporosis Int 1992; 2:285-289.
2. Ray NF, Chan JK, Thamer M, Melton LJ Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 1997; 12:24-35
3. Kanis JA, Delmas P, Burckhardt P et al. on behalf of the European Foundation for Osteoporosis and Bone Disease. Guidelines for diagnosis and treatment of osteoporosis. Osteoporosis Int 1997; 7:390-406.
4. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. J Clin Endocrinol Metab 2000; 85:4118-4124.
5. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001; 344:333-340.
6. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1-34) fragment on spine and non-spine fractures and bone mineral density in postmenopausal osteoporosis. N Engl J Med 2001; 344:1434-1441
7. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2001; 87:3609-3617.
8. Royal College of Physicians Osteoporosis: clinical guidelines for prevention and treatment. Update on pharmacological interventions and an algorithm for management. RCP 2000, London.
9. US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Arch Intern Med 2002; 137:526-528.
10. Bonjour J-P and Rizzoli R. Bone acquisition in adolescence. In Marcus R, Feldman D, Kelsey J (eds). Osteoporosis 1996; pp465-476. Academic Press, San Diego.
11. Kanis JA, Gluer C-C. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporosis International. 2000; 11: pp. 192-202.
12. Cashman KD. Calcium intake, calcium bioavailability and bone health. British Journal of Nutrition. 2002; 87 (Supplement S2): pp. S169-S177.
13. Rideout CA, McKay HA, Barr SI. Self-reported lifetime physical activity and areal bone mineral density in healthy postmenopausal women: the importance of teenage activity. Calcified Tissue International. 2006; 79 (4): pp. 214-222.
14. Pons F, Peris P, Guanabens N et al. The effect of systemic lupus erythematosus and long-term steroid therapy on bone mass in pre-menopausal women. British Journal of Rheumatology. 1995; 34: pp. 742-6.
15. Chappard D, Josselin N, Rouge-Maillart C, et al. Bone microarchitecture in males with corticosteroid-induced osteoporosis. Osteoporosis International. 2007; 18 (4): pp. 487-494.
16. Bainbridge PR, Eastell R. Indications for bone densitometry: do they identify patients with low bone mineral density? Current research in osteoporosis and bone mineral management. British Journal of Radiology. 1998; 5: pp. 5-6.
17. Seriolo B, Paolino S, Sulli A, et al. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Annals of the New York Academy of Sciences. 2006; 1069 (1): pp. 420-7.
18. Aitken JM, Hart DM, Anderson JB, et al. Osteoporosis after oophorectomy for non-malignant disease in premenopausal women. British Medical Journal. 1973; 2: pp. 325-8.
19. Genant HK, Cooper C, Poor G et al. Interim report and recommendations of the World Health Organisation task-force for osteoporosis. Osteoporosis International. 1999; 10: pp. 259-264.
20. Ensrud KE, Palermo L, Black DM, et al. Hip and calcaneal bone loss increase with advancing age: longitudinal results from the study of osteoporotic fractures. Journal of Bone and Mineral Research. 1995; 10: pp. 1778-87.
21. Kazerooni T, Talei AR, Sadeghi-Hassanabadi A, et al. Reproductive behaviour in women in Shiraz, Islamic Republic of Iran. Eastern Mediterranean Health Journal. 2000; 6 (2): pp. 517-521.
22. Uygur D, Sengul O, Bayar D, et al. Bone loss in young women with premature ovarian failure. Archives of Gynecology and Obstetrics. 2005; 273: pp. 17-19.
23. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. Journal of Bone and Mineral Research. 2005; 20: pp. 1185-94.
24. National Osteoporosis Foundation Risk assessment. In: Physician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation 1998; Washington DC, USA.
25. International Society for Clinical Densitometry. Official Positions and Official Pediatric Positions of the ISCD 2007.
26. Alexandersen P, de Terlizzi F, Tanko LB, et al. Comparison of quantitative ultrasound of the phalanges with conventional bone densitometry in healthy postmenopausal women. Osteoporosis International. 2005; 16: pp. 1071-78.
27. Gluer CC, Wu CY, Genant HK. Broadband ultrasound attenuation signals depend on trabecular orientation: an in vitro study. Osteoporosis International. 1993; 3: pp. 185-191.
28. Bouxsein ML, Radloff SE. Quantitative ultrasound of the calcaneus reflects the mechanical properties of calcaneal trabecular bone. Journal of Bone and Mineral Research. 1997; 12: pp. 839-46.
29. Frost ML, Blake GM, Fogelman I. Does quantitative ultrasound imaging enhance precision and discrimination? Osteoporosis International. 2000; 11: pp. 425-433.
30. Frost ML, Blake GM, Fogelman I. Contact quantitative ultrasound: an evaluation of precision, fracture discrimination, age-related bone loss and applicability of the WHO criteria. Osteoporosis Interantional. 1999; 10: pp. 441-449.
31. He YQ, Fan B, Hans D, et al. Assessment of a new quantitative ultrasound calcaneus measurement: precision and discrimination of hip fractures in elderly women compared with dual X-ray absorptiometry. Osteoporosis International. 2000; 11 (4): pp. 354-360.
32. Bauer DC, Gluer CC, Cauley JA, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. Archives of Internal Medicine. 1997; 157: pp. 629-634.
33. Woodhouse A, Black DM. BMD at various sites for the prediction of hip fractures: a meta analysis. Journal of Bone and Mineral Research. 2000; 15: pp. 1-145.
34. Johansen A, Stone MD. The effect of ankle oedema on bone ultrasound assessment at the heel. Osteoporosis International. 1997; 7: pp. 44-47.
35. Cadossi R, Cane V. Pathways of transmission of ultrasound energy through the distal metaphysis of the second phalanx of pigs. Osteoporosis International. 1996; 6: pp. 196-206.
36. Kleerekoper M, Nelson DA, Flynn MJ, et al. Comparison of radiographic absorptiometry with dual-X-ray absorptiometry and quantitative computed tomography in normal older white and black women. Journal of Bone and Mineral Research. 1994; 9: pp. 1745-9.
37. Di Stefano M and Isaia GV. Ability of ultrasound bone profile score(UBPS) to discriminate between fractured and not fractured osteoporotic women. Ultrasound in Medicine & Biology 2002; 28(11-12), pp1485-1489.

38. Pluskiewicz W, Drozdzowska B. Quantitative ultrasound (QUS) at the calcaneus and hand phalanges in Polish healthy postmenopausal women. Ultrasound in Medicine and Biology. 2001; 27 (3): pp. 373-7.
39. Guglielmi G, de Terlizzi F, Torrente I, et al. Quantitative ultrasound of the hand phalanges in a cohort of monozygotic twins: influence of genetic and environmental factors. Skeletal Radiology. 2005; 34 (11): pp. 727-735.
40. Pocock NA, Babichev A, Culton N, et al. Temperature dependency of quantitative ultrasound. Osteoporosis International. 2000; 11: pp. 316-320.
41. Ventura V, Mauloni M, Mura M, et al. Ultrasound velocity changes at the proximal phalanxes of the hand in pre-, peri- and postmenopausal women. Osteoporosis International. 1996; 6: pp. 368-375.
42. Joly J, Westhovens R, Borghs H, et al. Reference curves and diagnostic sensitivity for a new ultrasound device for the phalanges, the DBMsonic 1200, in Belgian women. Osteoporosis International. 1999; 9 (4): pp. 284-9.
43. Shepherd J, Fan B, Lu Y, et al. Comparison of BMD precision for Prodigy and Delphi spine and femur scans. Osteoporosis International. 2006; 17 (9): pp. 1303-8.
44. Montagnani A, Gonnelli S, Cepollaro C, et al. Usefulness of bone quantitative ultrasound in management of osteoporosis in men. Journal of Clinical Densitometry. 2001; 4 (3): pp. 231-7.
45. Valerio G, del Puente A, Buono P, et al. Quantitative ultrasound of proximal phalanges in patients with type I diabetes mellitus. Diabetes Research and Clinical Practice. 2004; 64 (3): pp. 161-6.
46. Halaba ZP, Konstantynowicz J, Pluskiewicz W, et al. Comparison of phalangeal ultrasound and dual energy X-ray absorptiometry in healthy male and female adolescents. Ultrasound in Medicine and Biology. 2005; 31 (12): pp. 1617-22.
47. Rico H, Aguado F, Arribas I, et al. Behaviour of phalangeal bone ultrasound in normal women with relation to gonadal status and body mass index. Osteoporosis International. 2001; 12: pp. 450-5.
48. Alenfeld FE, Wuster C, Funck C, et al. Ultrasound measurements at the proximal phalanges in healthy women and patients with hip fractures. Osteoporosis International. 1998; 8: pp. 393-8.
49. Gregg EW, Kriska AM, Salamone LM, et al. Correlates of quantitative ultrasound in the Women's Healthy Lifestyle Project. Osteoporosis International. 1999; 10: pp. 416-424.
50. Royal College of Physicians. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: RCP; 2002.
51. Wuster C, Albanese C, De Aloysio D, et al. Phalangeal Osteosonogrammetry Study: age-related changes, diagnostic sensitivity, and discrimination power. Journal of Bone and Mineral Research. 2000; 15: pp. 1603-14.
52. Mele R, Masci G, Ventura V, et al. Three-year longitudinal study with quantitative ultrasound at the hand phalanx in a female population. Osteoporosis International. 1997; 7 (6): pp. 550-7.
53. Krieg MA, Cornuz J, Ruffieux C, et al. Prediction of hip fracture risk by quantitative ultrasound in more than 7000 Swiss women ≥70 years of age: comparison of three technologically different bone ultrasound devices in the SEMOF study. Journal of Bone and Mineral Research. 2006; 21 (9): pp. 1457-63.
54. Rico H, Revilla M, Fraile E, et al. Metacarpal cortical thickness by computer radiography in osteoporosis. Bone. 1994; 15: pp. 303-6.
55. Schneider J, Bundschuh B, Spath C, et al. Discrimination of patients with and without vertebral fractures as measured by ultrasound and DXA osteodensitometry. Calcified Tissue International. 2004; 74 (3): pp. 246-254.
56. Roben P, Barkmann R, Ullrich S, et al. Assessment of phalangeal bone loss in patients with rheumatoid arthritis by quantitative ultrasound. Annals of the rheumatic diseases. 2001; 60: pp. 670-7.
57. Pluskiewicz W, Drozdzowska B. Ultrasound measurements of proximal phalanges in Polish early postmenopausal women. Osteoporosis International. 1998; 8: pp. 578-583.
58. Hartl F, Tyndall A, Kraenzlin M, et al. Discriminatory ability of quantitative ultrasound parameters and bone mineral density in a population-based sample of postmenopausal women with vertebral fractures: result of the Basel Osteoporosis Study. Journal of Bone and Mineral Research. 2002; 17: pp. 321-330.
59. Guglielmi G, Cammisa M, De Serio A, et al. Phalangeal US velocity discriminates between normal and vertebrally fractured subjects. European Radiology. 1999; 9: pp. 1632-7.
60. Pluskiewicz W, Nowakowska J. Bone status after long-term anticonvulsant therapy in epileptic patients: evaluation using quantitative ultrasound of calcaneus and phalanges. Ultrasound Med Biol. 1997; 23: pp. 553-8.
61. Pongchaiyakul C, Panichkul S, Songpatanasilp T et al. A normogram for predicting osteoporosis risk based on age, weight and quantitative ultrasound measurement. Osteoporosis International. 2007; 18: pp. 525-531.

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ORIGINAL ARTICLE

Adverse Reproductive Outcomes Associated With Teenage Pregnancy

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ABSTRACT: Introduction– It is debated whether teenage pregnancy is associated with an adverse reproductive outcome. This study assessed the reproductive outcomes in teenage pregnancy in Nepal, a developing setting.

Methods – A hospital based retrospective cohort study of 4,101 deliveries to compare the outcomes between teenage and non-teenage pregnancies.

Results – Pregnancy in teenagers was associated with significantly increased risk ($P<0.05$) of delivery of very and moderately preterm births and Low Birth Weight babies. There was no significant difference in risk of having small for gestational age babies, low APGAR score at birth at 1 min and 5min, stillbirth, neonatal death, and post partum hemorrhage. However, the risk of having delivery by episiotomy, vacuum or forceps and Caesarean section was significantly lower ($P<0.05$) among teenage mothers.

Conclusion – Teenage women were more likely to have preterm births and low birth weight babies. However, they were less likely to have delivery by episiotomy, forceps or vacuum and Caesarean sections. In other respects, there were no significant differences between teenage and non-teenage mothers.

KEYWORDS: Teenage; Pregnancy; Outcome; Preterm; Low Birth Weight; SGA; Caesarean

INTRODUCTION

Teenage pregnancy is an important public health problem worldwide as it often occurs in the context of poor social support. It has been associated with maternal complications, premature birth, low birth weight, perinatal mortality and increased infant mortality [1]. It has also been observed that in developing countries, teenage mothers were at increased risk of maternal anemia, pre-term birth and Caesarean delivery [2]. Hence, the United Nations remarks that early child bearing is a high health risk for both the mother and the child [3].

In Nepal, a significant number of teenage women get married and bear children. However, they are not equally distributed across urban and rural areas and exact data is not available [4]. Adolescents comprise 23 % of 23 millions of the Nepalese population [5]. The median age at first marriage for a woman in Nepal is 16.6 years, suggesting that the majority of newly married couples are teenagers [6]. Considering the social structure where women get pregnant within the first few years of their marriage, teenage pregnancy (<20 years) is common in Nepal. Teenage pregnancy with first Ante Natal Checkup (ANC) visit accounts for 15.5% of the total expected pregnancies [7]. According to the 1996 National Family Health Survey (NFHS), nearly half of all female adolescents were married in 1996 and over half of these were already mothers or were pregnant, as were 90% of married young adult women aged 20–24 [8].

The social structure, ante-natal care, perinatal care and the quality of services available in developing countries differ from that of developed countries. This study was conducted to determine whether teenage pregnancy is associated with adverse outcomes in a developing setting.

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MATERIALS AND METHODS

Design

A hospital based retrospective cohort study.

Setting

Mahendra Adarsh Chikitsalaya, a 150 bed government hospital in Chitwan, Nepal.

Data collection and selection criteria

The maternity discharge register was used to identify singleton births that resulted in a live or stillborn baby during the Nepali fiscal year 2062/63 (July 2005 to June 2006). Inclusion in the study group was restricted to maternal age between 15-29, Parity 0 or 1, birth weight >500gm and delivery at or after 28 weeks of gestation at birth. Only those cases fulfilling the above criteria and for which data on all variables were available were included. This study was ethically approved by the Hospital Administration, Mahendra Adarsha Chikitsalaya, Chitwan, Nepal.

Comparison groups

Data collected from the cohort was stratified into teenage (15-19) and non-teenage (20-29) groups and outcomes were compared between these groups.

Definitions and denominators

The age of pregnant woman in completed years at the time of birth of baby was considered as maternal age. Ethnicity and type of delivery was recorded as mentioned in the register. For simplicity, episiotomy with instrumental delivery was considered as instrumental delivery. Post Partum Hemorrhage (PPH) was defined as blood loss greater than 500 ml following birth of baby during the hospital stay.

Gestational age at birth was the age from the last menstrual period (LMP) in completed weeks. Parity 'zero' was births to women who had no previous childbirths or whose previous pregnancies had all ended in abortions. Parity 'one' was defined as births preceded by only one pregnancy that did not result in abortion. Small for gestational age (SGA) baby was a live baby who was less than 10th percentile of birth weight for the given week of gestation derived from Babson and Benda growth graphs [9]. Birth weight below 2,500 grams at birth irrespective of the gestational age was considered as Low Birth Weight (LBW).

Birth of a live baby at 28 to 32 weeks' gestation was considered as very pre-term delivery and that between 33 to 36 weeks as moderately pre-term delivery. APGAR score less than 7 was considered as low APGAR score at birth. Still birth was defined as delivery of a dead baby after 28 weeks of gestation while neonatal death referred to death of a live born baby during the hospital stay of the mother.

For all outcomes, the denominator used was the total number of deliveries in their respective categories.

Statistical analysis

Data entry and statistical analysis were performed using Epi Info 2002 (Centre for Disease Control and Prevention, USA). The adjusted odds ratios for maternal and fetal outcomes were calculated by logistic regression analysis. Since the outcomes have been known to vary between different ethnic groups within Nepal [10] and also with parity [11], all logistic regression analysis included ethnic group and parity as dummy variables. Additional confounding factors, including logistic regression models for each outcome, have been mentioned in their respective tables.

RESULTS

Of the 5,076 deliveries recorded in the maternity register during the Nepali fiscal year 2062/063 in Mahendra Adarsha Chikitsalaya, 80.79% (n=4,101) satisfied our inclusion criteria. Of these 19.27% (n=790) were in the 15-19 age group and 80.73% (n=3,311) were in the 20-29 age group. The population characteristics are shown in Table 1.

Teenage mothers had a significantly increased incidence of delivery of very preterm babies (OR, 3.02; 95% CI, 1.61-5.66; P<0.001), moderately preterm babies (OR, 1.59; 95% CI, 1.14-2.20; P<0.05) and Low Birth Weight babies (OR, 1.54; 95% CI, 1.18-2.02; P<0.05). The risk of having small for gestational age babies (OR, 1.03; 95% CI, 0.83-1.27), low APGAR score at birth at 1 min (OR, 1.07; 95% CI, 0.82-1.38), and 5 min (OR, 1.19; 95% CI, 0.56-2.53), stillbirth (OR, 1.43; 95% CI, 0.81-2.52) and neonatal death (OR, 2.04; 95% CI, 0.70-5.89) was also higher in the teenage group, although these were not statistically significant (Table 2).

Among the maternal outcomes (Table 3), the risk of having delivery by episiotomy (OR, 0.76; 95% CI, 0.60-0.96; P<0.05), vacuum or forceps (OR, 0.67; 95%

	Total (%)	Women aged 15-19 (%)	Women aged 20-29 (%)	P-value
Total	4,101 (100)	790 (100)	3,311 (100)	
Mean age ± S.D	21.91±2.76	18.15±0.90	22.81±2.25	<0.001
Ethnicity				
Brahmin/Chhetri	2,328 (56.76)	328 (41.51)	2,000 (60.40)	
Newars	255 (06.21)	45 (05.69)	210 (06.34)	
Mongolians	680 (16.58)	160 (20.25)	520 (15.70)	
Others	838 (20.43)	257 (32.53)	581 (17.54)	
Parity				
Zero	2744 (66.91)	726 (91.89)	2018 (60.94)	
One	1357 (33.09)	64 (08.10)	1293 (39.05)	

Table 1: Study Group Demographics

	Women aged 15-19 (%) (n=790)	Women aged 20-29 (%) (n=3,311)	Odds Ratio (95% CI)	P-Value
Weeks of Gestation				
Very Preterm	21 (02.65)	29 (00.87)	3.02 (1.61-5.66)	<0.001
Mod. Preterm	63 (07.97)	164 (04.95)	1.59(1.14-2.20)	<0.05
Low Birth Weight	83 (10.50)	212 (06.40)	1.54 (1.18-2.02)	<0.05
Small for Gestational Age	143 (18.10)	521 (15.73)	1.03 (0.83-1.27)	NS,0.78
Low APGAR score*				
1 min	92 (11.64)	313 (09.45)	1.07 (0.82-1.38)	NS,0.60
5 min	11 (01.39)	27 (00.81)	1.19 (0.56-2.53)	NS,0.64
Still Birth	19 (02.40)	49 (01.47)	1.43 (0.81-2.52)	NS,0.21
Neonatal Death	6 (00.75)	12 (00.36)	2.04 (0.70-5.89)	NS,0.18

Table 2: Fetal Outcomes
CI = Confidence Interval, NS = Not Significant Logistic regression analyses included ethnic group and parity.
* Weeks of Gestation (Additional confounding factor in logistic regression model)

CI, 0.46-0.97; P<0.05) and Caesarean section (OR, 0.69; 95% CI, 0.51-0.91; P<0.05) was significantly lower among teenage mothers. The risk of developing Post Partum Hemorrhage was not significantly different between the two groups (OR, 1.15; 95% CI, 0.59-2.21).

DISCUSSION

This study shows that teenage pregnancy is associated with preterm delivery and low birth weight babies. Many previous studies have shown similar findings [12-14]. In contrast to these studies, we did not find an association between teenage pregnancy and delivery of small for gestational age babies. Also the high proportion of small for gestational age babies seen in both teenage and non-teenage age groups may be due to the use of Babson and Benda growth chart which is based on a different population [9].

It is often argued that the adverse reproductive outcome in teenage pregnancy is due to the social, economic and behavioural factors rather the biological effect of young age [15-17]. One earlier study has shown that significant differences in the socioeconomic status between teenage mothers and older mothers exist in Nepal as well [18]. The weight of the mother also plays an important role in outcomes such as small for gestational age [19]. We have not taken account of socioeconomic factors or maternal weight which is one of the major limitations of our study.

Teenage mothers have been shown to more likely be unmarried and smokers which adversely affect the delivery outcomes [20-22]. However, this unlikely to be true in our study. In South-East Asia, early marriage is a social norm. Smoking, though common in older women, is not socially acceptable among younger women. Not including smoking habit of mothers is another limitation of this study.

This study identified that the odds of having low APGAR score, neonatal death in teenage age group is not statistically significant compared to the non-teenage women. This is in agreement with recent studies [23-24]. However, this is a hospital based study where most of the complications that would otherwise have adverse outcomes in a community setting, are well-managed. This could also be the reason for non-significant differences in post-partum haemorrhage between the two groups.

Some studies have shown that the risk of Caesarean section is increased in teenage pregnancy [25] while some have shown the opposite [20, 23]. This study shows that this risk is decreased significantly, which could be due to a higher incidence of low birth weight in teenage pregnancies as this would be associated with

	Women aged 15-19 (%) (n=790)	Women aged 20-29 (%) (n=3,311)	Odds ratio (95% CI)	P-Value
Type of Delivery#				
Episiotomy	112 (14.17)	404 (12.20)	0.76 (0.60-0.96)	<0.05
Instrumental	37 (04.68)	178 (5.37)	0.67 (0.46-0.97)	<0.05
Caesarean	72 (09.11)	391 (11.80)	0.69 (0.51-0.91)	<0.05
PPH$	13 (01.64)	50 (01.51)	1.15 (0.59-2.21)	NS, 0.67

Table 3: Maternal Outcomes
CI = Confidence Interval, NS = Not Significant
All logistic regression analyses included ethnic group and parity. Additional confounding factors in the logistic regression are indicated by superscript symbols.# Presentation $ Type of delivery

a higher chance of successful vaginal delivery20. In addition, local gynecologists are reluctant to perform surgical procedures on teenagers (personal communication). The decreased risk of episiotomy and instrumental delivery among teenage groups in this study adds on to suggest gynecologists' reluctance to perform surgical procedures in teenagers. Another possibility is that teenage women understand that teenage pregnancy is a risk and may present to the hospital early compared to non-teenage women. This is supported by the fact that this was a hospital-based study that included women from a good socioeconomic status relative to the majority of the population, suggesting an increased awareness of pregnancy related complications.

Further information on socioeconomic and behavioral variables is needed to confidently conclude on adverse effects of teenage pregnancy. We suggest a community based prospective collection of data for this.

REFERENCES

1. Mapanga KG. The perils of adolescent pregnancy. World Health 1997; 50: 16-18.
2. Scholl TO, Hediger ML, Belsky DH. Prenatal care and maternal health during adolescent pregnancy: A review and meta-analysis. Adolesc Health 1994; 15: 444-456.
3. United Nations. Adolescent reproductive behavior: evidence from developing countries: volume 2. New York: United Nations; 1989.
4. Ganesh Dangal: An Update on Teenage Pregnancy. The Internet Journal of Gynecology and Obstetrics. 2005. Volume 5 Number1. http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijgo/vol5n1/teenage.xml (Accessed on 18th Jan, 2007)
5. Central Bureau of Statistics. Population census 2001 national report. Kathmandu: National Planning Commission Secretariat and Central Bureau of Statistics- Government of Nepal in collaboration with UNFPA; 2002.
6. Family Health Division- Government of Nepal, New ERA and ORC Macro. Nepal demographic and health survey 2001. Maryland, USA: Family Health Division, Government of Nepal, New ERA and ORC Macro; 2002.
7. Department of Health Services. Annual report 2061/62 (2004/2005). Kathmandu: Department of Health Services, Government of Nepal, 2006.
8. Nepal Ministry of Health, New Era, Macro International Inc. (1996) Nepal Family Health Survey. Kathmandu, Nepal Ministry of Health, Department of Health Services, Family Health Division and New Era, Macro International Inc.
9. Babson SG, Benda GI.Growth graphs for the clinical assessment of infants of varying gestational age. J Pediatr 1976;89:814-820.
10. Acharya PP, Alpass F, Birth outcomes across ethnic groups of women in Nepal Health Care Women Int. 2004 Jan;25(1):40-54.
11. Smith GCS, Pell JP. Teenage Pregnancy and risk of adverse perinatal outcomes associated with first and second births: population based retrospective cohort study. BMJ 2001;323:476-81.
12. Fraser AM, Brockert JE and Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med 1995;332:1113-7.
13. Friede A, Baldwin W, Rhodes PH, et al. Young Maternal age and infant mortality: the role of low birth weight. Public Health Rep 1987;102:192-9.
14. Brown HL, Fan YD, Gonsoulin WJ. Obstetric complications in young teenagers. South Med J 1991;84:46-48.
15. Hollingsworth DR, Felice M. Teenage Pregnancy: A multiracial sociologic problem. Am J Obstet Gynecol 1986;155:741-6.
16. McAnarney ER. Young Maternal age and adverse neonatal outcome. Am J Dis Child 1987;141:1053-9.
17. Reichman NE, Pagnini DL. Maternal age and birth outcomes: Data from New Jersey. Fam Plann Perspect 1997;29:268-72,295.
18. Sharma AK, Verma K, Khatri S, Kannan AT. Pregnancy in adolescents: A Study of Risks and Outcome in Eastern Nepal. Indian Pediatrics 2001; 38: 1405-1409.
19. Ojha N, Malla DS. Low birth weight at term: relationship with maternal anthropometry. J Nepal Med Assoc. 2007 Apr-Jun;46(166):52-6.
20. Lao TT, Ho LF. Obstetric outcome of teenage pregnancies. Human Reprod 1998;13:3228-32.
21. Olausson PM, Cnattingius S, Goldenberg RL. Determinants of poor pregnancy outcomes among teenagers in Sweden. Obstet Gynecol 1997;89:451-7.
22. Ketterlinus RD, Henderson SH, Lamb ME. Maternal age, sociodemographics, perinatal health and behavior: influences on neonatal risk status. J Adolesc Health Care 1990;11:423-31.
23. Jolly et al. Obstetric riks of pregnancy in women less than 18 years old. Obstet Gynecol 2000;96(6):962-6.
24. Lao TT, Ho LF. The Obstetric implications of teenage pregnancy. Human Reprod 1997;12(10):2303-5.
25. Bacci A, Manhica GM, Machungo F and et al. Outcome of teenage pregnancy in Maputo. Int J Gynaecol. Obstet 1993;40:19-23.

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ORIGINAL ARTICLE

Effects of Repeatedly Heated Palm Oil on Serum Lipid Profile, Lipid Peroxidation and Homocysteine Levels in a Post-Menopausal Rat Model

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ABSTRACT: Oxidized unsaturated fatty acids may contribute to the pathogenesis of atherosclerosis. In the present study, we examined the effects of heated palm oil mixed with 2% cholesterol diet on serum lipid profile, homocysteine and thiobarbituric acid reactive substances (TBARS) levels in estrogen-deficient rats. Twenty-four female Sprague Dawley rats were ovariectomized and then were divided equally into four groups. The control group was given 2% cholesterol diet only throughout the study period. The three treatment groups received 2% cholesterol diet fortified with fresh, once-heated or five-times-heated palm oil, respectively. Serum TBARS, lipid profile and homocysteine levels were measured prior to ovariectomy and at the end of four months of the study. Five-times-heated palm oil caused a significant increase in TBARS and total cholesterol (TC) compared to control ($F = 22.529$, $p < 0.05$). There was a significant increase in serum homocysteine in the control as well as five-times heated palm oil group compared to fresh and once-heated palm oil groups ($F = 4.432$, $p < 0.05$). The findings suggest that repeatedly heated palm oil increase lipid peroxidation and TC. Ovariectomy increases the development of atherosclerosis as seen in this study. Feeding with fresh and once-heated palm oil does not cause any deleterious effect but repeatedly heated oil may be harmful because it causes oxidative damage thereby predisposing to atherosclerosis.

KEYWORDS: palm oil, heated oil, menopause, atherosclerosis, lipid peroxidation

INTRODUCTION

Atherosclerosis is one of the leading causes of death in the developed countries. It is a slow but progressive disease, which may begin in childhood with the development of fatty streaks. The incidence of atherosclerosis and cardiovascular disease in women is lower compared to men of similar age (1). However, the incidence of atherosclerosis in women increases after menopause due to a decrease in estrogen, a hormone thought to have cardioprotective effects during the pre-menopausal period (2). Estrogen therapy was shown to reduce low-density lipoprotein (LDL) levels and increase high-density lipoprotein (HDL) levels in postmenopausal women (3). Estrogen also has antioxidant properties (4, 5) which is protective against lipid peroxidation. Atherosclerotic lesions in humans and animals appear to be related to elevated plasma total cholesterol (TC), LDL and decreased HDL. The exact mechanisms explaining how hypercholesterolemia can cause atherosclerosis are still unclear. Lipid deposition on the arterial wall likely starts with the movement of LDL from the blood into the vessel wall. LDL is oxidized becoming particularly atherogenic (6). Oxidized LDL (oLDL) may directly alter both the structure and the function of the endothelial cells.

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Consequently, oLDL also may chemotactically attract monocytes and macrophages to the endothelium which then develop into the lipid laden foam cells of an atheromatous plaque (7). oLDL is also more avidly taken up by macrophages via their scavenger receptors than unoxidized LDL (8).

Homocysteine is known as an independent risk factor of atherosclerosis (9). Homocysteine promotes atherosclerosis by a variety of mechanisms (10). In addition to directly damaging blood vessels, altered metabolism of homocysteine is also involved in the oxidative process occuring in atherogenesis (11).

Much of the fat consumed in our diet has been exposed to heat during processing and in the preparation of food during cooking. In deep-frying, oil is heated above 150oC for a long period of time. This heating process causes changes in the properties of the oil by chemical reactions of oxidation, hydrolysis and polymerization. When frying oil is heated, hydroperoxides and aldehydes are mainly formed (12) and are absorbed into the fried foods. Thus, these products enter systemic circulation. Malondialdehyde (MDA) is usually measured as a marker for lipid peroxidation level. Thibarbituric acid (TBA) assay is the most common method to be used to measure MDA. However, it is more appropriate to express the results as thiobarbituric acid reactive substances (TBARS) rather than MDA because other products may also form during the assay (13).

The common practice of repeatedly using the oil for frying may generate free radicals that are harmful to our health. Such practice appears to cut the cost of cooking without considering its effects on health. Several studies had demonstrated the adverse effects of oxidized dietary fats on human and experimental animals. Owu DU et al (14) and Izaki Y et al (15) reported that consumption of oxidized oil caused liver dysfunction. Acceleration of fatty streak formation had been reported in rabbits fed oxidized lipid (16). Rats fed thermally oxidized oil showed an increase in plasma glucose as well as a decrease in plasma vitamin E and vitamin A in the liver (17).

In view of the potential hazardous effect of heated oils on health, this study was planned to determine the effects of thermally oxidized palm oil taken together with 2% cholesterol diet on the factors related to atherosclerosis in female rats made estrogen-deficient by ovariectomy. This gives us information on the effects of reheated palm oil on post-menopausal women in particular, and the population in general.

MATERIALS AND METHODS

Experimental animals

Twenty-four healthy and mature female Sprague-Dawley rats (200-250g) were obtained from the Animal Unit, Universiti Kebangsaan Malaysia. The rats were housed in cages at room temperature and a 12-hour light cycle. They had access to tap water ad libitum and were administered 150g of test diet/week. All procedures were reviewed and approved by the Universiti Kebangsaan Malaysia Animal Ethic Committee (UKM AEC: FAR/2003/Kamsiah/25Jan/090).

Source and preparation of diets

Palm oil (Lam Soon Edible Oil, Malaysia) used was fresh, once-heated or five-times-heated as described by Owu et al (14). Briefly, 2.5L of palm oil was used to fry 1kg (approximately 25 pieces) of 'keropok lekor' (fish-flavoured chips) in a metal wok at 180oC for 10 minutes. To prepare five-times-heated oil, the whole frying process was repeated four more times with a fresh batch of 'keropok lekor' and five hours cooling interval. No fresh oil was added between batches to replace oil absorbed by the frying material.

The test diets were formulated by mixing 15% (w/w) of palm oil with ground 2% cholesterol diet (MP Biomedicals Inc, Australia). The pellets were reformed and dried in an oven at 80oC overnight.

Study design

The rats (n=24) were allowed to acclimatize for 1 week prior to treatment and were ovariectomized ahead of the study. They were randomly divided equally into four groups; with six rats per group. Group I was fed with 2% cholesterol diet (control), group II, III and IV were fed with 2% cholesterol diet fortified with fresh palm oil (FPO), once-heated palm oil (1HPO) and five-times-heated palm oil (5HPO), respectively for four months. The mean body weight and food intake were taken weekly during the study period. The fasting (18 hours) serum for lipid profile, thiobarbituric acid reactive substances (TBARS) and homocysteine analyses was taken prior to ovariectomy and at the end of four months of study. Serum was stored at -70oC for further analyses.

Serum thiobarbituric acid reactive substances (TBARS)

TBARS level in the serum was determined using a method described by Ledwozyw A et al (18) with some modifications. A value of 0.5ml serum was acidified with 2.5ml of 1.22M trichloroacetic acid (TCA)/0.6M hydrochloric acid (HCl) and left to stand at room temperature for 15 minutes. Next, 1.5ml of 0.67% thiobarbituric acid (TBA)/0.05M sodium hydroxide (NaOH) was added. The samples were incubated in a 100oC water bath for 30 minutes. They were left to cool at room temperature before the addition of 4ml of n-

buthanol. After thorough mixing, the mixture was centrifuged for 10 minutes at 3000rpm. The absorbency of the upper phase was read at Ex: 515 Em: 553 by using spectroflurometer (Shimadzu RF500, Japan).

The protein content in the serum was determined using a method described by Lowry et al (19) with some modifications. A value of 0.5ml serum was added with 5ml mixture of 2% sodium carbonate (Na2CO3), 2% sodium or potassium tartrate (Na/K tartrate) and 1% copper sulphate solution (CuSO4.5H2O) with ratio 100:1:1. Subsequently, they were left to stand at room temperature for 15 minutes before the addition of 0.5ml of diluted Folin-Ciocalteau phenol reagent. After 35 minutes, the absorbency of the sample was measured at 700nm with spectrophotometer (Shimadzu UV-160A, Japan). The serum TBARS was expressed as serum TBARS/protein.

Serum lipid profile

Serum lipid profile was determined enzymatically using commercially available kits from Randox Laboratories Ltd. (United Kingdom). These tests were performed using Vitalab Selectra E (Netherlands) following the manufacturer's instructions

Serum homocysteine

Serum homocysteine was determined by Fluorescence Polarization Immunoassay (FPIA) using commercially available kits from Abbott Laboratories (USA). The test was performed using Cobas Integra (Roche Professional Diagnostics, Switzerland) following manufacturer's instructions.

Statistics

The data was presented as the mean ± standard error of mean (SEM). Normally distributed data were analyzed using parametric tests, i.e. Student's paired t-test and analysis of variance (ANOVA) followed by Tukey hsd post-hoc test. Data which were not normally distributed were analyzed using non-parametric tests, i.e. Kruskal-Wallis, Mann-Whitney U and Wilcoxon-Signed Rank tests. A value of $p < 0.05$ was considered significant. All analysis was conducted using Statistical Product and Service Solutions (SPSS) software (Chicago, IL, USA).

RESULTS

Twenty-four ovariectomized rats were divided equally into four groups; control, fresh palm oil (FPO), once-heated palm oil (1HPO) and five-times-heated palm oil (5HPO). The initial weight of the rats were taken and shown in Table 1. Subsequently, all the rats were given 2% cholesterol diet. The cholesterol diet for FPO, 1HPO and 5HPO were fortified with fresh, once-heated or five-times-heated palm oil, respectively. After four months of treatment, their average food intake was calculated. There was no significance difference in food intake among the oil-fed groups. However, the treatment groups showed a lower food intake compared to the control. Their weight gain also was calculated by deducting the weight at the end of the study with their respective initial weight. There was a significant increase in body weight at the end of the study for all groups ($p < 0.05$). The highest body weight increase was observed in 5HPO group.

Their fasting serum was taken prior to treatment and at the end of four months of study to analyse the thiobarbituric acid reactive substance (TBARS) level, lipid profile and homocysteine level. The results are expressed as percentage based on baseline values. All groups showed an increase in TBARS but the percentage increase was higher in 1HPO and 5HPO compared to control and FPO (Figure 1). There was no significance difference between 1HPO and 5HPO.

For lipid profile; total cholesterol (TC), low-density lipoprotein (LDL), triglyceride and high-density lipoprotein (HDL) were measured. Similar to TBARS, there was an increasing trend in serum TC in the treatment groups (Figure 2). The percentage increase was significantly higher in 5HPO compared to control. Both LDL and triglyceride showed no significant difference amongst the groups (Figure 3 and 4). On the other hand, there was reduction of HDL at the end of the study in all groups (Figure 5). However, there was no significant difference in the percentage of reduction among the groups even though there was a trend seen in the figure.

The homocysteine level increased at the end of the study (Figure 6). The percentage increase in 5HPO as well as control which received only 2% cholesterol diet throughout the study period were significant compared to FPO and 1HPO.

DISCUSSION

Table 1: Food intake and body weight gain of rats fed respective diets after months.
Results are mean ± S.E.M (n=6). Different superscript letters are significant based on dietary treatment ($p<0.05$)

Group	Food intake (g/week)	Initial body weight (g)	Final body weight (g)	Body weight gain after 4 months (g)
Control	109.83 ± 3.55 ^{a}	211.17	324.67	113.50 ± 14.79 ^{a}
FPO	84.83 ± 0.70 ^{b}	209.17	333.50	124.33 ± 22.62 ^{a}
1HPO	83.17 ± 1.01 ^{b}	213.50	334.33	120.83 ± 23.38 ^{a}
5HPO	83.83 ± 2.80 ^{b}	211.17	339.17	128.00 ± 26.21 ^{b}

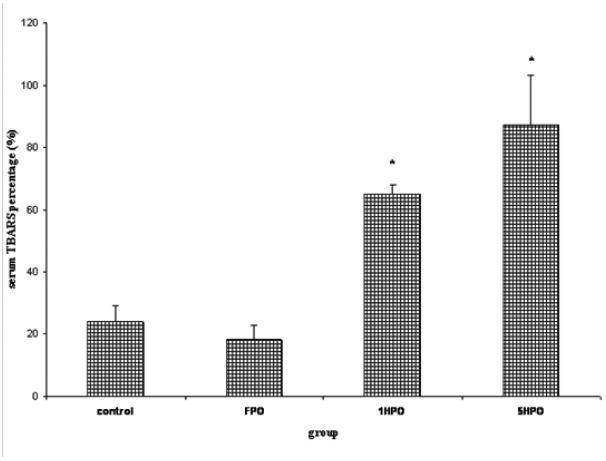

Figure 1: Percentage changes in serum TBARS with fresh and heated palm oil after four months of feeding.
Error bars represent the S.E.M.
* significant compared to control and FPO.
TBARS, thiobarbituric acid reactive substances; FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

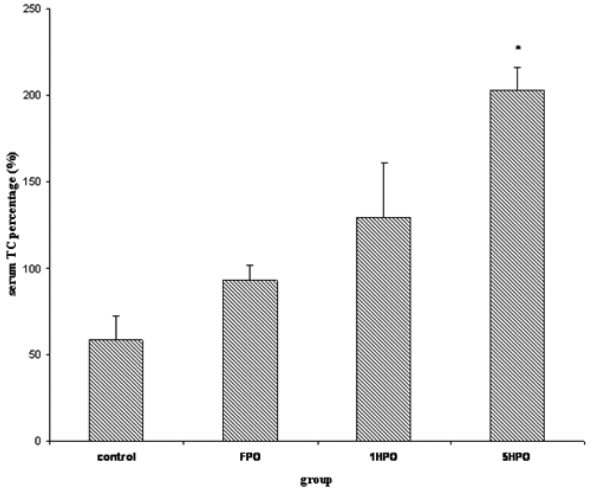

Figure 2: Percentage changes in serum TC with fresh and heated palm oil after four months of feeding. Error bars represent the S.E.M.
* significant compared to control.
TC, total cholesterol; FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

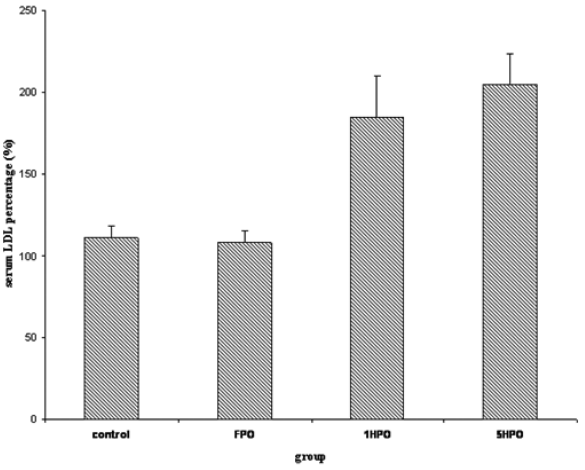

Figure 3: Percentage changes in serum LDL with fresh and heated palm oil after four months of feeding. Error bars represent the S.E.M.
LDL, low-density lipoprotein; FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

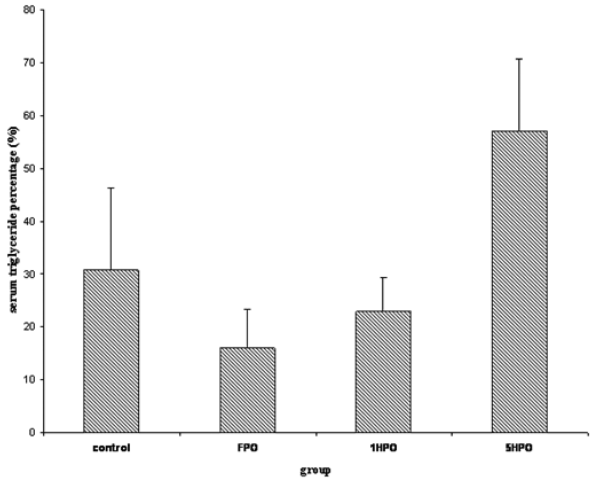

Figure 4: Percentage changes in serum triglyceride with fresh and heated palm oil after four months of feeding. Error bars represent the S.E.M.
FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

This study was conducted in post-menopausal rat model to ascertain the effects of repeatedly heated palm oil on factors related to cardiovascular disease, particularly lipid peroxidation, lipid profile and homocysteine level in menopausal subject. We postulated that thermally oxidized palm oil which generates free radicals, enhances the oxidative stress secondary to estrogen deficiency and high cholesterol diet. These parameters have been attributed to atherosclerosis (20). We used 2% cholesterol diet to intensify the oxidative stress to the post-menopausal rat model. Moreover, our previous study has shown that 2% cholesterol diet was atherogenic in rabbits (21). Palm oil was chosen in this study because it is widely used in Malaysia as cooking oil. The oil is often used repeatedly for deep frying in many food outlets in order to lower costs.

The heating process which causes physical changes in the oil did not have any significant effects on the food intake. This was proven by similar food intake in all the treatment groups and was associated with similar increase in their body weight, except 5HPO which observed higher increase in body weight gain compared to other groups. The reason for this is not well

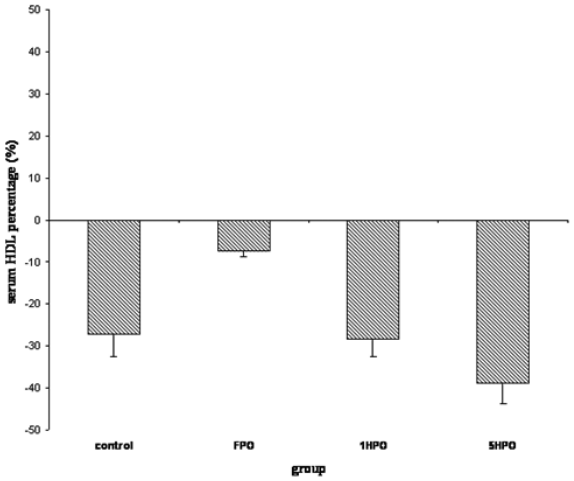

Figure 5: Percentage changes in serum HDL with fresh and heated palm oil after four months of feeding. Error bars represent the S.E.M. HDL, high-density lipoprotein; FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

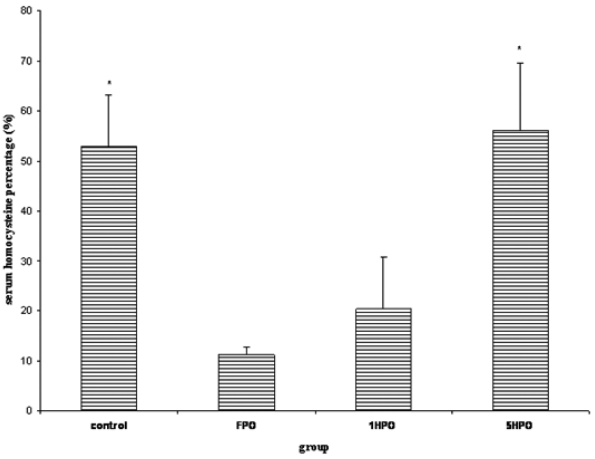

Figure 6: Percentage changes in serum homocysteine with fresh and heated palm oil after four months of feeding. Error bars represent the S.E.M.
* significant compared to FPO and 1HPO.
FPO, fresh palm oil treated group; 1HPO, once-heated palm oil treated group; 5HPO, five-times-heated palm oil treated group.

understood.

This present study showed that once-heated and five-times-heated palm oil increased lipid peroxidation as indicated by a significant increase in serum TBARS in these groups compared to control and FPO. It thus appears that percentage of rise in serum TBARS was higher in 5HPO group compared to 1HPO. However, the difference was not significant. This may suggest that repeated heating might not affect free radical formation. This finding was contrary to our expectations, as we expected repeated heating to generate more free radicals, as reported by Nwanguma et al (22). The percentage changes in TBARS in 5HPO group might attain a significant level if the period of study was prolonged. The effects of heated palm oil on serum TBARS in this study was not comparable to the finding of Benedetti et al who also reported that oxidized corn oil affect neither plasma nor liver MDA levels (17). Izaki et al also found that serum and kidney TBA-RS level were unchanged in the rats fed with thermally oxidized rapeseed oil (15). The reason for the discrepancies in the result might be due to the different types of oil: indeed, they had used unsaturated oil while we used palm oil which contains at least 50% saturated fats (23). There is a possibility that estrogen deficiency in our study might contribute to the significant increase in serum TBARS level. In previous study by Hageman et al (24), feeding rats with heated oils also did not cause an increase in hepatic and renal microsomal fractions TBARS. We assume that the incorporation of those oils at a level of only 10% in the diet, followed by shorter duration of the study might be the contributing factors to these findings.

There was an increasing trend in serum TC in all oil-fed groups. The percentage increase in TC was only significant in 5HPO group compared to control. The increase in serum TC in the study groups is probably secondary to 2% cholesterol diet intake. Feeding with repeatedly heated palm oil appears to accelerate the increase in serum TC in this group. The effect of heating on TC in this present study was not in agreement with Hur et al who reported that heated corn oil reduced plasma cholesterol in rabbits (25). The type of animal, the oil used and the ovariectomy procedure might be the contributing factors.

In this study we found that there was a significant increase in serum homocysteine level in the control as well as 5HPO. There were no significant changes in serum homocysteine in FPO and 1HPO groups. The increase in serum homocysteine level in the control might be due to estrogen deficiency as a result of ovariectomy. Feeding with either fresh or once-heated palm oil appears to offer some protective effects. The protective effects against the rise in serum homocysteine by palm oil reduced while heating the oil, repeatedly. The loss in the protective effects of palm oil could be attributed to destruction of the heat labile vitamin such as tocotrienol (26).

There was an increasing trend in serum LDL, TG and decreasing trend in HDL cholesterol in all the groups. However, the changes were not significant. The changes in LDL cholesterol in this study were not comparable to our earlier work in which we found that fresh and heated palm oil increase LDL level (27). The duration of feeding which is shorter (4 months) in the present study and 2% cholesterol diet might responsible for the

differences in the results.

The changes in serum TG level in this study are similar to those reported by Staprans et al who found that there was no difference in serum TG concentrations between control and oxidized-diet group (16). On the other hand, it was contradictory to the findings of Rueda-Clausen et al who reported that consumption of deep-fried palm oil increased serum TG level in humans (28). These contradictory results could be due to factors such as the oil preparation process, the subject's metabolic conditions and the duration of the study.

It was expected that high cholesterol diet increases HDL cholesterol. However, this was not observed in our study even though the animals were fed with 2% cholesterol diet throughout the study period. Instead, we found that there was a decreasing trend in HDL cholesterol in all the groups. The decreasing trend in HDL cholesterol might be due to estrogen deficiency. Repeatedly heated palm oil did not interfere with changes in HDL cholesterol.

A limitation of this study is the small sample used; further, larger studies are appropriate. Our previous study (29) had used soy oil, which contains higher level of polyunsaturated fatty acids (PUFA) compared to palm oil (23) showed some appealing results. Interestingly, the TBARS level of the group fed with repeatedly heated soy oil was higher compared to other treatment groups. This proves that palm oil which contains high amount of monounsaturated fatty acids (MUFA) is less susceptible to oxidation compared to soy oil (30, 31). In earlier studies, we had found that consumption of repeatedly heated palm and soy oils caused adverse effects on bone histomorphometry ovariectomy-induced rats (32). Moreover, the study also showed that soy oil had further deteriorated the bone changes compared to palm oil. From these results, it was obvious that repeatedly heated oils, especially soy oil may contribute to the pathogenesis of atherosclerosis and osteoporosis in post-menopausal woman, particularly.

In conclusion, repeatedly heated palm oil appears to increase lipid peroxidation and cholesterol level in a post-menopausal rat model. Ovariectomy increases serum homocysteine level and feeding with either fresh or once-heated palm oil offers some protection which is lost when the oil was repeatedly heated. Further studies are acquired to ascertain whether the increase in these parameters has detrimental effects on blood vessels and is a potential danger for cardiovascular disease in menopausal subject.

ACKNOWLEDGMENTS

This study was funded by grant IRPA 06-02-02-0050-EA242. The authors wish to thank Puan Azizah Othman, Puan Sinar Suriya Muhamad as well as other staffs in Chemical Pathology Laboratory, HUKM for valuable assistance.

REFERENCES

1. Rossouw JE. Hormones, genetic factors and gender differences in cardiovascular disease. Cardiovasc Res. 2002; 53(3): 550-557.
2. Baker L, Meldrum KK, Wang M, et al. The role of estrogen in cardiovascular disease. J Surg Res. 2003; 115(2): 325-344.
3. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. N Eng J Med. 1993; 328(15): 1069-1075.
4. Ayres S, Tang M, Ravi Subbiah MT. Estradiol-17β as an antioxidant: some distinct features when compared with common fat-soluble antioxidants. J Lab Clin Med. 1996; 128(4): 367-375.
5. Badeau M, Adlercreutz H, Kaihovaara P, Tikkanen MJ. Estrogen A-ring structure and antioxidative effect on lipoproteins. J Steroid Biochem Mol Biol. 2005; 96(3-4): 271-278.
6. Osterud B, Bjorklid E. Role of monocytes in atherogenesis. Physiol Rev. 2003; 83(4): 1069-1112.
7. Plutzky J, Libby P. Pathophysiology of atherosclerotic heart disease. In: Tonkin AM, editor. Atherosclerosis and heart disease. London, UK: Martin Dunitz; 2003. p. 1-12.
8. Steinberg D, Witztum JL. Lipoproteins and atherogenesis. Current concepts. JAMA. 1990; 264(23): 3047-3052.
9. Su SJ, Huang LW, Pai LS, Liu HW, Chang KL. Homocysteine at pathophysiologic concentrations activates human monocyte and induces cytokine expression and inhibits macrophage migration inhibitory factor expression. Nutrition 2005; 21(10): 994-1002.
10. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med. 1998; 338(15): 1042-1050
11. Olszewski AJ, McCully KS. Homocysteine metabolism and the oxidative modification of proteins and lipids. Free Radic Biol Med. 1993; 14(6): 683-693.
12. Dobarganes C, Márquez-Ruiz G. Oxidized fats in foods. Curr Opin Clin Nutr Metab Care 2003; 6(2): 157-163.
13. Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med. 1991; 11(1): 81-128.
14. Owu DU, Osim EE, Ebong PE. Serum liver enzymes profile of Wistar rats following chronic consumption of fresh or oxidized palm oil diets. Acta Trop. 1998; 69(1): 65-73.
15. Izaki Y, Yoshikawa S, Uchiyama M. Effect of ingestion thermally oxidized frying oil on peroxidative criteria in rats. Lipids 1984; 19(5): 324-331.
16. Staprans I, Rapp JH, Pan XM, Hardman DA, Feingold KR. Oxidized lipids in the diet accelerate the development of fatty streaks in cholesterol-fed rabbits. Arterioscl Throm Vasc Biol. 1996; 16(4): 533-538.
17. Benedetti PC, D'Aquino M, Di Felice M, Gentili V, Tagliamonte B, Tomassi G. Effects of a fraction of thermally oxidized soy bean oil on growing rats. Nutr Rep Int. 1987; 36(2): 387-401.
18. Ledwozyw A, Michalak J, Stepien A, Kadziolka A. The relationship between plasma triglycerides, cholesterol, total lipids and lipid peroxidation products during human atherosclerosis. Clin Chim Acta 1986; 155(3): 275-283.
19. Lowry OH, Rosebrugh NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem. 1951; 193(1): 265-75.

20. Maxwell SRJ, Lip GYH. Free radicals and antioxidants in cardiovascular disease. Br J Clin Pharmacol 1997; 44(4): 307-317.
21. Kamsiah J, Nafeeza MI, Ngang AC. Suppression of atherogenesis in cholesterol-fed rabbits treated with nicardipine. Asia Pac J Pharm. 1994; 9(3): 183-187.
22. Nwanguma BC, Achebe AC, Ezeanyika LUS, Eze LC. Toxicity of oxidized fats II: tissue levels of lipid peroxides in rats fed a thermally oxidized corn oil diet. Food Chem Toxicol. 1999; 37(4): 413-416.
23. Cottrell RC. Introduction: nutritional aspects of palm oil. Am J Clin Nutr. 1991; 53(4 Suppl): 989S-1009S.
24. Hageman G, Verhagen H, Schutte B, Kleinjans J. Biological effects of short-term feeding to rats of repeatedly used deep-frying fats in relation to fat mutagen content. Food Chem Toxicol. 1991; 29(10): 689-698.
25. Hur SJ, Du M, Nam K, Williamson M, Ahn DU. Effect of dietary fats on blood cholesterol and lipid and the development of atherosclerosis in rabbits. Nutr Res. 2005; 25(10): 925-935.
26. Adam SK, Sulaiman NA, Md Top AG, Jaarin K. Heating reduces vitamin E content in palm and soy oils. Malays J Biochem Molec Biol. 2007; 15(2): 76-79.
27. Kamsiah J, Norhayati M, Norzana G, Nor Aini U, Ima-Nirwana S. Effects of heated vegetable oils on serum lipids and aorta of ovariectomized rats. Pak J Nutr. 2006; 5(1): 19-29.
28. Rueda-Clausen CF, Silva FA, Lindarte MA, et al. Olive, soybean and palm oils intake have a similar acute detrimental effect over the endotelial function in healthy young subjects. Nutr Metab Cardiovas Dis. 2007; 17(1): 50-57.
29. Adam SK, Das S, Soelaiman IN, Umar NA, Jaarin K. Consumption of repeatedly heated soy oil increases the serum parameters related to atherosclerosis in ovariectomised rats. Tohoku J Exp Med. 2008; 215(3): 219-226.
30. Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest. 1991; 88(6): 1785-1792.
31. Lapointe A, Couillard C, Lemieux S. Effects of dietary factors on oxidation of low-density lipoprotein particles. J Nutr Biochem. 2006; 17(10): 645-658.
32. Shuid AN, Chuan LH, Mohamed N, Jaarin K, Fong YS,

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CASE REPORT

A Case Of Atypical Gastric Carcinoma With Osteoclast Like Giant Cells

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ABSTRACT: Out of all the different types of neoplasms affecting the stomach, gastric carcinomas with Osteoclast-like Giant Cells (OGC) is one of the most uncommon. Although OGC are typically found in osseous neoplasms and tumors of the tendon sheath, few cases of extra-skeletal neoplasms with OGC have been documented. These typically involve organs such as the pancreas, gall-bladder, kidney, and breast. Even though the role of OGC in histogenesis of such tumors still remains unclear, their presence in extra-osseous neoplasms may indicate a certain level of immune reaction of the host towards the neoplastic transformation of normal tissue. We report a case of a 70-year-old Caucasian female hospitalized for evaluation of epigastric pain. Further examinations including endoscopy and biopsy of the stomach revealed gastric adenocarcinoma with OGC. This report also provides a brief insight into the possible immune reaction in such neoplasms

KEYWORDS: Osteoclast like Giant Cells (OGC), adeno-carcinoma

INTRODUCTION

Osteoclast-Like Giant Cells (OGC) are multinucleated large cells with clear cytoplasm and are encountered in relatively uncommon tumors of the bone tissue and the tendon sheath. Although these osseous tumors are generally benign by nature and have a slow growth, they still have a recurrence rate of over 50% and may give pulmonary metastasis.

The presence of OGC in different extra-skeletal neoplasms has been cited in various literatures [1,2,3,4] with the involvement of organs including the skin, breast, pancreas, gall-bladder and the kidneys. Though the origin of these cells has been proposed to be of the mononuclear-macrophage lineage, their actual role in the histogenesis in these extra-osseous tumors is ill-defined.

In this case report we present a detailed case of a patient with gastric adeno-carcinoma with OGC. A special focus will be laid on the immune reaction in the tumor tissue of such neoplasms with a brief discussion on the differential diagnosis of such neoplasms with anaplastic carcinomas which also manifest with atypical giant nucleated cells.

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CASE REPORT

A 70-year-old Caucasian female was admitted to the Surgical Department of the St. Petersburg State Medical Academy with complaints of epigastric pain in May 2004. Detailed history revealed a 6-month history of nausea, epigastrial pain and progressive generalized weakness. A soft abdomen with slight epigastrial tenderness was found on palpation. Laboratory investigations showed anemia, hypoproteinemia and dysproteinemia. A fibro-oesophago-gastro-duodeno-scopy revealed a stomach with relatively rigid walls. A polypoid protrusion of the gastric mucosa along with multiple erosions with a tendency to bleed in the region of the gastric cardia and the small curvature was noticed. Of the three biopsy specimens, the one obtained from the esophagus displayed signs of inflammation whereas the ones from the erosions depicted definite malignant changes corresponding to gastric adeno-carcinoma. Following diagnosis, a gastrectomy with D1 lymph node dissection and oesophago-jejunostomy with an inter-intestinal anastomosis was performed. The surgical TNM was finalized as ST3N2M0.

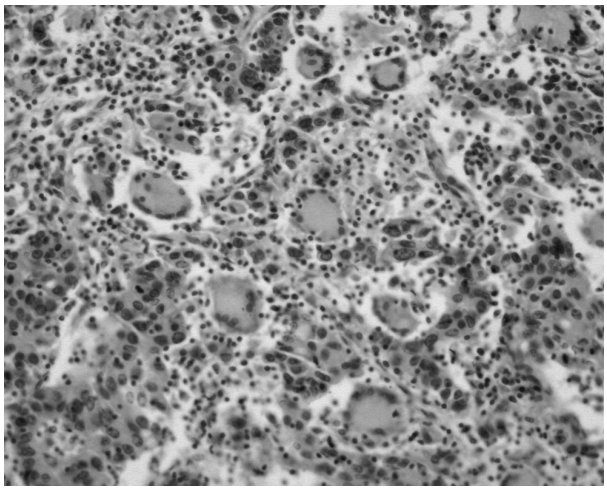

Figure 1. Moderately differentiated malignant glands with prominent lympho-histocytic infiltration of the stroma. Magnification 100X.

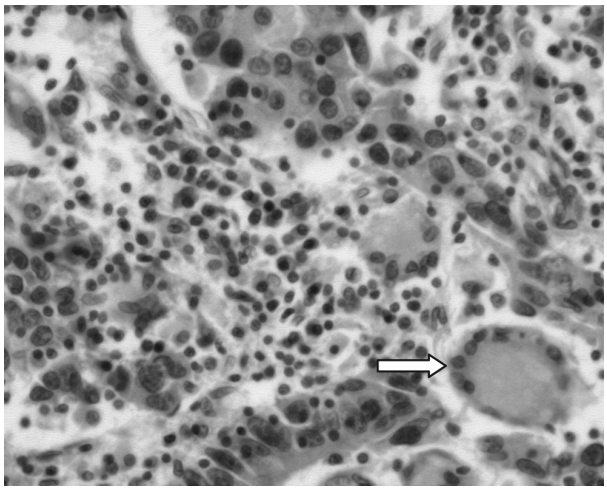

Figure 2. Arrow indicating stromal localization of a typical giant cell with multiple nuclei distributed circumferentially. Magnification 400X.

MACROSCOPIC FINDINGS

A tumor involving the gastric cardia and small curvature was presented as a polyp like mass with distinct ulcerative changes and blood clots on its surface. Noted dimensions were 10×10×6 cm. The cut surface of the tumor revealed a whitish-pink mass that had an invasive pattern of growth and involved all the layers of the stomach wall but without any encroachment into the surrounding organs. The tumor was classified as Bor 2 according to Bormann's scale.

MICROSCOPIC FINDINGS

The tumor was diagnosed as being a low differentiated adeno-carcinoma with specific stromal infiltration accompanying multinucleated giant cells and extensive lympho-histiocytic infiltration (Figure 1 and Figure 2). The giant cells were predominantly located in the stroma around the malignant glands with seldom peri-glandular localization. The giant cells were characterized by a clear cytoplasm and multiple nuclei ranging between 3 to 7, arranged either circumferentially or randomly in the cytoplasm. Eight of the lymph nodes isolated from the region of the small curvature of the stomach were positive for metastases. The margins of gastrectomy presented with normal gastric tissue, thus confirming the success of the operation. The pTNM was inferred as pT3N2M0.

Antibodies	Source	Staining	Dilution
CD 8	*	Membrane	RTU
CD 4	*	Membrane	RTU
CD68	*	Cytoplasmic	1:40
PCK	*	Cytoplasmic	RTU
PCNA	**	Nuclear	1:200
BCL2	**	Cytoplasmic	1:50
EBV	*	Cytoplasmic	1:100
Ki 67	**	Nuclear	

Table 1. List of primary monoclonal antibodies used in immunohistochemistry. PCK-Pan- cytokeratin, EBV-Epstein Barr Virus, PCNA- Proliferating Cell Nuclear Antigen, *Novocastra England, **DAKO,Germany RTU- Ready to Use antibodies

IMMUNOHISTOCHEMISTRY

Staining for different immunohistochemical markers, listed in Table 1 were carried out on 6μm thick tissue samples placed on polyvinyl slides, with appropriate positive and negative controls. The Labeled Streptavidin Biotin (LSAB-DAKO) detection system was used for detection of primary antibodies.

Staining with Pan- cytokeratin (Figure 4) was strongly positive for the poorly differentiated malignant gastric glands without any staining of the intervening stromal compartment. In contrast, the stromal compartment was highly stained by the CD68 marker, whereas the staining in the malignant epithelium was almost negligible (Figure 3). Interestingly, staining with CD4 and CD8 revealed mostly stromal infiltration by the latter and dual stromal and glandular infiltration by the former.

Note that the tumor tissue, and the regional lymph nodes, were positively stained for the latent nuclear antigen of EBV. Ki67 immunostaining surprisingly showed total absence of any proliferation in the tumor tissue sample, while the anti-apoptotic marker, BCL 2, was only moderately expressed.

CONCLUSION

Giant cell carcinomas of the stomach belong to a

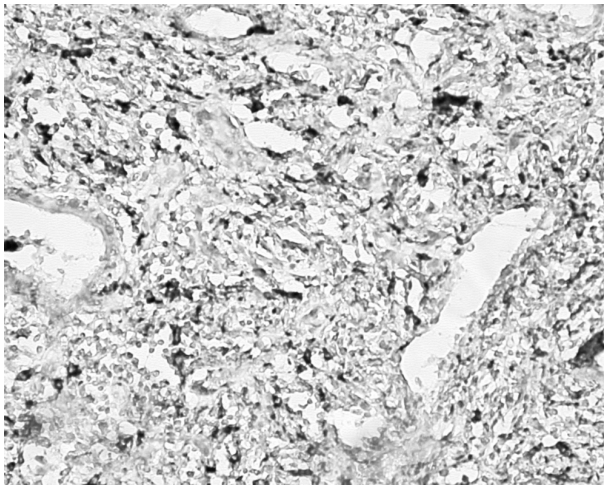

Figure 3. CD68 staining showing the positive staining of stromal elements with relatively free glands. Magnification 200X.

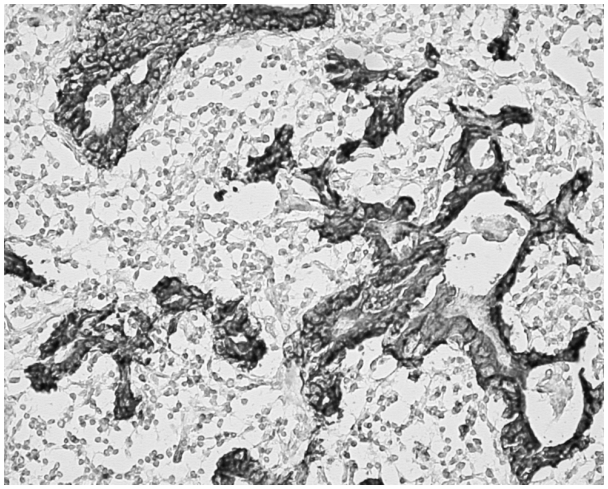

Figure 4. Positive staining of malignant glands for Pan-Cytokeratin antibodies . Magnification 200X.

group of rare neoplasms. These neoplasms are of epithelial origin and were confirmed by positive pancytokeratin staining. Given the intense immune reaction in these tumors, and presence of multinuclear giant cells, a crucial question remains as to whether such neoplasms are more aggressive than other adenocarcinomas without such elements.

Adeno-carcinomas of the stomach with OGC have to be also carefully differentiated from anaplastic carcinomas, which are usually characterized by faster growth, early metastasis and a much poorer prognosis. Anaplastic cancer cells may present with several morphological features and may have from a single to multiple nuclei but in all cases the giant cells will be of epithelial origin and hence will stain negative to CD68 or other mesenchymal markers thus validating their epithelial nature.

Although the etiology of the lymphocytic infiltration of the tumors is not entirely known, EBV infection has been argued to be a probable cause and has been isolated in various cases of lymphoepithelioma-like tumors (LELT) [5,6] . These tumors, although typical for the nasopharynx, have also been encountered in the stomach, bladder and intestinal mucosa, and are identifiable by lympho-histiocytic infiltration. Furthermore, such tumors have also been cited to have a better prognosis in comparison to GC cases without EBV infection [7].

The prognostic index in this case was proposed by running immunohistochemical tests on prominent independent markers, Ki67 and Bcl2. Researchers have diverse opinions on the prognostic value of Bcl2 expression in gastric cancer [8,9,10,11,12]. While traditional view connects the over-expression of Bcl2 to low tumor apoptotic ability and hence a poorer prognosis, studies have also linked the expression of Bcl2 as an indicator for biological activity of tumor [13]. In our case, we see mild expression of Bcl2 and negative expression of Ki67, thus suggesting a low biological activity of the tumor i.e. higher index of apoptosis and lower proliferative index. These results must be, however, considered in the light of the advanced TNM staging, which remains the best predictor in terms of survival.

To conclude, OGC represent uncommon tumors of the stomach. The rarity with which such neoplasms present in clinical practice makes it difficult to make universal conclusions about the prognosis. They must, however, be distinguished from anaplastic carcinomas of the stomach, with a more diffuse pattern of growth and a poorer prognosis overall.

ACKNOWLEDGMENTS:

We would like to thank Dr. Irina Kostochek, D.O. Ott Research Institute of Obstetrics and Gynecology, St. Petersburg, Russia for her help and guidance with our immunohistochemical studies.

REFERENCES:

1. Young-E J et all -A Case of Osteoclast-like Giant Cell Tumor of the Pancreas with Ductal Adenocarcinoma: Histopathological, Immunohistochemical, Ultrastructural and Molecular Biological Studies-J Korean Med Sci 2005; 20: 516-20 ISSN 1011-8934
2. Shoichi D et all - Undifferentiated Spindle and Giant Cell Carcinoma of the Common Bile Duct- Tokai J Exp Clin Med., Vol. 28, No. 3, pp. 127-130, 2003
3. Baschinsky DY, Frankel WL, Niemann TH-Gastric carcinoma with osteoclast-like giant cells-Am J Gastroenterol. 1999 Jun; 94(6):1678-81
4. Stracca-Pansa V et all- Gastric carcinoma with osteoclast-like giant cells : report of four cases- Am So of Cl Patholo and the College of Am Patholo. Spring meeting, Orlando FL , (22/04/1995) 1995, vol. 103, no 4, pp. 500-528

5. Mayer, E. K , Beckley I. and Winkler M.H,- Lymphoepithelioma-like carcinoma of the urinary bladder—diagnostic and clinical implications- Nature clinical practice urology (2007) 4 pp 197-171
6. Torlakovic G, Snover D. C., and Torlakovic E. -Simultaneous EBV-Positive Lymphoepithelioma-like Carcinoma and EBV-Negative Intestinal-Type Adenocarcinoma in a Patient With Helicobacter pylori–Associated Chronic Gastritis- Am J Clin Pathol 2004
7. Shibata D, Tokunaga M, Uemura Y, Sato E, Tanaka S and Weiss L M- Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Am J of Pathol, Vol 139, 469-474
8. Müller W, Schneiders A, Hommel G, Gabbert HE.-Prognostic value of BCL2 in gastric cancer- Anticancer research 1998 Nov-Dec;18(6B):4699-704.
9. Zafirellis K, Karameris A, Milingos N, Androulakis G.- Molecular markers in gastric cancer: can p53 and bcl-2 protein expressions be used as prognostic factors? Anticancer Research 2005 Sep-Oct;25(5):3629-36.
10. Forones NM, Carvalho AP, Giannotti-Filho O, Lourenço LG, Oshima CT.- Cell proliferation and apoptosis in gastric cancer and intestinal metaplasia.- Arq Gastroenterol. 2005 Jan-Mar;42(1):30-4. Epub 2005 Jun 22
11. Ishii H, Gobé G, Kawakubo Y, Sato Y, Ebihara Y.- Interrelationship between Epstein-Barr virus infection in gastric carcinomas and the expression of apoptosis-associated proteins.- Histopathology. 2001 Feb;38(2):111-9
12. Chang MS, Lee HS, Jung EJ, Kim CW, Lee BL, Kim WH.- Role and prognostic significance of proapoptotic proteins in Epstein-Barr virus-infected gastric carcinomas-Anticancer Research 2007 Mar-Apr;27(2):785-9
13. Kume T, Oshima K, Shinohara T, Takeo H, Yamashita Y, Shirakusa T, Kikuchi M.- Low rate of apoptosis and overexpression of bcl-2 in Epstein-Barr virus-associated gastric carcinoma.-Histopathology-1999 Jun;34(6):502-9

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CASE REPORT

A case of Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Syndrome) from Western India

Priyanka A. Jani and Deepa Banjan

KEYWORDS: Rosai-Dorfman Syndrome, Histiocytosis, Emperipolesis, Lymphadenopathy, Ascaris

INTRODUCTION

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman Syndrome, a non-malignant variant of histiocytosis (1) is a chronic reactive disorder. It presents as a benign, chronic, massive enlargement of cervical lymph nodes (LN) accompanied by fever, leukocytosis, elevated erythrocyte sedimentation rate (ESR) and hyperglobulinamia (2). There is no malignant proliferation of the class II histiocytes (i.e. normal macrophages and monocytes).

The etiology of this disease is currently unclear. Sinus histiocytosis with massive lymphadenopathy may be of two types – either familial or infection induced (2). With respect to the latter, increased antibody titers to Epstein Barr and measles viruses have been observed; however, etiological evidence is lacking (1). Immune disturbances are likely to be a feature in some patients. Subtle undefined immunological defects are also considered as a causal factor. Human Herpes Virus-6 DNA has been detected in biopsy specimens and is considered as a contributing factor (6).

Sinuous histiocytosis with massive lymphadenopathy (SHML) most frequently occurs in first and second decades of life, with a peak incidence at twenty years of age (1). There is a higher prevalence in males, and among Afro-Caribbeans as compared to Caucasians and Asians. Also, a familial association has been observed in some cases (3).

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CASE

A twelve years-old Indian girl residing in Maharashtra, Western India, presented with bilaterally symmetrical lymphadenopathy with a “bull neck” appearance of three years duration.

Three years prior to presentation, the patient developed a small reddish papule, which gradually increased in size. The patient noticed enlargement of glands initially on the site of the papule and then bilaterally. Lymph nodes were discreet, mobile, non-tender, non-matted, and about 2-4cm in diameter. A primary biopsy of cervical LN showed non-specific lymphadenopathy with sinus histiocytosis. There was no history of fever, upper respiratory tract disease, dental caries or viral infections. No constitutional symptoms were suggestive of malignancy. No other organ involvement was documented.

The neck swellings regressed over 7-8 months. However they did not disappear completely. Symptomatic treatment was offered by the physician.

One year later, in 2002, the patient presented with increase in cervical swellings along with bilateral solid axillary swellings. Swellings were tender, solid, non matted, mobile and preceded by fever. The second cervical LN biopsy revealed histiocytic lymphadenopathy and dilated sinuses filled with histiocytes. The supporting investigations are shown in Table 1. This table shows prominent eosinophilia with mild normochromic anemia.

The patient again presented after three years with a

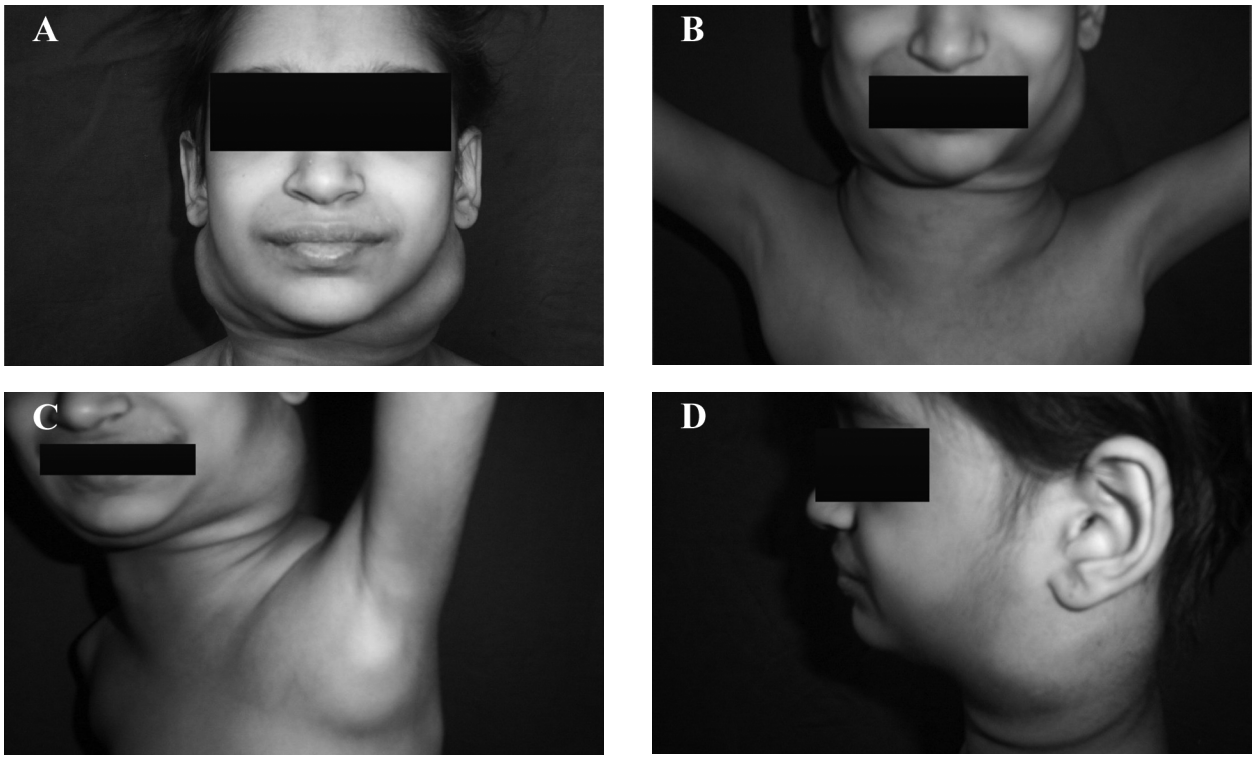

Figure 1. (a) bilateral cervical swelling, (b) bilateral cervical and axillary LN enlargement, (c) left axillary nodal enlargement, and (d) left cervical LN enlargement.

third episode of glandular proliferation mainly involving bilateral cervical LN. Clinical findings included bilateral tender enlarged cervical lymph nodes, fever, ascites, and pedal edema. The investigations done this time (Table 1; 2004) showed anemia, hypoproteinemia, and low serum iron levels. The ESR remained low with no immunological or histopathological cause for lymphadenopathy found.

The lymphadenopathy was stated to be non-malignant on three repeated biopsies and no malignant advancement was noted over the period of three years. An ultrasound showed multiple LN involvement with mild hepatosplenomegaly. Other causes of cervical lymphadenopathy like tuberculosis, sarcoidosis, Epstein Barr virus, hepatitis virus, HIV, autoimmune disease have been ruled out by performing specific tests. Malignant potential has also been negated by absence of supportive clinical evidence.

Other vital parameters of the patient remained stable throughout the span of three years. The patient had not attained menarche. Bowel and bladder habits were normal, sleep and appetite adequate. There was no history of any drug or alcohol intake. The family history was negative for episodes of any such disorder.

COURSE AFTER ADMISSION

The patient had severe anemia, hypoproteinamia and eosinophilia. Stool examination showed eggs of ascaris, which could account for the eosinophilia.

Patient was given standard treatment with pyrantel palmoate 20-25mg/kg/day and mebendazole 100mg bid for three days, which lead to expulsion of fully grown 15-20 adult round worms in the feces.

A regression in the size of the cervical LN and systemic involvement (i.e. hepatosplenomegaly) was seen over 2 weeks post-treatment. There was significant decrease in the cervical LN size. The abdominal symptoms and presence of ascites and pedal edema regressed after treatment of anemia. This regression in cervical LN following deworming points towards the probability of ascaris antigen acting as a trigger factor to the basic underlying hyper immunogenic status of the patient. However, no documented evidence for the same has been found.

The patient was discharged from the wards following significant cervical LN regression. She was continued on haematinics and was counseled well about the non-progressive, benign nature of the sinus histiocytosis.

Table 1. Investigations

Investigations	Results/Comments
September 2001:	
Hemoglobin	9.6gm%
Leukocytes	18,000/cm^2
Neutrophils	70%
Eosinophils	12%: Significant eosinophilia.
ESR	35mm/hr: Elevated ESR
Right cervical lymph node biopsy	Sinus histiocytosis with non specific lymphadenitis.
December 2002	
Hemoglobin	9.5gm%
Leukocytes	21,000/cm^2: Leukocytosis
Eosinophils	12%: Marked eosinophilia
Random blood glucose	80.5gm%, Normal
Blood urea nitrogen	8.6mg% Normal
Serum creatinine	0.63 Normal
Uric acid	4.2 Normal
Chest X-ray	No abnormalities seen.
Ultrasound abdomen/pelvis	
Liver	Mild hepatomegaly.normal echotexture.no focal lesion.liver span-13cms.
Abdominal LN	Pre and Para aortic lymph nodes seen.largest LN-18mm.
Cervical LN biopsy (April 2002)	Histiocytic lymphadenitis
Cervical LN biopsy (Tata Memorial Hospital, Dec 2002)	Dilated sinuses with histiocytic proliferation and lymphophagocytosis. Evidence of sinus histiocytosis with massive lympadenopathy. Diagnosis of Rosai-Dorfman Syndrome.
Bone marrow biopsy	Normocellular marrow showing normal maturation of all cells.
February 2004	
Hemoglobin	3.6gm%
Leukocytes	16,100/cmm leucocytosis
Serum total protein	5.4
Serum albumin	2.3
Serum globulin	3.1
Blood urea nitrogen	10.8
Ultrasound- abdomen	Mild ascites, multiple peri-pancreatic, para-portal enlarged LN. Liver normal
Specific investigations Sept 2001	
Mantoux test	Negative
Antibody test for infectious mononucleosis	Non reactive
HIV test	Non reactive
Australia antigen	Negative
Anti-dsDNA antibody	Negative
Antinuclear antibody	Negative

The family was also educated about the disease. She now attends the outpatient department for follow up at 1 month intervals and to date shows no reversal to previous symptoms.

DISCUSSION

A) Histopathological features

In sinus histiocytosis, there is a progressive filling up of the LN sinuses with normal histiocytes and lymphocytes. The histiocytes in SHML are S100 positive and CD1 negative (2). The constant feature on histology, 'emperipolesis' or lymphophagocytosis', is the presence of intact lymphocytes within the cytoplasm of histiocytes. This is of great diagnostic significance (3). Pericapsular fibrosis and inflammation are also seen. Ultrastructurally, histiocytes in SHML lack Birbeck granules and viral particles (3).

B) Clinical features

More than 90% of the patients with SHML present with massive bilateral, mobile, and non tender cervical lymphadenopathy (2). These nodes may at times be matted and prominent by periportal fibrosis. Forty percent of the cases may show extra nodal involvement. Soft tissues, generally eyelids, orbits and ocular adnexa, skin and subcutaneous tissue, gastro-intestinal tract, upper respiratory tract and central nervous system can also be involved. Low-grade fever is generally present along with mild, normochromic anemia (3), elevated ESR, leukocytosis, and hyperglobulinemia.

C) Diagnosis

In our case, there are a few characteristics that point to the diagnosis of sinus histiocytosis: 1) Clinical presentation of exclusive involvement and massive enlargement of cervical LN followed by axillary LN and abdominal LN. 2) Histopathological picture of dilated LN sinuses filled with histiocytes showing evidence of emperipolesis and absence of Birbeck granules. 3) Exclusion of the other differential.

D) Progression

The prognosis is excellent in most cases. Complete spontaneous regression is known to occur (3). The course of disease however may be protracted over three to nine months. Only two cases of progression, one to malignant lymphoma and another to amyloidosis have been documented (2).

E) Complications

Complications are mostly due to the pressure effects exerted by the enlarged cervical LN (1). Extensive disease may lead to complications due to

immunological abnormality that may be present (3).

F) Treatment

No standard treatment for SHML is known. Corticosteroids and radiotherapy usage have been documented. Steroids in low doses can be used when there are compression symptoms or in presence of bull neck. Radiation is best avoided since it may result in hypothyroidism or malignant transformation of the pre-existing benign condition (6). SHML is a generally benign condition with no significant malignant potential, which argues against the use of aggressive immunosuppressant therapy.

CONCLUSION

We have presented a case study with clinical and histopathological evidence pointing to the diagnosis of SHML or Rosai Dorfman syndrome. The patient presented with atypical features of anemia, accompanied by ascaris infestation. Following treatment of the parasite, there was significant regression of the size of the cervical LN and improvement in clinical condition.

The underlining immunogenic defects and the cause/environmental trigger factor (ascaris in this case) remain to be fully elucidated.

REFERENCES:

1. Weatherall, DJ. Disorders of blood. In: Oxford Textbook Of Medicine Volume 3, 4th ed, UK; 1996. p. 2610, 3604, 3610
2. Nathen D, Oski, F. Lymphohistiocytic Disorders. In: Haematology of Infancy and Childhood. Volume 2, 4th ed, Philedelphia; 1992: 1364
3. Rosai, J. Bone Marrow. In: Ackerman's Surgical Pathology Volume 2, 7th ed, USA; 1989. p. 1297
4. Forfar, Arneil. Oncology and Terminal care. In: Textbook Of Paediatrics, 5th ed, UK; 1998. p. 926
6. Levine PH, Jahan N, Murari P, Manak M, Jaffe ES. Detection of human herpesvirus 6 in tissues involved by sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). J Infect Dis 1992; 166: 291–295.

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CASE REPORT

Neurosyphilis in a Non-HIV Patient: More than a Psychiatric Concern

Michael K. Tso, Kevin Koo* and Grace Y. Tso

ABSTRACT: Neurosyphilis is a form of tertiary syphilis infection caused by the spirochete bacterium Treponema pallidum. Patients suffering from this illness can present with neurological manifestations such as headaches, seizures, hearing loss, and ataxia. However, the typical presentation of neurosyphilis is the insidious onset of psychiatric symptoms including personality changes. A good history and clinical work-up is essential in the diagnostic process. There has been a recent increase in the incidence of infectious syphilis in Canada (1). However, in other parts of the world including China, infectious syphilis rates have remained high due to limited access to primary care and affordable treatments (2 Here, we present a case of neurosyphilis in a 40 year old Chinese male residing in China who presents with an 18 month history of personality changes as well as neurological and physical manifestations of the infection.

CASE

A 40 year old Chinese man residing in China was brought into the emergency room by his family presenting with grandiose delusions, irritability, and memory deterioration, which have become progressively worse in the past 6 months. The patient was hostile, uncooperative, and was not able to provide any personal or medical history. Over the past 18 months, the family had noticed dramatic personality changes that included constricted affect, irritability, and apathy. They had also noted that the patient demonstrated ataxia, dysarthria, and progressive behavioural disturbances such as loss of social graces and impairment of activities of daily living. The family recalled that the patient frequently complained of headaches, vertigo, and non-specific abdominal pain in the past 6 months. There was no known history of trauma, malignancy, or vascular disease. He had developed urinary incontinence 3 weeks ago. The patient had no known history of substance abuse or chronic alcohol use. He was not on any medications. There was no personal or family history of psychiatric illness. According to the family, the patient was heterosexual and had been single for at least the past 8 months. It was unknown whether he had a history of a sexually-transmitted infection or any previous genital manifestations. The family believes he had been sexually-active since his early twenties, but it is unclear as to the number of sexual partners or the use of condoms. The patient's mood was highly irritable with blunted affect. He denied having any suicidal or homicidal ideation and there was no evidence of perceptual disturbances. He was admitted for further evaluation and treatment by neurology and clinical psychiatry.

PHYSICAL EXAMINATION

The physical examination was remarkable for neurological findings but was otherwise normal. The patient was afebrile and vital signs were within normal limits. Neurological examination revealed a wide-based gait and ataxia. Pupils in both eyes responded to accommodation and convergence, but they were not reactive to light (Argyll Robertson pupils). Cranial nerve exam was otherwise unremarkable. No lateralizing signs were present. The patient had cognitive impairment and grandiose delusions. He appeared withdrawn and apathetic. The Mini-mental status examination (MMSE) score was 7/30. MMSE score and psychiatric symptoms were compatible with severe cognitive impairment and dementia.

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INVESTIGATIONS

Hematological tests were unremarkable. Hepatitis B and C as well as Human Immunodeficiency Virus (HIV) tests were all negative. Both Treponema Pallidum Agglutination Assay (TPPA) and Rapid Plasma Reagin (RPR) yielded positive serum results (RPR serum titre 1:64). Urine toxicology screen was negative. Chest X-ray and electrocardiogram were normal. Brain MRI revealed diffuse frontocortical atrophy. A lumbar puncture revealed a transparent, colourless cerebrospinal fluid (CSF) with protein of 98mg/dL (normal: 20-45 mg/dL), white blood cell count of 21/µl (normal: ≤5µl), and glucose of 3.75mmol/L (normal: 2.5-4.4mmol/l). CSF-RPR and CSF-TPPA were both positive (CSF-RPR titre 1:8).

TREATMENT AND MANAGEMENT

Based on the investigations, the patient was diagnosed with neurosyphilis and was treated with Penicillin G 4 million units IV every 4 hours for 14 days, followed by Penicillin G procaine 2.4 million units IM daily and probenecid 500mg by mouth four times dailyfor 14 days. His MMSE score before and 8 weeks after treatment were 7/30 and 21/30 respectively. He regained bladder control 6 days after the start of treatment. The patient was discharged after 8 weeks and is currently being monitored by neurology and psychiatry for at least the next 2 years. Syphilis serology will be performed regularly during that time.

DISCUSSION

In Canada, the reported rate of infectious syphilis was an all-time low of 0.4/100,000 in 1997 with a dramatic rise to 3.5/100,000 in 2004 (1). The reason for this increase is unclear, although it appears to be associated with unsafe sexual practices especially in men who have sex with men (MSM), illicit intravenous drug use, and concurrent HIV infection (3). Unfortunately, data regarding the incidence of neurosyphilis in Canada is not available. In a systematic review of China's syphilis seroprevalence from 2000 to 2005, 660/100,000 of premarital individuals were reported to have both a positive screening nontreponemal test (i.e. RPR, Venereal Disease Research Laboratory (VDRL)) and a positive treponemal-based confirmatory test (i.e. Treponema Pallidum Agglutination Assay) (2). In select high-risk groups in China, incarcerated female sex workers, drug users, and MSM had syphilis seroprevalence rates of 12.49%, 6.81%, and 14.56%, respectively (2). New infections can be vertically transmitted from mother to baby or more typically, acquired by sexual contact (4). Syphilis also enhances the transmission of HIV by 3 to 5 times due to inflammation in the genital area and the association with high risk behaviours (5).

Syphilis is caused by the spirochete bacteria Treponema pallidum. The clinical course can be divided into several distinct stages: primary, secondary, early latent, late latent and tertiary stages (6). Primary syphilis manifests as a painless chancre at the site of inoculation, typically involving the penis, vagina, vulva, cervix, anal canal, perianal region, or mouth. Incubation period ranges from 9 to 90 days from initial exposure and the infection resolves spontaneously within 4-5 weeks if untreated (7). Syphilis may recur systemically as secondary syphilis and is characterized by constitutional symptoms (fever, malaise, anorexia), headache, lymphadenopathy, condyloma lata, mucosal ulceration and a generalized, symmetrical macular-papular rash involving the trunk, soles and palms (6). The patient may experience relapsing episodes of secondary syphilis for several years. After spontaneous resolution, the infection enters an early latent stage in which the patient is asymptomatic but has positive serologic testing and remains highly infectious. Beyond one year of latency, the asymptomatic infection is classified as late latent syphilis. Failure to treat may result in progression to the most serious stage called late symptomatic syphilis or tertiary syphilis (6).

If untreated in the latent phase, approximately 40% of patients would then develop tertiary syphilis (4). Manifestations of tertiary syphilis include cardiovascular syphilis, gummatous syphilis and neurosyphilis. Cardiovascular syphilis may occur 15-30 years after primary infection and mainly involve large vessels, resulting in proximal aortic aneurysm, aortic regurgitation and angina (7). Gummatous syphilis presents 3-12 years after primary infection as inflammatory fibrous nodules that are locally destructive (7). These lesions can involve any organ of the body, but usually affect skin or bone. Neurosyphilis may be divided into early and late forms, of which only the latter is considered to be tertiary.

Early neurosyphilis commonly affects the CSF, meninges, and vasculature (8). Manifestations include asymptomatic or symptomatic meningitis and meningovascular disease. Less than 2 years after primary infection, patients may present with asymptomatic meningitis with CSF abnormalities including a reactive VDRL, a lymphocytic pleocytosis, and elevated protein. Lack of treatment at this stage may result in progression toward more serious forms of neurosyphilis. Symptomatic meningitis most often presents in the first year after inoculation. Patients typically complain of headache, confusion, nausea/vomiting, stiff neck and decreased visual acuity. Syphilis may also cause inflammation of the intracranial vasculature and must be part of the

differential diagnosis for an ischemic stroke in a young patient. Meningovascular disease may be visualized on angiography showing focal narrowing or occlusion (9).

Common forms of late neurosyphilis affect CNS parenchyma and include general paresis of the insane (also known as general paresis) and tabes dorsalis (8). Both forms have poor prognoses without treatment but are very uncommon in the antibiotic era. General paresis develops 10-25 years after initial infection and manifests as a progressive dementia with symptoms of personality change and poor memory (7). Common abnormal neurologic findings include facial and limb hypotonia, dysarthria, and intention tremor. Patients may exhibit psychiatric symptoms such as depression, mania, or psychosis and may inadvertently be admitted to psychiatry. Tabes dorsalis presents with ataxia and lancinating pains secondary to destruction of the posterior columns and dorsal roots of the spinal cord. The pain affects the limbs, trunk and face and described as sudden, brief and severe. Characteristic Argyll-Robertson pupils may be present – the pupils respond to accommodation and convergence but do not react to light. Other signs and symptoms include paresthesias, severe episodic nausea/vomiting, impaired vibration sense and proprioception, and absent lower extremity reflexes (8).

The diagnosis of neurosyphilis in particular relies heavily on clinical exam, CSF analysis, and risk factors including positive HIV status, multiple sexual partners, illicit IV drug use, MSM, and a previously documented syphilis infection. If a genital lesion is present, dark-field microscopy may reveal spirochetes moving with a spiralling motion (10). Systemic syphilis is detected by screening serum nontreponemal tests (VDRL, RPR) and confirmatory treponemal tests (fluorescent treponemal antibody absorption, FTA-ABS and Treponemal pallidum particle agglutination assay, TPPA). Late neurosyphilis may have nonreactive serum non-treponemal tests. CSF-VDRL is the gold standard for diagnosing neurosyphilis, although it is not as sensitive as the less-specific CSF FTA-ABS (11). CSF demonstrating lymphocytic pleocytosis, high WBC count, and a high protein concentration is consistent with neurosyphilis. In a recent, multi-center prospective study, it was found that patients with serum RPR titres >= 1:32 were highly predictive of also having neurosyphilis (defined as a positive CSF-VDRL or CSF WBC > 20 cells/microliter), regardless of syphilitic stage, HIV status, or previous non-neurosyphilis treatment (12). In HIV-positive patients infected with syphilis, serum RPR titres may be elevated in early HIV infection compared to HIV-negative patients. In late stage HIV infection, serologic response to syphilis may be delayed or absent. These paradoxical findings may be attributed to B-cell hyperfunctioning and failure, respectively (13).

The patient in question presented with an insidious onset of personality change, delusions, and memory loss. The differential diagnosis of these psychiatric symptoms in a 40 year old male includes psychiatric conditions such as schizophrenia, bipolar disorder, and early-onset Alzheimer's dementia as well as infectious causes such as HIV dementia, CNS tuberculosis, herpes encephalitis, and neurosyphilis, among others. As neurosyphilis is often called "the great masquerader," it is critical to have this diagnosis on the differential of any patient presenting with insidious onset of psychiatric symptoms with atypical features. Although possible, forty years of age is fairly old for new onset schizophrenia and too young for Alzheimer's. However, despite the absence of syphilis risk factors outlined above, the presence of frequent headaches and the characteristic Argyll-Robertson pupils in this patient strongly supported the diagnosis of neurosyphilis even before formal investigations were carried out.

The standard of treatment for neurosyphilis is Penicillin G 3-4 million units IV q4h or 24 million units continuous IV infusion for 10-14 days (14). Penicillin G procaine 2.4 million units IM qd plus probenecid 500mg po qid for 10-14 days may be given as an alternative (15). Ceftriaxone 2g IV qd for 10-14 is also an option (14). Follow-up clinical examination and lumbar puncture should be scheduled at 3-6 months after treatment and every 6 months thereafter until the CSF-VDRL becomes nonreactive and the CSF white blood cell count normalizes (8). CSF abnormalities clear typically in 2 years. Prognosis is excellent with early treatment initiation, but can be poor with irreversible brain damage.

SUMMARY

Untreated syphilis can progress to a form of tertiary syphilis called neurosyphilis. This is a serious concern as the patient begins to demonstrate marked cognitive and/or behavioural impairment as well as many other neurological and physical symptoms. Clinical suspicion of neurosyphilis can be made based on a detailed medical history and physical exam including a history of high-risk behaviours, previous documented syphilis infection, insidious onset of psychiatric symptoms, headaches and characteristic neurological findings such as Argyll-Robertson pupils. The diagnosis can be confirmed with serum non-treponemal tests such as VDRL and RPR, serum treponemal tests such as FTA-ABS and TPPA, and neurosyphilis-specific tests, such as CSF-RPR and CSF-VDRL. The outcome of patient with neurosyphilis is highly dependent on the amount of brain damage and the extent of disability before the

initiation of treatment.

ACKNOWLEDGMENT

The authors would like to sincerely thank Dr. Hui Li for his support and encouragement in the preparation of this case report.

REFERENCES

1. Public Health Agency of Canada. 2004 Canadian Sexually Transmitted Infections Surveillance Report. CCDR 2007; 33S1:1-69.
2. Lin CC, Gao X, Chen, X-S, Chen Q and MS Cohen. China's Syphilis Epidemic: A Systematic Review of Seroprevalence Studies. Sexually Transmitted Diseases. December 2006; 33(12):726-736.
3. Goldon MR, Marra CM and KK Holmes. Update on Syphilis: Resurgence of an old problem. JAMA 2003; 290:1510-1514.
4. Goh BT. Syphilis in Adults. Sexually Transmitted Infections 2005; 81: 448-452.
5. Wasserheit JN. Epidemiological synergy: Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sexually Transmitted Diseases. March-April 1992; 19(2):61-77.
6. LaFond RE and SA Lukehart. Biological Basis for Syphilis. Clin Microbiol Rev. 2006 January; 19(1): 29–49.
7. French P. Clinical Review: Syphilis. BMJ 2007; 334:143-7.
8. Mandell GL, Bennett JE and R Dolin. Mandel, Douglas, and Bennett's: Principles and Practice of Infectious Diseases. 6th edition. Churchill Livingstone. 2005. Chapter 235.
9. Cohen J, Powderly WG, et al. Cohen & Powderly: Infectious Diseases. 2nd edition. Mosby. 2004. Chapter 75.
10. Birnbaum NR, Goldschmidt RH, and WO Buffett. Resolving the common clinical dilemmas of syphilis. Am Fam Physician. 1999 April; 59(8):2233-40, 2245-6.
11. Jaffe HW, Larsen SA, Peters M, et al. Tests for treponemal antibody in CSF. Arch Intern Med 1978; 138:252.
12. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 2004; 189: 369-79.
13. Hicks CB. Serologic testing for syphilis. Uptodate.com. 2006.
14. Drugs for Sexually transmitted diseases. Treat Guidel Med Lett 2004; 2:67

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CASE REPORT

A Case Of Atypical Presentation of Thoracic Osteomyelitis & Paraspinal Abscess

Utkarsh Acharya

ABSTRACT: Here presented is a case involving a 44-year-old man with a chief complaint of sharp lateral right-sided rib pain with notable radiation to the anterior portion of the thorax and minor radiation around the lateral back. The etiology of the pain and radiculopathy, which was initially attributed to a right-sided rib fracture, was later accurately credited to a paraspinal abscess discovered on a lateral X-ray of the thoracic spine. Subsequently, studies including Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and bone scan all confirmed the diagnosis of a paraspinal abscess between the right lobe and its neighboring T9 and T10 vertebrae. The mass was biopsied and methicillin sensitive Staphylococcus aureus was isolated. Appropriate surgical and medical intervention was possible due to the early diagnosis of the abscess.

INTRODUCTION

Diagnosis of a paraspinal abscess is a rare and clinically significant finding. Previous case reports of paraspinal abscess have indicated back pain as a common symptom in those affected, with 50% of patients exhibiting pyrexia during the initial presentation (1). Here we present a case of a paraspinal abscess exhibiting sharp lateral right-sided rib pain in an afebrile patient. This report is designed to discuss the pertinent features of the case and its implications in the future diagnosis of paraspinal abscess, a condition that could lead to catastrophic events if not detected early.

CASE

A 44-year-old Caucasian male with a noncontributory previous medical history of peptic ulcer disease and asthma presented to his primary care provider with complaints of sharp lateral right-sided rib pain with radiation to the anteriolateral portion of the thorax and minor radiation around the lateral portion of the back. The patient denied any known trauma to the costal regions previous to the onset of symptoms. Symptom review elicited a history of pain with deep inspiration suggesting possible pleuritic involvement. The patient's symptoms started ten days prior to presentation with a gradual worsening of the pain. He concurrently reported muscle spasms for which he was taking muscle relaxants. Initial consultation with an acute care clinician yielded a diagnosis of rib fracture based on clinical findings, which was empirically treated with narcotics and non-steroidal anti-inflammatory for pain management. However, this regimen resulted in little improvement and further work up was pursued.

Pertinent physical examination of the patient demonstrated an alert, oriented and well-nourished male in no acute distress. The patient was afebrile and normotensive. Cardiac and lung examinations were unremarkable. Musculoskeletal examination exhibited pain with palpation of the right lateral ribcage. No pain was produced upon palpation along the paraspinal muscles and no muscle spasms were noted or palpated. Neurological examination was normal.

Laboratory results were obtained: WBC: 15.1 X 10^9/μL [Differentials: neutrophils: 85%, lymphocytes: 12.0 %], RBC: 4.45 M/μL, Hb: 13.9 g/dL, Hct: 39.7%, PLT: 394 K/μL.

Anterior-posterior and lateral views of the chest via X-ray were found to be negative for any evidence of cardiopulmonary disease. Radiographic imaging of the right costal cage was ordered to assess for possible rib fracture. However, findings revealed no displaced

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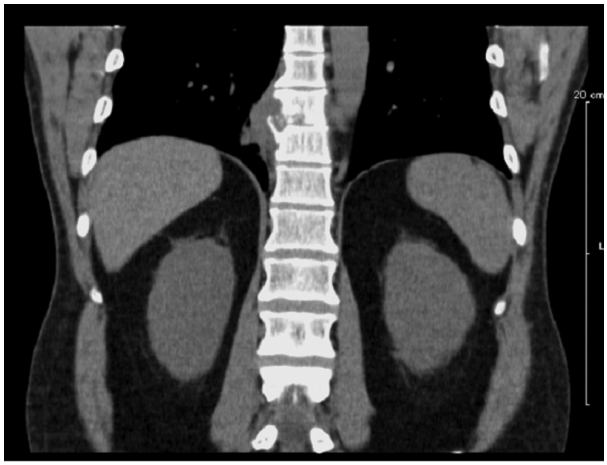

Figure 1. CT exhibiting paraspinal mass associated with destruction of portions of the T9 and T10 vertebral bodies with involvement of the pleura and medial aspect the right lung.

right-sided rib fractures, pneumothorax, or pleural effusion. An X-ray of the thoracic spine was conducted and showed normal spinal column free of any acute bony thoracic spine abnormality. However, an impressive opacity superimposed over the lower thoracic spine was noted. A subsequent non-contrast MRI of the thoracic spine found this opacity to be a paraspinal mass extending into the medial right lower lobe of the lung, measuring 5 x 4 x 2 cm, adjacent to the T9 and T10 vertebrae.

At this stage, the differential diagnosis included neoplastic, inflammatory, and infectious processes. The possible existence and metastasis of a neoplasm warranted further work up. CT and bone scan studies were conducted as part of a neoplastic work up and to look for nodes suggesting inflammatory, infectious or malignant process.

Contrast CT of the pelvis and abdomen were unremarkable for lymphadenopathy or metastasis. Non-contrast CT of the chest did not show mediastinal adenopathy but confirmed a soft tissue mass associated with osseous destruction of portions of the T9 and T10 vertebral bodies with involvement of the pleura and medial aspect of the right lung (Figure 1) suggesting an infectious or neoplastic process. As a result, a bone scan was performed showing increased activity within the lower thoracic spine at the levels of T9 and T10 without involvement of the rest of the skeleton (Figure 2). As metastatic disease was still a potential diagnosis, the patient was referred for a biopsy.

Needle biopsy and aspiration isolated methycillin-sensitive *Staphylococcus aureus* (MSSA) and the patient was referred for decompression and drainage and a full recovery was evidenced shortly thereafter.

DISCUSSION

Osteomyelitis and paraspinal abscesses of the spine is a rare condition, reported as 1 in 100,000 – 250,000 of the general population in developing countries (1). Epidemiological data on the overall prevalence of osteomyelitis in North America among the general population is lacking as the condition is infrequently reported in adults. Paraspinal abscesses mostly occur in the setting of invasive procedures (2). This includes transcutaneous infection of deep tissue by needles or catheters, bone surgery, blunt trauma, and hematogenous spread from distant sites (2). Hematogenous osteomyelitis and subsequent paraspinal abscess formation is most commonly caused by gram-positive organisms irrespective of the geographical setting (1). While gram-negative organisms may also inflict similar symptoms, Staphylococcus aureus remains the most common cause (3,4). Back pain, pyrexia (50% of patients), and muscular weakness are the most common presenting symptoms of paraspinal abscess (5) but were not prominent symptoms in this case. Sun et al. reported that local paraspinal tenderness should be considered a sign of infection (2). Clinical features may extend over several weeks or several months. However, neurological deficits, paralysis, and even death (1) may ensue if the source of the anomaly is not identified. Prior to the avail of imaging technology, Heusner et al. first described in detail the clinical progression of spontaneous abscess formation (6). The first phase includes back pain associated with tenderness, pyrexia, leucocytosis and an increased erythrocyte sedimentation rate (ESR). The involvement of radicular pain accompanied by fever defines phase II. Phases III and IV are defined by neurological deficit, altered sensation, motor function, bowel and urinary dysfunction, and ultimately, paralysis.

X-rays typically become abnormal after 3 to 4 weeks, showing bone destruction, soft tissue swelling, periosteal elevation, loss of vertebral body height or narrowing of adjacent infected intervertebral disk space, and destruction of the end plates above and below the disk. MRI has been found to be an optimal tool in identifying paraspinal abscess formation but has limited potential in being able to distinguish between infectious and neoplastic etiology in the presence of abnormal findings (7, 8). Bone biopsy with needle or surgical excision and aspiration of debridment of abscesses provide tissue for culture and antibiotic sensitivity testing.

Empiric antibiotic therapy is often justified in the setting of pending biopsy results. Antibiotic selection should be substantially dependent on biopsy cultures

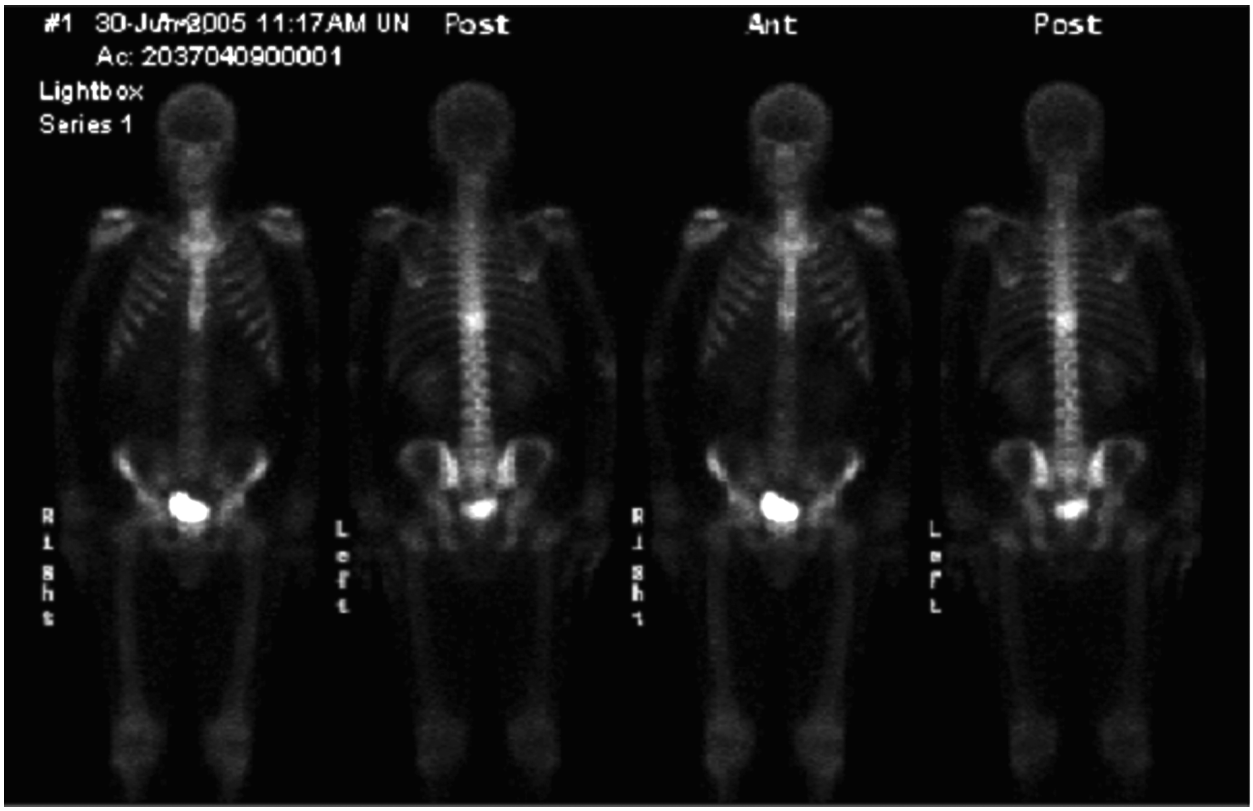

Figure 2. Bone scan exhibiting increased activity within the lower thoracic spine at the levels of T9 and T10

and sensitivity testing. Evidence attesting to standardized antibiotic therapy in the venue of osteomyelitis is limited. For patients expressing MSSA, treatment with intravenous nafcillin, oxacillin, or oral dicloxicillin is recommended. However, first-generation cephalosporins may be a justifiable alternative for patients with penicillin allergies. Vancomycin remains the gold standard antibiotic in cases of methicillin resistant staphylococcal infections. Alternative uses of quinolones in the context of MRSA have also been proposed (9). Parenteral administration is highly recommended for a period of 4 to 8 weeks and surgical intervention is often necessary to absolve large areas of spinal compression. Unfortunately, standardized guidelines in the management of patients with complicated osteomyelitis are lacking.

The relatively subtle presentation of this patient was somewhat deviant from that of reported cases of osteomyelitis. As a result, the diagnosis of a paraspinal abscess was not considered in the differential diagnosis on initial presentation. Physical findings suggestive of paraspinal abscess were relatively inconspicuous, such as the absence of generalized back pain, pyrexia, and paraspinal tenderness. Therefore, empirical treatment was considered before ordering MRI and CT scans of the thorax. This case characterizes the diagnostic challenge of suspecting a paraspinal abscess in the venue of an uncharacteristic presentation. The report emphasizes the importance of suspecting a paraspinal abscess in patients that exhibit refractory somatic symptoms despite a subtle presentation as unnecessary diagnostic delay could render catastrophic consequences.

ACKNOWLEDGMENTS

The author wishes to thank Jennifer Bain, MD and Edward Onusko, MD for their invaluable guidance with the preparation of this manuscript.

REFERENCES:

1. Sharma RR, Sethu AU, Mahapatra AK, Pawar SJ. Neonatal Cervical Osteomyelitis with Paraspinal Abscess and Erb's Palsy. Pediatric Neurosurgery. 2000;32-230-233.
2. Sun HL, Cheng CY. Paraspinal muscle abscess after Chinese Kong Fu practitioner manipulation--a case report. Acta Anaesthesiol Sin. 1998 Jun;36(2):107-10.
3. Waldvogel FA, Papageorgiou PS: Osteomyelitis. The past decade. New England Journal of Medicine. 1980; 303:360.
4. Winters JL, Cahen I. Acute hematogenous osteomyelitis. A review of sixty-six cases. Journal of Bone Joint Surgery America. 1960; 42:97.
5. Stone DB, Bonfiglio M. Pyogenic vertebral osteomyelitis – A diagnostic pitfall for the internist. Archives of Internal Medicine. 1963;112:491.
6. Heusner AP. Nontuberculous spinal epidural infections. New

England Journal of Medicine. 1948; 239: 845-54.
7. Meyers SP, Weiner SN. Diagnosis of hematogenous pyogenic vertebral osteomyelitis by magnetic resonance imaging. Archives of Internal Medicine.1991; 151:683.
8. Modic MT, Feiglin DH, Piraino DW, et al: Vertebral osteomyelitis: Assessment using MR. Radiology. 1985; 157:157.
9. Bamberger DM. Diagnosis and treatment of osteomyelitis. Comprehensive Therapy. 2000;26:89-95.
10. Hill JS, Hughes EW, Robertson PA: A Staphylococcus aureus paraspinal abscess associated with epidural analgesia in labour. Anaesthesia. 2001;56:871-878.
11. Digby JM, Kersley JB: Pyogenic non-tuberculous spinal infection. Analysis of 30 cases. Journal of Bone Joint Surgery (Br). 1979;61:47.
12. Silverthorn KG, Gillepsie WJ: Pyogenic spinal osteomyelitis. A review of 61 cases. NZ Medical Journal. 986; 99:62.
13. Joughin E, Me Dougall C, Parfitt C, et al: Causes and clinical management of vertebral osteomyelitis in Saskatchewan. Spine. 1991;16:261.
14. Liebergal M, Chiamsky G, Lome T, et al: Pyogenic vertebral osteomyelitis with paralysis, prognosis and treatment. Clinical Orthopedics. 1991;269:142.

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REVIEW ARTICLE

Loud Music Listening

Nicolae Petrescu*

ABSTRACT: Over the past four decades, there has been increasing interest in the effects of music listening on hearing. The purpose of this paper is to review published studies that detail the noise levels, the potential effects (e.g. noise-induced hearing loss), and the perceptions of those affected by music exposure in occupational and non-occupational settings. The review employed Medline, PubMed, PsychINFO, and the World Wide Web to find relevant studies in the scientific literature. Considered in this review are 43 studies concerning the currently most significant occupational sources of high-intensity music: rock and pop music playing and employment at music venues, as well as the most significant sources of non-occupational high-intensity music: concerts, dicotheques (clubs), and personal music players. Although all of the activities listed above have the potential for hearing damage, the most serious threat to hearing comes from prolonged exposures to amplified live music (concerts). The review concludes that more research is needed to clarify the hearing loss risks of music exposure from personal music players and that current scientific literature clearly recognizes an unmet hearing health need for more education regarding the risks of loud music exposure and the benefits of wearing hearing protection, for more hearing protection use by those at risk, and for more regulations limiting music intensity levels at music entertainment venues.

Keywords: noise-induced hearing loss, music, occupational noise, health knowledge, health attitudes, ear protective devices

INTRODUCTION

Noise-induced hearing loss (NIHL) refers to a gradual, cumulative and preventable decline in auditory function that follows repeated exposure to loud noise. It is the leading cause of preventable hearing loss (1,2). It is also estimated that 10% (30 million) of Americans are encountering hazardous levels of noise, that 25% of those working in the construction, mining, agriculture, manufacturing, transportation, and military industries routinely encounter noise leves above 90 dB (A), and that such noise exposure has already generated a sizeable population of workers who meet the Occupational Safety and Health Administration's (OSHA) definition for "material impairment of hearing" (over 25 dB threshold at 1000, 2000, and 3000 Hz). Since workers experiencing such losses can have significant effects on their employment, social interactions, and family interactions, protecting hearing health in the workplace has become an important undertaking. Occupational exposure to noise programs and regulations (for e.g. maximum allowed daily noise doses) have been designed (3,4), but no standards have been set for recreational noise, an emerging contributor to noise-induced hearing loss (5). There are numerous sources of non-occupational noise exposure. Clark and Bohne (6) have compiled a partial list of significant sources of leisure noise, and music figures prominently in their construct. Music, in addition, transcends the recreational setting to pose an occupational risk of NIHL for groups such as music venue workers and music performers (7,8).

Three decades ago, experts in the field suggested that damage risk criteria be set for music using temporary threshold shift measurements (9). Temporary threshold shift (TTS) refers to the temporary hearing impairment

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that usually occurs after exposure to

intense noise, the threshold being the quietest sound distinguished by the subject. TTS is known to increase in constant noise in direct proportion to the logarithm of exposure time and to decay in inverse proportion to the logarithm of recovery time(9). It is now widely accepted that repeated TTSs can lead to accumulated cellular damage which can cause permanent threshold shifts (PTS) (2). The precise relationship between temporary and permanent threshold shifts has not yet been elucidated, and TTS cannot be used to predict the magnitude of PTS(2), but according to an animal study, TTS is considered to be a good predictor of early development of PTS(10). For more details on the manifestation of TTS and PTS phenomena at the cellular level readers are directed to articles by May (1) and Clark et a.(42).

The purpose of this review is to summarize the scientific literature concerning exposure to music as a risk of NIHL, an important health concern. An exhaustive review of all the relevant literature is beyond the scope of this paper; for an extensive review of this topic, the reader is referred to Davis et al(11). The present review is limited to what could be considered the major sources of occupational and non-occupational music exposures. For each type of exposure, the review summarizes data on noise emissions, information on the knowledge, attitudes, behaviors, and effects on those at risk, and, where possible, an assessment of hearing damage risks. Wherever sources were found to be contradictory, attempts were made to examine the quality of the studies and draw the most reasonable conclusions.

METHODS

A literature search was performed using Medline (1950 to May 2007), Pubmed, PsychINFO, and the World Wide Web. Only English language articles were reviewed. The search was performed with both subject headings and free text words to increase the sensitivity of the search. Searches were performed using a number of key words and phrases, used alone or in combination: music, noise, occupational, noise-induced hearing loss, recreational noise exposure, rock music, discotheque, personal listening devices, attitudes, prevention, hearing protector, ear plugs, and hearing protecting device. The references listed by the identified relevant studies were also scrutinized for additional useful citations. No specialists in the field or authors were contacted for unpublished data. The collected published studies were read in their entirety, and the information most pertinent to the present study was included in the review. The author used a simple method, abbreviated as ODDCHAIR, to review each article and to determine the quality of the particular study. The objectives, design, definitions of the study as well as the data collection, handling, analysis, interpretation, and reporting (ODDCHAIR) were clearly identified for each study before inclusion in the review.

LITERATURE FINDINGS

Music Exposure: Occupational Setting

I. Musicians

Rock musicians have been found to be at a significant risk of music-based NIHL. A publication which reviewed seven publications concerning the hearing of rock musicians found that an average of 20% of rock musicians suffer from permanent hearing loss, the prevalence ranging from 5 to 41%(7). This review also found that hearing disturbances like tinnitus and hyperacusis (a collapsed tolerance to normal environmental sounds) appear significantly more often in rock musicians than in non-musicians(7). A study that examined a group of 139 rock and jazz musicians found that 74% suffered from one or a combination of multiple hearing disorders: hearing loss, tinnitus, hyperacusis (sounds of low intensity are uncomfortably loud), distortion, and/or diplacusis (hearing the same tone at two different pitches), with the first three being the most commonly reported disorders(12). The study also found that tinnitus and hyperacusis were found in musicians significantly more frequently than in reference populations(12). In addition, two studies that investigated pop/rock musicians found interesting results. One found that after five years of playing music, a group of pop/rock Swiss musicians that never wore hearing protection experienced permanent moderated hearing loss (6 dB of threshold enhancement compared to the control group), hyperacusis (26%), and tinnitus (17%), while a group that regularly wore hearing protection showed minimal average hearing threshold increase (0.9 dB)(7). On the other hand, a study covering 53 Swedish and British pop and rock musicians found that after sixteen years of music playing, only 15% of them experienced any hearing loss on objective audiometric measurements(14). This was surprising since sound levels at rock concerts routinely reach sound levels above 100 dB (5,15,16) which are considered unsafe for any unprotected exposures exceeding fifteen minutes(3,4).

Symphony orchestra musicians may also be at risk of occupational music-induced NIHL(17). Jansson and Karlsson attempted to map the sound levels in a symphony orchestra and found that ‘heavy’ symphonic music, such as that experienced by musicians immediately in front of trumpets, exceeds the permitted dose for industrial noise equivalent after only ten hours

of weekly playing(18). A study undertaken in England also showed the potential for hearing loss in classical orchestral musicians, as trumpet and piccolo players receive noise doses 160% and 124% respectively of the then (1992) national occupational standard (namely 90 dB for 8 hours)(19). Royster et al (20) found that during practices and concerts, the average industrial noise equivalent exposure of classical musicians is like that of a standard working day (8 hours) at 85.5 dB, only slightly above the recommended safe threshold of 85 dB in industrial occupational settings(3,4). However, they also observed notched audiograms consistent with noise-induced hearing damage in 52.5% of individual musicians, noting that violinists and violists showed poorer thresholds (in the 3-6 kHz range) in the left ear when compared to the right, consistent with the left ear's greater exposure through proximity to the sound source(20). Notched audiograms and poorer left-ear thresholds were also detected by Ostri et al.(21) who studied 95 musicians of the Royal Danish Theater. They found hearing deficits (qualified as 20 dB or more over normal hearing thresholds in frequencies between 3 and 6 Hz) in 58% of the participants (21).

Not all studies showed hearing deficiencies in orchestra musicians, however. In a 16-year follow-up study, Kahari et al (22) found that 56 classical musicians experienced no extended negative progress in their pure-tone hearing threshold values. A larger study, working with a population of 417 musicians, showed that when compared to reference values, classical musicians' measured tone thresholds did not differ significantly from those of normal controls (non-musicians and no significan noise exposure population from Spoor & Passchier-Vermeer (53)), although the measured sound exposure in some situations exceeded the recommended sound level exposures to industrial noise (23). Of note, the authors also reported on a 10 dB threshold enhancement over the high frequencies (6000 Hz and beyond) in flute players as well as a 30 dB left ear threshold increase for double bass players, in the 4000-8000 frequency range. At least 123 of the assessed professional musicians had been playing music for over 6 years at the time of the study(23).

One study showed that disc jockeys (DJs) are at substantial risk for developing noise-induced hearing loss, as average sound levels reached 96 dB during observed performances(24). Seventy per cent of the 23 DJs taking part in the study reported TTSs after playing sessions, and 74% reported post-exposure tinnitus(24).

II. Employees of music venues

According to a study that investigated eight live-music clubs in the United States, employees of establishments hosting regular live music performances were found to be exposed to sound levels ranging from 94.9 to 106.7 Db (25). The study also found that symptoms of sound exposure (tinnitus) and subjective threshold shifts correlated with the sound intensity and that only 16% of the employees reported regularly using hearing protection(25). University students working part-time jobs in a campus music entertainment venue were found to be regularly exposed to sound intensities averaging 90 dB; the same study found moderate post-exposure temporary threshold shifts (TTSs) that correlated well with personal exposure doses and permanent hearing loss of more than 30 dB at various frequencies in the 250 to 6000 Hz range in 29% of the subjects (26).

Music Exposure: Recreational Setting

Two significant studies revealed the frequency and habitual exposure to music in the recreational setting. Mercier and Hohmann(27) surveyed a group of 700 Swiss young men and women, aged 16 to 25, and found that, overall, 79% of the subjects regularly attend discotheques (76% once or less per week, 19.6% twice per week, 4.8% thrice per week, and 1.3% at least thrice per week), 52% pop and rock concerts, and 35% techno parties (e.g. raves) (pop, rock, techno combined: 68.2% once or less per week, 13.3 % twice per week, 4.9% thrice per week, and 13.6% more than thrice per week). In all cases, nearly 75% of the population had been upholding their particular habits for at least one year. Furthermore, 71% of those surveyed had suffered tinnitus following attendance at a music event and 11% had audiometry-confirmed hearing damage (27). Eggemann et al(28). reporting only on exposures in youngsters aged 14 to 20, found their populationexposed to an average of 3 hours of music listening daily, via concerts, discotheques, and headphones. Among others, they found that 85% of those surveyed attend clubs and concert venues where music sound intensity ranged from 89 to 110 dB (A), while 10% of those who regularly listened to music through headphones (80% of all surveyed) were found to be exposed to average sound intensities of 100 dB (A).

I. Concerts

Concerts attendees have been repeatedly found to suffer hearing damages from exceedingly high music sound intensities, rock concerts being the settings of highest risk. On average, rock concert sound levels exceed 100 dB (A) (5,15,16) unsafe for any exposure lasting longer than 15 minutes (3,4). Classical music concerts are not considered to pose any risk of NIHL because attendance habits do not exceed twenty hours per week and average exposures are less than 90 dB

(A)(29, 30)

A number of the earliest studies on the effects of rock music concerts on attendants' hearing found TTSs of up to 30 dB at the 4 kHz frequency mark of the hearing spectrum (5,31,32,33). More recent studies support these findings(15,16,34). A Canadian study found that 81% of 22 rock concert attending volunteers showed a TTS of 10dB or more 5 to 25 minutes after a concert, while 50 minutes after the concert, 76% showed continued TTS(15). A prospective, randomized study in which 29 volunteers attended non-consecutive rock and pop concerts found that 64% of those not wearing ear plugs experienced significant threshold shifts compared to the 27% incidence of TTS in those who used ear plugs(16). Another study that investigated the risk of hearing loss from short-term exposures to high sound levels found that a group of 24 patients requiring rheologic therapy for acoustic trauma reported impairment symptoms after exposures to rock or pop concerts (67%); discothques (17%), parties (12%), and cassette players (4%)(34). The maximum threshold changes, reaching 40-60 dB, were in the 3-4 kHz range, and all patients suffered from tinnitus. Interestingly, only 33% of these patients experienced an improvement in tinnitus following hearing rehabilitation , while all patients benefited froman improvement in hearing loss through therapeutic intervention (34). Tinnitus was also found to be a very common (84.7%) form of hearing disturbance in a group of rock concert attendees surveyed by Bogoch et al.(35) and in 61% of those participating in an MTV web survey completed by 9693 subjects (36).

In terms of long-term hearing deficits, a significant increase in average hearing thresholds in the 0.5 to 8 kHz range compared to matched controls (age and sex matched subjects who rarely attend rock and variety concerts) was found in 87 individuals aged 12 to 40 who attend concerts (measured sound intensity of 100 to 115 dB (A)) at least twice per month(37). Another study that focused on the long-term effects of listening to amplified music found that a group of 505 university students with a high self-reported rate (at least one event per month) of pop music event attendance (concerts and discos) exhibited statistically significant hearing losses compared to a control group (attended less than four events per year) (38). With regards to perceptions regarding loud music, Bogoch et al.(38) found that 75% of the surveyed rock concert attendees thought it was at least somewhat likely that sound levels at music concerts can damage hearing, 11.4% did not think that to be the case, and 14.4% did not know what effects concert sound levels can have. Concerning a wide variety of publicly played music, a European study looking at the perceptions of 700 participants found that 35% of those surveyed thought pop and rock concerts are too loud, 39% held a similar view of techno parties, and 42% considered discotheque music to be too loud(27).

II. Discotheques

Discotheque sound levels are similarly hazardous to hearing as they can cause significant tinnitus and significant temporary hearing loss in the 3-4 kHz range(34). Lending support to these findings, a web-based survey reported that 43% of those participating experience tinnitus after attending clubs(36). Such findings are less surprising in light of reports on music sound levels in discotheques routinely exceeding 90 dB (A) (26) and occasionally 100 dB (A)(28). A number of studies on attitudes and behaviours regarding discotheque music levels have been undertaken by an Austrian group, Weichbold and Zorowka. They examined whether adolescents (ages 14-19) exhibit preventive behavior when attending discotheques if informed on the risks of hearing-damage from loud music; surprisingly although 85% of 253 were informed of the risks, awareness improved the appraisal of music loudness yet had no effect on disco attendance frequency or use of ear plugs(39). Next, the same investigators analyzed the effect of a hearing education campaign on hearing-protective behavior and revealed a moderate change in hearing-protective behavior: frequenting discos at a rate of ten times in six months decreased from 34% to 24%, and the use of earplugs increased from 0% to 3.7% post-campaign(40). In a following study, Weichbold and Zorowka investigated the efficacy of hearing impairment preventive measures if such measures were to become the responsibility of the music venue; they surveyed over one thousand high school students to find the effects of lowering disco music levels on student behaviour. The study found that 43.8% of those surveyed wanted a decrease in music volume, while only 2.5% would like an increase(41). In the case of a moderate decrease in music volume, 5% of those surveyed would decrease disco attendance, 10% would increase their attendance, and the rest would not change attendance habits(41).

III. Personal music players

The role of personal music players (PMPs) (walkman, diskman, mp3 players, etc.) in music induced hearing loss is not clear, although ownership of such devices has been quoted as high in the past(5), is believed to be increasing(42), and several studies have reported risky exposures(43,44). One study found that 16 volunteers who regularly used their PMPs averaged three hours of music listening per day at an average of 92 dB (A),(43) while a more recent investigation, Hellstrom et al.(44)

reported listening habit findings of daily hour-long listening at intensities in the range of 91-97 dB (A). In the latter study, subjects were advised to listen for one hour to "loud but still comfortable music level" aiming to investigate discomfort perceptions as well as changes in hearing post-exposure. Both studies reported positive TTSs for all of their subjects 60 minutes post-exposure(43,44). Other investigators show reason for no concern regarding the risks of PMP use to hearing health(45,46). Upon not finding, respectively, no convincing evidence of permanent hearing damage(45) and only mild post-use TTS in one population(46), Mostafapour et al. (45) and Turunen-Rise et al.(46), concluded that the risk of acquiring permanent NIHL from use of PMPs is very small. Lastly, several studies form the middle ground of the dispute. In one instance, hearing damage from PMPs has been documented as increased hearing thresholds in 54 subjects using their devices for longer than 7 hours per week, compared to nearly normal thresholds in 195 subjects using PMPs only 2-7 hours per week(37). In a survey of 52,000 young male subjects, Buffe et al.(47) concluded that only listeners who habitually exceed 7 hours of moderate (average intensities between 70 and 80 dB (A)) music intensity listening per week are at risk of developing permanent music-induced hearing loss.

DISCUSSION

The reviewed literature shows the significant risks of noise-induced hearing loss (NIHL) from music playing in rock musicians(7,12,13). Only one study on the topic found no significant hearing damage in rock and pop musicians after twenty-six years of professional playing(14). The authors were surprised by the findings and proposed that "there might be a protective effect by the generally positive attitude from the musicians toward their performance and audience;"(14) notably, they neglected to make mention of the fact that the study did not inquire into the use of hearing protection nor did they consider significant that only 53 out of the 83 initially participating musicians (26 years prior) participated in the followup threshold measurement study. Most significantly, however, the difference in findings can be explained by the authors' high threshold for reporting hearing impairment; while Axelsson et al.(14) consider pure tone audiogram threshold under 20 dB and very limited (>25 dB) high frequency loss as well preserved hearing, other rock musician study authors report notable hearing impairments in musicians averaging 10-15dB threshold enhancement. In light of this and the heterogeneity of rock music performing environments, which is difficult to control for, it is unreasonable to consider the discrepancy between these study findings as significant.

Since rock music-induced hearing loss risks have been clearly established, Hearing Education and Awareness for Rockers (H.E.A.R.), an organization created by veteran musicians, among them Pete Townsend of The Who, has taken a strong initiative in educating the public on the dangers of excessive music sound exposure as well as in providing free hearing protecting ear plugs at various concerts and venues in the San Francisco Bay area(48). Since their inauguration in 1990, H.E.A.R. has been creating public service announcements, enlisting the help of famous musicians such as Mick Fleetwood of Fleetwood Mac and Lars Ulrich of Metallica, and has strongly encouraged hearing protection use during concert attendance for both music fans and musicians(48). The protective effect of ear plugs in music professionals has been mentioned and encouraged for both rock musicians(13) and orchestra musicians(17) in studies included in this review. Since musicians represent a group especially dependent on optimally functional hearing, other proposed strategies to improve musician hearing health, such as regular evaluations for types of loud-music induced hearing problems other than hearing loss (tinnitus, hyperacusis, and diplacusis) and continued education about the risks to hearing and the benefits of ear protection(13) should be taken seriously.

Furthermore, similar strategies should be used for symphony orchestra musicians, although the risk of music-induced hearing loss is not as clearly defined for the whole of this population(22,23).

Both studies regarding employees of music venues agree on the reality of a substantial risk of developing NIHL from occupational exposure to loud music(25,26). Their prevention strategies differ, however, since Gunderson et al.(25) suggest that hearing conservation programs should be developed for this occupational subgroup, while Sadhra et al.(26) suggest that the next appropriate steps should be to better educate employees about the risks and to improve noise exposure assessments in entertainment venues. Although different in their implication of hearing safety responsibility and readiness to enact change, both approaches are important to improve hearing health in this population.

In the non-occupational setting, high-intensity music listening has been clearly linked to temporary hearing impairment and disturbances in the setting of pop and rock music concerts(15,16,34,35,36). Meanwhile, data on discotheque attendees although sparse, shows considerable rates of post-exposure tinnitus in those attending(34,36); temporary threshold shifts have so far not been documented(37). Nevertheless, measured sound intensities alone are enough to suggest the possibility of hearing damage risks for discotheque

attendants(28).

An interesting conclusion can be drawn from the three studies undertaken by Weichbold and Zorowka: in the high-school age population under study, information on hearing risks alone leads to significantly limited hearing protection behaviour. Although this finding may yet be key in planning future prevention programs, such a conclusion undermines the value of risk education and must not be accepted without caution, for the information and educational campaigns mentioned and undertaken in these studies can reasonably be assumed to have a variety of impacts on their target population. These impacts may, for example, not be noticed because the post-educational assessment happens a year after the educational program. It is commendable that the course (PROjectEAR) consists of four 45-minute sessions, spread over three days, and uses not only a variety of didactic approaches (multimedia, demonstrations, role-play, and creative group work) but also interactions with patients that are hearing impaired and suffering from tinnitus. It may, however, be too short-lived to create an impact on healthy music listening behaviour. Alternatively, as also noted by Folmer et al.(54), educational sessions may have a positive impacts on knowledge and on attitudes, but may not be sufficient for behaviour change; this conclusion implies the need for further awareness and attitudes studies on this population and directs future prevention efforts towards introducing new interventions aimed at improving the chances of desirable impacts on adolescent hearing health behaviour.

Education about the hearing risks of loud music exposure can still play an important role in hearing health protection, as Chung et al.(36) showed that although only 14% of over nine thousand young adult responders to a web based survey reported using hearing protection, 66% could be motivated to try ear protection if they were aware of the potential for permanent hearing loss.

The dangers of listening to personal music players have been difficult to define because of the lack of consensus in the literature. While concluding that more studies should be undertaken to clarify risks, it could also be useful to agree to a temporary consensus guided by findings suggesting that using PMPs for less than seven hours per week at moderate volumes is not likely to cause NIHL, while listening in excess increases the risk of music-induced NIHL(47,48). Increasing the knowledge of the risks to hearing from listening to PMPs is certainly advisable in light of the accepted and increasing popularity of such devices(42).

Besides awareness of the risks of music-induced hearing loss, attitudes are also important in protecting the hearing of those at risk. Interestingly, the Chung et al(36). study found that only 8% of those participating in the web-based survey thought hearing loss “a very big problem.” On the other hand, investigating the willingness to wear hearing protection found promising results; as mentioned previously, 66% could be motivated to try hearing protection if they were aware of the risks of permanent hearing loss.

Furthermore, despite very low current usage of hearing protection among young music lovers(35,36), 85% of those surveyed by Crandell et al.(49) and 42.1% of those surveyed by Bogoch et al.(35) said they would wear hearing protection at concerts if it were freely provided. The same two studies reported a significantly common self-reported reason for not wearing ear plugs: “it would not look good.”(35,49) With an outlook to a remedy, Bogoch et al.(35) suggest that if more concert attendees wore hearing protection and if hearing protection became normal attire at concerts, such negative perceptions of self-image would fade.

The studies presented in this review are those most recently part of the literature. If no clear answer has been provided here regarding certain aspects of the risks of loud music exposures, it is due to the lack of consensus on the topic in the literature. Of the weaknesses of this review, two are very important. The review only included articles published in English, while a number of the articles found initially were published in other languages. Time and resource restraints did not permit translating and using these resources. Secondly, this study attempts to elaborate on the sources of music-induced hearing loss that the author has found most important, and it has consciously restricted the review to those only, choosing to not address several other occupational and non-occupational sources of potentially dangerous loud music exposures. In partial reparation for such omissions, the author suggests the reviews by Clark (5) and Davis et al.(11).

There have been proposed explanations, albeit not formally investigated, for why, despite knowledge of the risks, loud music exposure continues. Conservative sources have suggested that since sounds are not clearly offensive to the ear until they reach 120 dB (A) (28), and since TTS is often insidious(15), the exposure of those not yet affected by NIHL continues unabated. A bolder study mentions the unique response in listeners to the sound of music: unlike other sounds (airplanes, lawn mowers, etc.), music can be played quite loudly without becoming annoying, especially if the music is well liked(50). Calvert and Clark have coined the term “social noise phenomenon” to describe the tendency of youths and young adults to frequent discotheques, hypothesizing that high levels of noise prevent communication at distances greater than a few

feet, thus encouraging and allowing those who seek members of the opposite sex to move inside "personal space" in order to communicate(51). Finally, a study conducted by Florentine et al.(52) found that 8 out of 90 surveyed music listeners showed a pattern of maladaptive loud-music listening behaviour similar to that exhibited by the drinking behaviours of alcohol addicts. The group found that, according to the clinical conceptualization of an addictive syndrome, the 8 subjects scored above diagnostic threshold criteria on the NEMLS (Northeastern Excessive Music Listening Survey), a questionnaire based on the MAST (Michigan Alcoholism Screening Test) and on criteria used in the formal assessment and treatment of people with addictions. These individuals were found to be similar to addicts via their self-reported maladaptive music-listening behaviour based on criteria such as continued listening despite negative consequences (e.g. tinnitus) and tolerance for loud music.

These hypotheses indicate that there is still much to investigate and uncover regarding music exposure as a risk for noise-induced hearing loss. While questions about exposures, effects, attitudes, and behaviours in the music-listening settings of work, leisure, and changing technologies await answers, there is currently ample evidence to strongly support establishing and ongoing efforts to educate and protect the public, music professionals, and music venue employees from the hazards of high intensity music exposure.

ACKNOWLEDGMENTS

The author would like to thank Dr. Ron House for his crucial support throughout the project's duration, Dr. Isaac Bogoch for the impetus he provided to the project idea, and Dr. Rob Sargeant whose expertise and guidance has been very helpful.

REFERENCES

1. May JJ. Occupational hearing loss. Am J Indust Med 2000; 37:112-20.
2. Consensus National Conference. Noise and hearing loss. JAMA 1990; 263:3185-90.
3. Canadian Centre for Occupational Health and Safety [homepage on the Internet]. Hamilton: The Centre; c2007. [updated 2007 Mar 19; cited 2007 May 20]. Available from: http://www.ccohs.ca/oshanswers/phys_agents/exposure_can.html
4. American Academy of Audiology [homepage on the Internet]. Reston: The Academy; c2007 [updated 2003; cited 2007 May 20]. Available from: www.audiology.org/publications/documents/positions/Hearingconservation/
5. Clark WW. Noise exposure from leisure activities: A review. J Acoust Soc Am 1991;90(1):175-81.
6. Clark WW, Bohne BA. The effects of noise on hearing and the ear. Med Times. 1984 122, 17-22.
7. Stormer CC, Stenklev NC. Rock music and Hearing Disorders. Tidsskr Nor Laegeforen. 2007 Mar 29; 127(7):874-7.
8. www.hearnet.com [homepage on the Internet]. San Francisco: Hearing Education and Awareness Rockers, Inc.; c1991-2006 [cited 2007 May 20]. Available from: http://www.hearnet.com/index.shtml
9. Dey F. Auditory fatigue and predicted permanent hearing defects from rock and roll music. N Eng J Med 1970;282(9):467-70.
10. Luz GA, Fletcher JL, Fravel WJ, Mosko JD. The relation between TTS and PTS in rhesus monkeys exposed to impulse noise. Acta Otolaryngol Suppl (Stockh) 1973;Suppl 312:5-15.
11. Davis AC, Fortnum HM, Coles RRA, Haggard MP, Lutman ME. Damage to hearing from leisure noise: A review of the literature. MRC Institute of Research. Nottingham, 1985.
12. Kahari K, Zachau G, Eklof M, Sandsjo L, Moller C. Assessment of hearing and hearing disorders in rock/jazz musicians. Int J Audiol 2003;42:279-288.
13. Schmuziger N, Patscheke J, Probst R. Hearing in nonprofessional pop/rock musicians. Ear Hear. 2006 Aug;27(4):321-30.
14. Axelsson A, Eliasson A, Israelsson B. Hearing in pop/rock musicians: a follow-up study. Ear Hear. 1995 Jun;16(3):245-53.
15. Yassi A, Pollock N, Tran N, Cheang M. Risks to hearing from a rock concert. Can Fam Physician. 1993 May;39;1045-50.
16. Opperman DA. Reifman W. Schlauch R. Levine S. Incidence of spontaneous hearing threshold shifts during modern concert performances. Otolaryngol Head Neck Surg. 2006 Apr 134(4):667-73.
17. Teie PU. Noise-induced hearing loss and symphony orchestra musicians: risk factors, effects, and management. Md Med J. 1998 Jan;47(1):13-8.
18. Jansson E, Karlsson K. Sound levels recorded within the symphony orchestra and risk criteria for hearing loss. Scand Audiol 1983;12(3):215-21.
19. McBride D, Gill F, Proops D, Harrington M, Gardiner K, Attwell C. Noise and the classical musician. BMJ. 1992 Dec 19-26;305(6868):1561-3.
20. Royster JD, Royster LH, Killion MC. Sound exposures and hearing thresholds in symphony orchestra musicians. J Acoust Soc Am. 1991 Jun;89(6):2793-803.
21. Ostri B. Eller N. Dahlin E. Skylv G. Hearing impairment in orchestral musicians. Scand Audiol. 1989;18(4):243-9.
22. Kahrari KR, Axelsson A, Hellstrom PA, Zachau G. Hearing development in classical orchestral musicians. A follow-up study. Scand Audiol. 2001;30(3):141-9.
23. Karlsson K, Lindquist PG, Olaussen T. The hearing of symphony orchestra musicians. Scand Audiol. 1983;12(4);257-64.
24. Bray A, Szymanski M, Mills R. Noise induced hearing loss in dance music disc jockeys and an examination of sound levels in nightclubs. J Otolaryngol Otol. 2004 Feb; 118(2):124-8.
25. Gunderson E, Moline J, Catalano P. Risks of developing noise-induced hearing loss in employees of urban music clubs. Am J Ind Med. 1997 Jan; 31(1):75-9.
26. Sadhra S, Jackson CA, Ryder T, Brown MJ. Noise exposure and hearing loss among student employees working in university entertainment venues. Ann Occup Hyg. 2002 Jul; 46(5):455-63.
27. Mercier V, Hohmann BW. Is Electronically Amplified Music too Loud? What do Young People Think? Noise Health. 2002;4(16):47-55.
28. Eggemann C, Koester M, Zorowka P. [Hearing loss due to leisure time noise is on the rise. The ear also needs a rest period] MMW Fortschr Med. 2002 Dec 5;144(49):30-3.
27. Barry JP, Thomas IB. A clinical study to evaluate rock music, symphonic music and noise as sources of acoustic trauma. J Aud Eng Soc 1972;20:271-4.
29. Fearn RW. Level limits of music. J Sound Vib 1975;43:588-91.
30. Ulrich RF, Pinheiro ML. Temporary hearing losses in teenagers

attending repeated rock-and-roll sessions. Acta Otolaryngol 1974;77:51-55.
31. Clark WW, Bohne BA. Temporary hearing losses following attendance at a rock concert. J Acoust Soc Am Suppl 1.1986;79:S48.
33. Danenberg MA, Loos-Cosgrove M, and LoVerde M. Temporary hearing loss and rock music. Lang Speech Hear Serv Schools 1987;18:267-74.
34. Metternich FU, Brusis T. [Acute hearing loss and tinnitus caused by amplified recreational music] Larnygorhinootologie 1999 Nov;78(11):614-9.
35. Bogoch I, House RA, Kudla I. Perceptions about hearing protection and noise-induced hearing loss of attendees of rock concerts. Can J Public Health. 2005 Jan-Feb;96(1):69-72.
36. Chung JH, Des Roches DM, Meunier J, Eavey RD. Evaluation of noise-induced hearing loss in young people using a web-based survey technique. Pediatrics. 2005 Apr;115(4):861-7.
37. Meyer-Bisch C. Epidemiological evaluation of hearing damage related to strongly amplified music (personal cassette players, dicotheques, rock concerts)—high definition audiometric survey on 1364 subjects. Audiology. 1996 May-Jun;35(3):121-42.
38. Hanson DR, Fearn RW. Hearing acuity in young people exposed to pop music and other noise. Lancet. 1975 Aug 2;2(7927):203-5.
39. Weichbold V, Zorowka P. [Effect of information about hearing damage caused by loud music. For adolescents the music in discoteques is too loud despite loudness limits]. HNO. 2002 Jun;50(6):560-4. German.
40. Weichbold V, Zorowka P. Effects of a hearing protection campaign on the discotheque attendance habits of high-school students. Int J Audiol. 2003 Dec;42(8):489-93.
41. Weichbold V, Zorowka P. [Will adolescents visit discotheque less often if sound levels of music are decreased?]. HNO. 2005 Oct;53(10):845-8, 850-1. German.
42. Clark WW, Bohne BA. Effects of noise on hearing. JAMA. 1999 May 5;281(17):1658-9.
43. Lee PC, Senders CW, Gantz BJ, Otto SR. Transient sensorineural hearing loss after overuse of portable headphone cassette radios. Otolaryng Head Neck Surg. 1985;93:625-33.
44. Hellstrom PA, Axelsson A, Costa O. Temporary threshold shift induced by music. Scandinavian Audiology. 1998;48:87-94.
45. Mostafapour SP, Lahargoue K, Gates GA. Noise-induced hearing loss in young adults: the role of personal listening devices and other sources of leisure noise. Laryngoscope 1998 Dec;108(12):1832-9.
46. Turunen-Rise I, Flottop G, Tvete O. Personal cassette players ('Walkman'). Do they cause noise-induced hearing loss? Scand Audiol 1991;20:239-44.
47. Buffe P, Cudennec YF, Ben Azzouz M, Bassoumi T, Ferron JJ. Survey on the harmfulness of listening to music with headphones. Ann Otolaryngol Chir Cervicofac. 1986;103(5):351-5.
48. www.hearnet.com [homepage on the Internet]. San Francisco: Hearing Education and Awareness Rockers, Inc.; c1991-2007 [cited 2007 May 19]. Available from: http://www.hearnet.com/index.shtml
49. Crandell C, Mills TL, Gauthier R. Knowledge, behaviours, and attitudes about hearing loss and hearing protection among racial/ethnically diverse young adults. Journal of The National Medical Association. 2004:96(2):176-86.
50. Kuwano S, Namba S, Florentine M, Zheng D, Hashimoto T. Factor analysis of the timber of noise-comparison of the data obtained in three different laboratories. Proc Acoust Soc Japan. 1992 N92-4-3, 559-60.
51. Calvert DR, Clark WW. The Social Noise Phenomenon: Newsnotes. Central Institute for the Deaf. St. Louis, 1983.
52. Florentine M, Hunter W, Robinson M, Ballou M, Buus S. On the behavoiural characteristics of loud-music listening. Ear Hear. 1998;19(6):420-8.53. Spoor A, Passchier-Vermeer W. Spread in hearing levels of non-noise exposed people at various ages. Int J Audiol. 1969; 8(2):328-36.
54. Folmer RL, Griest SE, Martin WH. Hearing conservation education programs for children: A review. J Sch Health. 2002;72(2):51-7.

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REVIEW ARTICLE

Could there be a fine-tuning role for brain-derived adipokines in the regulation of bodyweight and prevention of obesity?

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ABSTRACT: Obesity is one of the most prevalent medical conditions, often associated with several negative stereotypes. Although it is true that weight gain occurs when food intake exceeds energy expenditure, it is important to note that even a 1% mismatch between the two can lead to a substantial weight gain after only a few years. Further, the body appears to balance energy metabolism via an endogenous lipostatic loop in which adipose stores send hormonal signals (e.g. adipokines such as leptin) to the hypothalamus in order to reduce appetite and increase energy expenditure. However, the brain is also a novel site of expression of many of these adipokine genes. This led to the hypothesis that hypothalamic-derived adipokines might also be involved in bodyweight regulation by exerting some effect on the control of appetite or hypothalamic function. When RNA interference (RNAi) was used to specifically silence adipokine gene expression in various in vitro models, this led to increases in cell death, modification of the expression of key signaling genes (i.e. suppressor of cytokine signaling-3; SOCS-3), and modulation of the activation of cellular energy sensors (i.e. adenosine monophosphate-activated protein kinase; AMPK). Subsequently, when RNAi was used to inhibit the expression of brain-derived leptin in adult rats this resulted in minor increases in weight gain in addition to modifying the expression of other adipokine genes (eg. resistin). In summary, although adipokines secreted by adipose tissue appear to the main regulator of lipostatic loop, this review shows that the fine tuning that is required to maintain a stable bodyweight by this system might be accomplished by hypothalamic-derived adipokines. Perturbations in this central adipokine system could lead to alterations in normal hypothalamic function which leads to unintended weight gain.

I. OBESITY AND INDUSTRIALIZED SOCIETIES

Obesity has reached epidemic proportions making it one of the most common, costliest and deadliest health conditions in industrial societies. Several hypotheses have been put forth to account for the escalating body mass indices (BMI) including overeating and lack of physical activity. However, novel factors also appear to be contributing to this modern day epidemic, including inadequate sleep, increased environmental concentrations of industrial endocrine disrupters, reductions in the number of smokers, to name a few (1). Although it remains clear that a positive energy imbalance exists, where food intake exceeds energy expenditure, it is worth noting that as little as a 1% imbalance can lead to a 1Kg weight gain within one year (2). 10Kg or more than 20 pound of weight gain over a single decade can be caused by mere 25 excessive calories per day. Thus even the most subtle mismatches in energy homeostasis can lead to significant changes in body weight over a relatively short period.

Within the last 15 years, the percentage of obese Canadians has more than doubled, and this trend does not appear to be subsiding (3). The proportion of overweight and obese children is also increasing at a staggering rate in North America (4). It has even been suggested that economically priced super sized car seats are now needed in the United States since nearly 300,000 children under the age of 6 exceed the current

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weight restrictions (5). For the first time in the last two centuries, population lifetime expectancy in the US is predicted to decrease by 0.33 to 0.75 years (6). This is due, in part, to the increased risk of developing diabetes, heart disease, cancer, and other co-morbidities that are associated with carrying excess body weight (6). Furthermore children are now being diagnosed with "adult" diseases such as non insulin-dependent diabetes mellitus (NIDDM). They are also at increased risk of developing cardiovascular diseases at much earlier ages. An estimated 10-20% of new pediatric diabetes patients in Canada are now due to type 2 diabetes (7). In addition to decreased life expectancy, it was estimated that obesity directly cost Canadians over $4.3billion in 2001 (8), a figure likely to be much higher today.

Although diet and exercise are known to be highly effective at inducing weight loss, few individuals successfully maintain these reductions over the long term, suggesting that these interventions alone are an ineffective means to treat obesity (9). Although obesity prevention becomes an important strategy, major investments are needed to target the underlying physiological mechanisms that will favor weight loss and prevent the development of obesity. More importantly, there is a need to identify effective therapies that promote sustainable reductions in bodyweight. One approach is to investigate potential molecular mechanisms that could be used as pharmaceutical targets to reduce bodyweight, in addition to facilitating the maintenance of this weight loss.

There is a large body of evidence suggesting that obesity includes a substantial genetic component (10-12). Early obesity studies lead to the hypothesis that humans developed thrifty genes that offered protection during times of famine and low availability of food sources (13). Combined with improvements in agriculture leading to an abundant and stable food supply, and reduced daily physical activity (14), thrifty genes have rendered us susceptible to gain and store the excessive weight. It has also become evident that not only do we need to consider what genes are present, but how they might be differently expressed due to imprinting and epigenetic modifications that can occur during fetal programming (12). For example, children born during the Dutch hunger winter of WWII are known to have a greater incidence of obesity than others of similar genetic background born just before or after the war and raised in the same environment (15).

One of the major drawbacks to most weight loss strategies is that they fail to consider how bodies defend themselves from losing energy during periods of starvation. An effective weight loss strategy should not only focus on weight loss, but also on the maintenance of a stable bodyweight afterwards. Traditional diet and exercise, despite being effective at reducing bodyweight acutely, often have a refractory period that favors weight gain, restoring body mass to the pre-intervention levels in both rodent and human models (16-18). This suggests that bodies have a preprogrammed weight they try to maintain by adjusting appetite and energy expenditure within the new metabolic milieu. It is also worth noting that experimental subjects resisted weight gain to a certain extent when they were force fed, suggesting that humans are equipped to maintain body mass within a relatively narrow range (19). Although our bodies aim to preserve a stable body mass, there does appear to be a slight bias towards weight gain (20).

2. THE BRAIN AS AN OBESITY TARGET TISSUE

The brain has long been recognized as a key tissue in the development of obesity and diabetes, a target that is sometimes overlooked in contemporary research. The French physiologist Claude Bernard established in 1849 that the brain plays a critical role in the regulation of blood glucose (21). By damaging the brain's fourth ventricle, by way of a "piqure diabetique", he was able to induce diabetes in dogs and others have successfully repeated these experiments in different animal models (22). Studies in the early part of this century revealed that other brain regions, including the hypothalamus, are also critical centers involved in the modulation of peripheral glucose homeostasis (23). Further, when a significant proportion of hypothalamic neurons are damaged , excessive weight gain and the development of diabetes ensued (24,25). It is now widely accepted that there are two key populations of hypothalamic neurons involved in bodyweight regulation; a) the anorexigenic melanocortin neurons which express proopiomelancortin (POMC) and reduce appetite while elevating energy expenditure and b) the orexigenic neurons that express neuropeptide Y (NPY) which have the opposite effects on central energy metabolism (26). Even slight imbalances between the outputs from these neurons can lead to an inappropriate increase in appetite and reduction in energy expenditure which can results in a progressive and significant weight gain over several years (27).

The efficiency and accuracy with which bodyweight is regulated is incredible given the daily variations in activity and food consumption (2,19). Hervey (1969) points out that between the ages of 25 and 65 a women will gain on average only 11Kg; however what is remarkable is that she will consume over 20 tons of food during that period (28). This suggests that our bodies are approximately 99.7% efficient at controlling

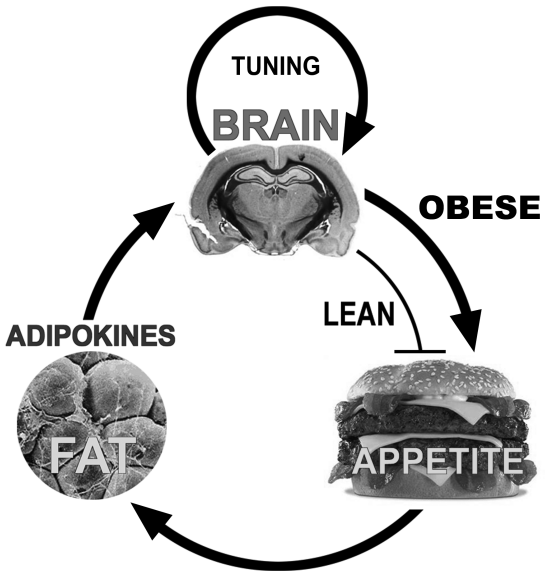

Figure 1: Brain adipokines and a modified lipostatic loop
It has been more than 50 years since Kennedy first proposed the existence of a lipostatic loop in which body fat controls energy metabolism via a hypothalamic-dependent mechanism. It is believed that when adipose tissue mass is increased by consuming an excess of food, leptin is then released into circulation in a proportionate manner so it gain access to the hypothalamus in order to reduce appetite and to promote energy expenditure. However obesity is characterized by a resistance to these peripheral adiposity signals, so normal satiety mechanisms fail to shut off appetite, which leads to further food consumption and a continuous cycle of weight gain. Since brain-derived adipokines appeared to modify key cell signaling (i.e. socs-3) and energy sensing (i.e. AMPK) pathways implicated in central energy metabolism, we hypothesize that centrally expressed adipokines might form a local hypothalamic 'tuning' mechanism which provides the finesse required to precisely match food intake and energy expenditure, which is approximately 99.7% efficient. Thus modifying the expression of hypothalamic-derived adipokines might provide us with a means to increase the brain's sensitivity to peripheral metabolic signals and help restore some of the metabolic mismatch that characterizes obesity.

our weight, as previously calculated by others (29). Although it is now widely accepted that bodyweight regulation involves a coordinated response with the aforementioned hypothalamic neuronal populations (i.e balance between NPY and POMC neuronal output), many hypotheses have been put forth over the years as to which metabolic signals are regulating the activity of these neurons. These hypotheses include: a body temperature-dependent indication of energy stores, a glucostatic system, and the now widely accepted lipostatic theory (30). In the latter model it was thought that increase or decrease in body fat generated changes in unknown adiposity signal(s) that could then modify the activity of the hypothalamic pathways involved in the control of appetite and energy expenditure (Figure 1). This model was validated following the cloning of the anorexigenic hormone leptin from adipose tissue, (31). It is also worth noting that several other peripheral metabolic signals including insulin, ghrelin, polypeptide Y3-36 (PYY3-36), cholecystokinin (CCK), which are produced in a variety of tissues, are also modulating the activity of the aforementioned hypothalamic feeding centers (26,32,33).

3. THE EMERGING ENDOCRINE ROLE OF ADIPOSE TISSUE

The cloning of the ob gene by J.M. Friedman's laboratory, which codes for leptin, is arguably one of the most critical steps that initiated the ongoing study of energy balance and bodyweight regulation (31). When leptin is provided to leptin-deficient mice (ob/ob), or humans, it is capable of inducing a pronounced and sustained weight loss (34,35). Subsequent investigations by several research groups revealed that leptin is but one of a large family of factors secreted by adipocytes (adipokines: (36)). These include resistin (37); adiponectin (38), FIAF (fasting-induced adipose factor)(39); visfatin (40); vaspin (41), and a few unexpected candidates including nerve growth factor (42). Application of mass spectrometry-based proteomic techniques will likely enlarge this list of adipocyte secreted proteins (43,44). Many of these targets have been implicated in the regulation of appetite, energy expenditure, insulin sensitivity, and glycemic control, in addition to several other functions(45,46). Thus adipokines represent a group of obesity-related drug targets that could potentially be harnessed to control bodyweight or treat obesity-related illnesses such as cardiovascular disease and diabetes, but might also impact local adipocyte metabolism via autocrine or paracrine mechanisms.

4. LEPTIN: COMPLETING THE FAT-BRAIN 'LIPOSTATIC' LOOP?

It has been more than fifty years since Kennedy first hypothesized that the brain senses fat stores in order to control food intake, thus forming an 'lipostatic' system which functions to maintain a relatively stable bodyweight (Figure 1) (30). As described above, this model postulated that an unknown adiposity signal was secreted in proportion to body fat stores which acted on the brain in order to regulate appetite and energy expenditure in order to maintain a stable energy balance. It took more than 4 decades in order for an adiposity factor(s) to be identified which could be responsible for influencing the central metabolic pathways. The cloning of the ob gene (leptin) revived the 'lipostatic' hypothesis since its expression directly correlates with the amount of adipose tissue present, i.e. large adipose stores are associated with increased levels of leptin mRNA in ob/ob mice (31) and the degree of adiposity is positively correlated with plasma leptin concentrations (47). Given that the expression and

release of leptin occurs in response to changes in metabolic status (i.e. high or low energy stores augment or reduce leptin levels respectively) (48), and that leptin influences central metabolic pathways (49), it was believed that leptin was the missing energy gauge that acted on the hypothalamus in order to regulate energy metabolism.

Defects in the lipostatic system are likely to contribute to great weight gain. However, it is exceedingly rare to find obese individuals who are totally devoid of leptin. Only a handful of leptin deficient individuals have been identified in the world (34,50), yet obesity rates are soaring. In fact, excess bodyweight has been positively correlated with higher circulating leptin levels in the majority of individuals (51). This suggests that the problem resides with how the brain is receiving and interpreting peripheral metabolic signals, which results in an energy imbalance and the inappropriate stimulation of appetite. In other words the brain in an obese patient fails to appropriately reduce appetite and food seeking behaviors, and does not feel satiety despite having an adequate nutrition (52). Obesity appears to be characterized by a state of resistance to anorexigenic signals, such as leptin. The hypothalamic insensitivity to peripheral adiposity signals has been attributed, in part, to modest increases in the level of signaling molecules such as suppressor of cytokine signaling-3 (SOCS-3)(53,54). SOCS-3 binds to the intracellular domains of leptin and insulin receptors thereby creating a molecular traffic jam which prevents these anorexigenic hormones from stimulating the signaling events which lead to reductions in appetite. Therefore very modest, but chronic, increases in hypothalamic SOCS-3 can lead to an inappropriate increase in hunger and hyperglycemia since the brain is unable to interpret the messages meant to indicate that the body is adequately nourished. Other molecular disrupters of hypothalamic adiposity signaling events have also been identified, including protein tyrosine phosphatase 1B. It has also been proposed that leptin resistance occurs at other sites, such as at the level of the blood brain barrier (BBB). In other words, leptin fails to cross the BBB, therefore is unable to gain access to the hypothalamus, failing to induce any weight lowering effect (55). Obesity appears to be characterized by a central desensitization to peripheral adiposity signals, which are often produced in excess.

5. COULD BRAIN-DERIVED ADIPOKINES BE IMPACTING THE LIPOSTATIC LOOP?

Subsequent studies have shown that leptin is expressed in a variety of tissues, most notably the central nervous system (56). In addition to leptin (57), the brain, pituitary gland and several brain cell line models expresses a variety of adipokines including adiponutrin (58), resistin (59,60) and FIAF (61). This led to the hypothesis that brain-derived adipokines might be serving an autocrine or paracrine role in which they influence the regulation of appetite and impact normal brain function (56). However a major criticism has been that adipokine gene expression in non-adipose tissues, in particular the brain and pituitary, is too low to serve any biological effect (62,63). However, low mRNA abundance does not preclude a functional role for brain-derived adipokines (56). A notable example includes the low level of leptin receptor mRNA detected in some brain areas, even though receptor protein levels are readily detected using immunocytochemistry (64,65). Likewise, despite the low levels of leptin mRNA present in the human hypothalamus, it was shown that there is a net release of leptin from the human brain (66,67). One approach to investigate the role of brain-derived adipokines is to specifically silence their expression and to evaluate the consequences on cell survival, signaling or metabolic pathways. Although advances in molecular biology have provided a variety of techniques that permit the specific manipulation of target gene expression, RNA interference (RNAi) is by far one of the most eminent. This technique has been instrumental in the establishment of gene function in a number of in vitro and in vivo models, most notably in the central nervous system (68-70).

Leptin has been implicated in a variety of brain functions in addition to its role in the control and regulation of appetite. One of the less prominent features of the leptin deficient ob/ob mouse is its reduced brain size and decreased cell number, which could be corrected by leptin treatment (71). Subsequent studies revealed that leptin also possesses trophic properties that impact the hard wiring of the hypothalamus during a critical neonatal period (72). Hypothalamic neuronal plasticity is also affected since leptin administration rapidly modified critical synaptic connections implicated in the control of appetite (73). Leptin gene expression was found to be developmentally regulated in the rat brain and pituitary gland (74). Leptin gene expression could also be induced in the rat brain following traumatic brain injury (TBI) (75). Subsequently, when RNAi was used to specifically silence leptin gene expression in rat C6 glioblastoma cell line, a model previously validated (76), the result was a significant 2-fold increase in cell death as detected using either TUNEL ($P < 0.005$) or ethidium homodimer-1 ($P < 0.015$) staining (77). This was also consistent with anti-apoptotic pathways that were induced by leptin treatment in the human SH-SY5Y neuroblastoma cell line (78). Together these

results suggest that centrally-derived leptin might be involved in normal brain function in addition to impacting the development of the central nervous system (CNS), neuronal plasticity and wiring, or even brain repair following injury.

To further investigate the novel interaction between brain adipokines, RNAi studies on resistin and fiaf, adipokines implicated in glucose and lipid metabolism (37,39), were carried out in the novel N-1 hypothalamic neuronal cell line (79). These cells were chosen since they were derived from the embryonic mouse hypothalamus and express a range of neuropeptides involved in normal hypothalamic function and metabolism. Although fiaf expression was significantly reduced using a chemically modified small interfering RNA (siRNA), this failed to significantly modify the expression of other genes being analysed (60). In marked contrast, the RNAi-mediated silencing of rstn induced significant increases (>50%) in both fiaf and suppressor of cytokine signaling-3 (socs-3) when N-1 cells were cultured in serum-deprived medium (60). Likewise, resistin knockdown also reduced the ratio of phosphorylated total adenosine monophosphate-activated protein kinase (AMPK) (80), a novel energy sensor implicated in the hypothalamic control of appetite and hepatic gluconeogenesis (81-83). Additionally the effects on fiaf and socs-3 expression, or changes in AMPK activation, were reversed when N-1 cells were treated with resistin, or transfected with a resistin-expressing plasmid (60). Thus brain-derived adipokines appear capable of regulating metabolic signaling events (e.g. socs-3) and cellular energy metabolism (e.g. AMPK) which might have significant consequences on the central regulation of appetite and energy expenditure.

Preliminary in vivo studies also confirmed that RNAi was an effective means to acutely block the nutritionally-mediated induction of brain-derived leptin in the adult male rat. The intracerebroventricular (icv) injection of a leptin-specific siRNA molecule into the dorsal 3rd ventricle (D3V) of fasted rats, as done by others for brain-derived neurotrophic factor (BDNF) (84), attenuated the feeding-induced increase in hypothalamic leptin mRNA by more than 75% ($p<0.01$). This acute knockdown (24h) resulted in a slightly greater overnight weight gain (+15%, $p<0.05$), relative to rats that received the non-specific control molecule. Similarly the continuous infusion of the 'naked' leptin-specific siRNA into the LV resulted in a modest, but non-significant, reduction of leptin mRNA (-30%) in the cortex and hypothalamus. Although no increases in body weight were detected in the rats that were continuously infused with the leptin-specific siRNA, this could be due to the poor leptin knockdown achieved. However leptin knockdown reduced the expression of cortical resistin (-35%, $p<0.05$), but paradoxically increased hypothalamic resistin by 2-fold ($p<0.05$), as measured by realtime RT-PCR. Thus brain-derived leptin appears to regulate the expression of other centrally derived adipokines, although these effects appear dependent on the cell-type or brain region being analyzed. An important technical goal remains to improve the magnitude and length of silencing achieved under basal conditions in vivo as this greater reduction in brain leptin expression might induce a more pronounced phenotype.

6. BRAIN ADIPOKINES AND AN ENDOGENOUS METABOLIC TUNING MECHANISM

These preliminary studies suggest that brain-derived adipokines are capable of influencing brain cell survival (e.g. leptin and C6), signaling (e.g. N-1 and socs-3), or metabolic sensing (e.g. N-1 and AMPK). In addition there appears to be a complex interrelationship between centrally-derived adipokines both in vitro and in vivo. Further studies are now needed to investigate the effects of silencing brain-derived adipokines during critical developmental periods, which might impact normal brain development and function. Although adipose tissue appears to provide the hypothalamus with the bulk of the peripheral metabolic signals that act as gross indicators of energy availability (26,32,85,86), it is uncertain whether these signals alone can provide the hypothalamus with the finesse that is required to delicately and efficiently control bodyweight (2,28). Perhaps the crosstalk that appears to be occurring between centrally-derived adipokines in vivo (e.g. leptin and resistin) could form a fine-tuning mechanism that contributes to the precise and accurate regulation of hypothalamic metabolic pathways via autocrine or paracrine mechanisms (Figure 1). Thus in the context of the lipostatic loop model, minor disruptions in hypothalamic adipokine gene expression appear capable of impacting the efficiency of this tightly regulated system. Slight perturbations in this hypothetical central adipokine system might lead to a metabolic mismatch that increases the risk of gaining weight or developing insulin resistance by impacting the hypothalamic sensitivity and receptivity to peripheral adiposity signals. As such, adjusting this central system might allow us to improve the efficiency of this lipostatic loop, and might even prove to be a means to promote weight loss and help change the bodyweight set point in obese individuals.

7. CONCLUSION

Obesity is a complex and often poorly understood medical condition that results in unnecessary

psychological and physical suffering. Despite the negative stereotypes associated with the obese, it is important to recognize that deeper physiological and genetic mechanisms might also contribute to excessive adiposity (10-12). It is worth considering how even the most minor of imbalances between food intake and energy expenditure can lead to a significant and unintended weight gain over only a few years (2,28), and this metabolic mismatch has only been further exacerbated in recent years by the over abundance of highly palatable foods that are readily available on a daily basis (14). Although we do not refute that diet and exercise can promote weight loss, we can not ignore the poor outcome of these programs in the long term (9,16-18). Therefore, it is necessary to investigate other avenues, such as the role of brain-derived adipokine in normal body weight regulation and energy metabolism which might prove useful to promote weight loss. However given the complexity and redundancy of the endogenous mechanisms that are in place to maintain bodyweight, it seems likely that multiple approaches will be required to effectively treat obesity.

ACKNOWLEDGMENTS

The studies in our laboratory were made possible by financial support from the NSHRF, the IWK Health Centre, the Atlee Endowment, UIMRF and Capital Health. RB was the recipient of a NSHRF Graduate Studentship. I am indebted to Dr D.D. Belsham (University of Toronto) for the generous gift of N-1 hypothalamic neurons, and to Drs. Imran, Ur and Wilkinson for their support. D.Wilkinson and P.Wilkinson provided invaluable support and technical assistance.

REFERENCES

1 Keith SW, Redden DT, et al. Putative contributors to the secular increase in obesity: Exploring the roads less traveled. Int J Obes 2006;30:1585-1594.
2 Bray GA. Good calories, bad calories by gary taubes; new york: Aa knopf. Obes Rev 2008
3 Katzmarzyk PT. The Canadian obesity epidemic, 1985-1998. CMAJ. 2002;166:1039-1040.
4 Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol 2006;35:93-99.
5 Trifiletti LB, Shields W, Bishai D, McDonald E, Reynaud F, Gielen A. Tipping the scales: Obese children and child safety seats. Pediatrics 2006;117:1197-1202.
6 Olshansky SJ, Passaro DJ,et al. A potential decline in life expectancy in the united states in the 21st century. N Engl J Med 2005;352:1138-1145.
7 Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005;146:693-700.
8 Katzmarzyk PT, Janssen I. The economic costs associated with physical inactivity and obesity in canada. An update. Can J Appl Physiol 2004;29:90-115.
9 Jeffery RW, Drewnowski A, Epstein LH, Stunkard AJ, Wilson GT, Wing RR, Hill DR. Long-term maintenance of weight loss: Current status. Health Psychol 2000;19:5-16.
10 Friedman JM, Leibel RL. Tackling a weighty problem. Cell 1992;69:217-220.
11 Blundell JE. Appetite disturbance and the problems of overweight. Drugs 1990;39 Suppl 3:1-19.
12 Stoger R. The thrifty epigenotype: An acquired and heritable predisposition for obesity and diabetes? Bioessays 2008;30:156-166.
13 Neel JV. Diabetes mellitus: A "Thrifty" Genotype rendered detrimental by "Progress"? Am J Hum Genet 1962;14:353-362.
14 Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: Where do we go from here? Science 2003;299:853-855.
15 Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349-353.
16 Kramer FM, Jeffery RW, Forster JL, Snell MK. Long-term follow-up of behavioral treatment for obesity: Patterns of weight regain among men and women. Int J Obes 1989;13:123-136.
17 Levin BE, Dunn-Meynell AA. Defense of body weight against chronic caloric restriction in obesity-prone and -resistant rats. Am J Physiol Regul Integr Comp Physiol 2000;278:R231-237.
18 Levin BE, Keesey RE. Defense of differing body weight set points in diet-induced obese and resistant rats. Am J Physiol 1998;274:R412-419.
19 Sims EA, Horton ES. Endocrine and metabolic adaptation to obesity and starvation. Am J Clin Nutr 1968;21:1455-1470.
20 Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis system inherently biased toward weight gain? Diabetes 2003;52:232-238.
21 Bernard C. Leçons de physiologie experimentale appliqués á là medecine. Paris, Baillere et Fils, 1854.
22 Feldberg W, Pyke D, Stubbs WA. Hyperglycaemia: Imitating claude bernard's piqure with drugs. J Auton Nerv Syst 1985;14:213-228.
23 Donhoffer C, MacLeod JJR. Studies in the nervous control of carbohydrate metabolism. I.--the position of the centre. Proc R Soc Lond B Biol Sci 1932;110:125-141.
24 Pizzi WJ, Barnhart JE. Effects of monosodium glutamate on somatic development, obesity and activity in the mouse. Pharmacol Biochem Behav 1976;5:551-557.
25 Cameron DP, Poon TK, Smith GC. Effects of monosodium glutamate administration in the neonatal period on the diabetic syndrome in kk mice. Diabetologia 1976;12:621-626.
26 Schwartz MW, Porte D, Jr.. Diabetes, obesity, and the brain. Science 2005;307:375-379.
27 Lee M, Korner J. Review of physiology, clinical manifestations, and management of hypothalamic obesity in humans. Pituitary 2008
28 Hervey GR. Regulation of energy balance. Nature 1969;222:629-631.
29 Harris RB. Role of set-point theory in regulation of body weight. Faseb J 1990;4:3310-3318.
30 Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc Lond B Biol Sci 1953;140:578-596.
31 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425-432.
32 Badman MK, Flier JS. The gut and energy balance: Visceral allies in the obesity wars. Science 2005;307:1909-1914.
33 Fry M, Hoyda TD, Ferguson AV. Making sense of it: Roles of the sensory circumventricular organs in feeding and regulation

of energy homeostasis. Exp Biol Med (Maywood) 2007;232:14-26.
34 Montague CT, Farooqi IS, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-908.
35 Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543-546.
36 Trayhurn P, Bing C, Wood IS. Adipose tissue and adipokines--energy regulation from the human perspective. J Nutr 2006;136:1935S-1939S.
37 Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature 2001;409:307-312.
38 Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to c1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-26749.
39 Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, Gonzalez FJ, Desvergne B, Wahli W. Characterization of the fasting-induced adipose factor fiaf, a novel peroxisome proliferator-activated receptor target gene. J Biol Chem 2000;275:28488-28493.
40 Fukuhara A, Matsuda M, et al. Visfatin. A protein secreted by visceral fat that mimics the effects of insulin. Science 2005;307:426-430.
41 Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, Shikata K, Hourai S, Futami J, Watanabe E, Matsuki Y, Hiramatsu R, Akagi S, Makino H, Kanwar YS. Visceral adipose tissue-derived serine protease inhibitor: A unique insulin-sensitizing adipocytokine in obesity. Proc Natl Acad Sci U S A 2005;102.10610-10615.
42 Bullo M, Peeraully MR, Trayhurn P: Stimulation of ngf expression and secretion in 3t3-l1 adipocytes by prostaglandins pgd2, pgj2, and delta12-pgj2. Am J Physiol Endocrinol Metab 2005;289.E62-67.
43 Kratchmarova I, Kalume DE, Blagoev B, Scherer PE, Podtelejnikov AV, Molina H, Bickel PE, Andersen JS, Fernandez MM, Bunkenborg J, Roepstorff P, Kristiansen K, Lodish HF, Mann M, Pandey A. A proteomic approach for identification of secreted proteins during the differentiation of 3t3-l1 preadipocytes to adipocytes. Mol Cell Proteomics 2002;1:213-222.
44 Yang YS, Song HD, Li RY, Zhou LB, Zhu ZD, Hu RM, Han ZG, Chen JL. The gene expression profiling of human visceral adipose tissue and its secretory functions. Biochem Biophys Res Commun 2003;300:839-846.
45 Ahima RS. Adipose tissue as an endocrine organ. Obesity (Silver Spring) 2006;14 Suppl 5:242S-249S.
46 Ahima RS, Lazar MA. Adipokines and the peripheral and neural control of energy balance. Mol Endocrinol 2008;22:1023-1031.
47 Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte D, Jr.. Cerebrospinal fluid leptin levels: Relationship to plasma levels and to adiposity in humans. Nat Med 1996;2:589-593.
48 Becker DJ, Ongemba LN, Brichard V, Henquin JC, Brichard SM. Diet- and diabetes-induced changes of ob gene expression in rat adipose tissue. FEBS Lett 1995;371:324-328.
49 Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse ob protein: Evidence for a peripheral signal linking adiposity and central neural networks. Science 1995;269:546-549.
50 Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, O'Kirwan F, Whitby R, Liang L, Cohen P, Bhasin S, Krauss RM, Veldhuis JD, Wagner AJ, DePaoli AM, McCann SM, Wong ML. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Natl Acad Sci U S A 2004;101:4531-4536.
51 Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: Evidence for diet-induced resistance to leptin action. Nat Med 1995;1:1311-1314.
52 Jackson MB, Ahima RS. Neuroendocrine and metabolic effects of adipocyte-derived hormones. Clin Sci (Lond) 2006;110:143-152.
53 Bjorbaek C, El-Haschimi K, Frantz JD, Flier JS. The role of socs-3 in leptin signaling and leptin resistance. J Biol Chem 1999;274:30059-30065.
54 Munzberg H, Myers MG, Jr.. Molecular and anatomical determinants of central leptin resistance. Nat Neurosci 2005;8:566-570.
55 Banks WA, Farrell CL. Impaired transport of leptin across the blood-brain barrier in obesity is acquired and reversible. Am J Physiol Endocrinol Metab 2003;285:E10-15.
56 Wilkinson M, Brown R, Imran SA, Ur E: Adipokine gene expression in brain and pituitary gland. Neuroendocrinology 2007;86:191-209.
57 Morash B, Li A, Murphy PR, Wilkinson M, Ur E. Leptin gene expression in the brain and pituitary gland. Endocrinology 1999;140:5995-5998.
58 Wiesner G, Morash BA, Ur E, Wilkinson M. Food restriction regulates adipose-specific cytokines in pituitary gland but not in hypothalamus. J Endocrinol 2004;180:R1-6.
59 Morash BA, Wilkinson D, Ur E, Wilkinson M. Resistin expression and regulation in mouse pituitary. FEBS Lett 2002;526:26-30.
60 Brown R, Imran SA, Belsham DD, Ur E, Wilkinson M. Adipokine gene expression in a novel hypothalamic neuronal cell line: Resistin-dependent regulation of fasting-induced adipose factor and socs-3. Neuroendocrinology 2007;85:232-241.
61 Wiesner G, Brown RE, Robertson GS, Imran SA, Ur E, Wilkinson M. Increased expression of the adipokine genes resistin and fasting-induced adipose factor in hypoxic/ischaemic mouse brain. Neuroreport 2006;17:1195-1198.
62 Steppan CM, Lazar MA: The current biology of resistin. J Intern Med 2004;255:439-447.
63 Sahu A. Leptin signaling in the hypothalamus: Emphasis on energy homeostasis and leptin resistance. Front Neuroendocrinol 2003;24:225-253.
64 Elmquist JK, Bjorbaek C, Ahima RS, Flier JS, Saper CB. Distributions of leptin receptor mrna isoforms in the rat brain. J Comp Neurol 1998;395:535-547.
65 Hakansson ML, Brown H, Ghilardi N, Skoda RC, Meister B. Leptin receptor immunoreactivity in chemically defined target neurons of the hypothalamus. J Neurosci 1998;18:559-572.
66 Wiesner G, Vaz M, Collier G, Seals D, Kaye D, Jennings G, Lambert G, Wilkinson D, Esler M. Leptin is released from the human brain: Influence of adiposity and gender. J Clin Endocrinol Metab 1999;84:2270-2274.
67 Eikelis N, Esler M, Barton D, Dawood T, Wiesner G, Lambert G. Reduced brain leptin in patients with major depressive disorder and in suicide victims. Mol Psychiatry 2006;11:800-801.
68 Thakker DR, Hoyer D, Cryan JF. Interfering with the brain: Use of rna interference for understanding the pathophysiology of psychiatric and neurological disorders. Pharmacol Ther 2006;109:413-438.
69 Gan L, Anton KE, Masterson BA, Vincent VA, Ye S, Gonzalez-Zulueta M. Specific interference with gene expression and gene function mediated by long dsrna in neural cells. J Neurosci Methods 2002;121:151-157.
70 Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded

rna in caenorhabditis elegans. Nature 1998;391:806-811.
71 Steppan CM, Swick AG. A role for leptin in brain development. Biochem Biophys Res Commun 1999;256:600-602.
72 Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004;304:108-110.
73 Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, Horvath TL. Rapid rewiring of arcuate nucleus feeding circuits by leptin. Science 2004;304:110-115.
74 Morash B, Wilkinson D, Murphy P, Ur E, Wilkinson M. Developmental regulation of leptin gene expression in rat brain and pituitary. Mol Cell Endocrinol 2001;185:151-159.
75 Brown R, Thompson HJ, Imran SA, Ur E, Wilkinson M. Traumatic brain injury induces adipokine gene expression in rat brain. Neurosci Lett 2008;432:73-78.
76 Morash B, Johnstone J, Leopold C, Li A, Murphy P, Ur E, Wilkinson M. The regulation of leptin gene expression in the c6 glioblastoma cell line. Mol Cell Endocrinol 2000;165:97-105.
77 Brown R, Morash B, Ur E, Wilkinson M. Rnai-mediated silencing of leptin gene expression increases cell death in c6 glioblastoma cells. Brain Res Mol Brain Res 2005;139:357-360.
78 Russo VC, Metaxas S, Kobayashi K, Harris M, Werther GA. Antiapoptotic effects of leptin in human neuroblastoma cells. Endocrinology 2004;145:4103-4112.
79 Belsham DD, Cai F, Cui H, Smukler SR, Salapatek AM, Shkreta L. Generation of a phenotypic array of hypothalamic neuronal cell models to study complex neuroendocrine disorders. Endocrinology 2004;145:393-400.
80 Brown R, Wilkinson P, Imran SA, Ur E, Wilkinson M. Resistin activates amp-activated protein kinase in a novel hypothalamic neuronal cell line: Implications for central energy metabolism. Endocrine abstracts 2008
81 Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foufelle F, Ferre P, Birnbaum MJ, Stuck BJ, Kahn BB. Amp-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 2004;428:569-574.
82 McCrimmon RJ, Fan X, Cheng H, McNay E, Chan O, Shaw M, Ding Y, Zhu W, Sherwin RS. Activation of amp-activated protein kinase within the ventromedial hypothalamus amplifies counterregulatory hormone responses in rats with defective counterregulation. Diabetes 2006;55:1755-1760.
83 Kahn BB, Alquier T, Carling D, Hardie DG. Amp-activated protein kinase: Ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab 2005;1:15-25.
84 Baker-Herman TL, Fuller DD, Bavis RW, Zabka AG, Golder FJ, Doperalski NJ, Johnson RA, Watters JJ, Mitchell GS. Bdnf is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. Nat Neurosci 2004;7:48-55.
85 Ahima RS. Central actions of adipocyte hormones. Trends Endocrinol Metab 2005;16:307-313.
86 Ahima RS, Qi Y, Singhal NS. Adipokines that link obesity and diabetes to the hypothalamus. Prog Brain Res 2006;153:155-174.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

AN INVITATION TO THE MEDICAL STUDENTS OF THE WORLD TO JOIN THE GLOBAL COALITION TO IMPROVE CARE FOR CHILDREN AND ADULTS WITH CONGENITAL HEART DISEASE ACROSS THE WORLD

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INTRODUCTION

Medical schools teach their students about anatomy, histology, cell biology, genetics, embryology, physiology, biochemistry, pathophysiology, pharmacology, and other subdivisions of the medical knowledge and know-how. Despite acquiring this complex science and having the opportunity to interact with patients in the clinical setting, very rarely do medical students gather a global understanding of what impact a disease represents on a personal, societal and global level. Congenital heart disease (CHD) is a condition that is present in approximately 1 in 100 births, has a remarkable heterogeneity and complexity and has a significant impact on the child's survival and quality of life if left untreated. Even when the initial congenital defect is successfully repaired, patients with CHD require a lifelong follow-up and the possibility of subsequent reinterventions. Physicians are involved from the beginning to the end with the diagnosis, counselling, every step of the treatment and the lifelong follow-up. The treatment of CHD requires an enormous effort, resources and the participation of a huge team made up of a multitude of highly trained medical specialists, such as cardiac surgeons, cardiologists, cardiac anaesthetists, cardiac intensivists and many others, who often have dedicated their entire professional lives to this exciting field of medicine.

Far from claiming to be a thorough and exhaustive exposé on CHD, this article rather aims to present to medical students from everywhere in the world an overview of the nature of this important disease and of its global impact. We will provide a definition of CHD, highlight a few examples, give a summary of its epidemiology, and finally summarize the history of the study and treatment modalities. Our focus will also be on the inequalities in the treatment of CHD between the western world and developing nations. Finally, the challenges that must be addressed to truly improve care around the world will be presented.

DEFINITION OF CONGENITAL HEART DISEASE

What is congenital heart disease? Simply put, one could say that it is a developmental malformation of the heart started during fetal development and present at birth, which results in abnormal anatomy and physiology of the heart, has a profound deleterious impact on the other organs and structures of the body and adversely affects the health of the child. Embryologically, it results from a multitude of factors,

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most of them unknown, which lead to abnormalities in the in-utero development of the fetal heart. Anatomically, CHD comprises a huge number of cardiac malformations from the simplest to the most complex, characterized by extreme heterogeneity, which alter the normal and optimal structure and function of the heart and of other organs in the body.

Every part of the heart and great vessels can be involved and malformed. The atria, ventricles, the great vessels, the atrioventricular and semilunar valves, and the coronary arteries can be affected to various degrees depending on the specific heart malformation present.

The many deleterious consequences affecting other organs further complicate CHD. As a whole, CHD can be present in many forms and across the entire age spectrum; from the blue newborn baby with profound cyanosis due to transposition of the great arteries to the old adult with progressive fatigue due to a previously undiagnosed atrial septal defect coming to medical attention with overt heart failure. Although considered by many a rare disease, CHD is the most common congenital illness and presents a significant burden to the children of this world and to mankind.

CHILDREN OF THE WORLD AFFECTED BY CONGENITAL HEART DISEASE

Globally, approximately 130 million babies are born every year. It is said that CHD affects approximately 0.8% of all live births. Simple calculations indicate that approximately 1 million babies are born each year with CHD and 90% of those newborns see the world in areas of the globe where access to appropriate medical care is either difficult or impossible. One can estimate that of the 280 000 babies who die each year from a congenital cardiac anomaly in the neonatal period, more than 250 000 are not offered the care that has been available over the past half-century and that has allowed cardiac surgeons and cardiologists from around the world to save countless lives, very often with fairly simple measures [1].

Listing every congenital lesion affecting the human heart is far beyond the scope of this paper. However, it is interesting to briefly ponder upon the natural history of some of those malformations to understand adequately their significance. The progression and severity of the disease is specific to every lesion and present in a wide spectrum. For example, individuals with large atrial septal defects face a risk of mortality of 5-15% before the age of 30 years. Similarly, the presence of a patent ductus arteriosus is associated with a 30% risk of mortality before the age of one year and a 42% risk of death before 45 years of age. Of all the individuals born with tetralogy of Fallot with pulmonary stenosis, 25% will die within their first year of life if left untreated. 40%, 70%, and 95% will be dead, respectively, by the age of 3, 10, and 40 years. Looking at more complex pathologies, transposition of the great arteries is associated, all varieties considered, with a 45%, 85%, and 90% mortality at one month, 6 months and one year respectively. Finally, hypoplastic left heart syndrome, which is the fourth most common congenital cardiac defect, results in the mortality of most neonates within one to two weeks of birth and survival beyond 6 weeks of age is unusual [2].

CHD is a major burden to the children of this world. However, despite being rather revealing, the mortality rates stated above do not give an accurate rendering of the misery children and young adults with CHD face. Indeed, the morbidity ensuing from unrepaired CHD is difficult to truly gauge and quantify but is immensely important. Therefore, one must consider with equal magnitude the decreased quality of life faced by those individuals. Suffering from frequent pulmonary infections, a high risk of bacterial endocarditis, chronic cyanosis, the risk of neurological events and decreased functional status, the existence of a child surviving with unrepaired CHD is far from normal and optimal.

HISTORY OF DIAGNOSIS AND TREATMENT OF CONGENITAL HEART DISEASE

In 1936, Dr. Maude Abbott (1869-1940), of McGill University in Montreal, published her famous Atlas of congenital cardiac disease. This work, proposing the first classification system for CHD, was based on her lifelong study of the clinical and post-mortem records of more than 1000 cases of cardiac malformations. The Atlas rapidly became the main international reference in CHD and Maude Abbott has since been considered the founder of the systematic study of CHD [3]. The development of the study of congenital cardiac disease quickly flourished thereafter. Maverick surgeons now remembered for their great sense of innovation paved the way to the successful treatment of CHD. An important milestone in the treatment of CHD was the development of a palliative operation to alleviate the profound cyanosis in patients with tetralogy of Fallot. This was the result of a historic collaboration between Alfred Blalock, Helen Taussig and Vivien Thomas, with the advent of the systemic pulmonary shunt bearing their name. However, the single most important step in the treatment of CHD was the invention of the heart-lung machine by John Gibbon Jr of Jefferson Medical College in Philadelphia who spent 20 year working on its development and was the first to use it successfully in a human in 1953. Subsequently, with the pioneering efforts of physicians and surgeons it soon became

possible to repair even complex cardiac malformations and consequently impact on the life of millions of children. Steady progress in diagnostic modalities, in surgical techniques, in establishment of new procedures, as well as improvement in preoperative care, intra-operative anaesthesia and perfusion management and intensive post-operative care have resulted in significant reduction in mortality and morbidity. Major improvement in early and late survival for CHD also ensued. Complex malformations such as transposition of the great arteries, tetralogy of Fallot, and hypoplastic left heart syndrome can now be treated with real optimism for the future lives of the afflicted children. However, much work needs to be done with the rapidly increasing number of adults with CHD and the realization of the long-term problems in many of the "repaired" CHD patients.

CURRENT STATUS IN TREATMENT FOR CONGENITAL HEART DISEASE

While we have some information regarding the status of congenital cardiac care in North America and the rest of the western world, little is known about the precise situation in the remainder of the globe.

Indeed, data published in 2005 by Jacobs and al. in the Report of the 2005 Society of Thoracic Surgeons Congenital Heart Surgery Practice and Manpower Survey gives a good picture of the state of our specialty in North America. At the time of the survey, there were 248 congenital cardiac surgeons in the United States of America and 15 in Canada. Each group is respectively distributed amongst 121 and 8 surgical centres. The average age of a congenital cardiac surgeon in North America is 48.3 years and, on average, surgeons have 9.2 years of post-graduate training. Only 4% of all congenital cardiac surgeons in North America are females. Based on those numbers, there is approximately one congenital cardiac surgeon per 1.5-2 millions population [4].

This information is available concerning North America, but data is scarce regarding the rest of the world. To palliate to this situation, the World Society for Pediatric and Congenital Heart Surgery (www.wspchs.org) embarked on a fact-finding mission in 2007. Preliminary results from the survey conducted confirm an important inconsistency between the various regions of the world. While western countries enjoy a proportion of approximately 1 congenital cardiac surgeon per 1.5-2 million inhabitants, our survey shows very different ratios in South America, Asia, and Africa; respectively 1 : 6 million, 1 : 25 million, and 1 : 38 million. Quick calculations, which are obviously limited by their inaccuracy and the imprecise nature of the data from which they are based on, indicate that the developing world is in need of approximately 1 000 to 1 500 additional congenital cardiac surgeons. This is a gross estimate which is, nonetheless, very revealing.

The data currently being gathered by the World Society is showing that the patterns of practice are otherwise quite similar on the five continents. Indeed, the average age, the proportions of males and females, and the duration of post-graduate training of congenital cardiac surgeons are quite comparable across the board. However, the funding sources of congenital cardiac surgery programs vary. In the United States, for example, most units are privately funded. However, in the rest of the world, it appears that government sources are the main financial supporters of congenital cardiac surgery centers. This information is incomplete and the World Society is planning to pursue its fact-finding effort in this regard.

The most important component of the treatment of CHD is teamwork. The concerted input of many specialists, i.e. surgeons, cardiologists, intensivists, anesthesiologists, perfusionists, nurses is needed. Although in a congenital cardiac surgery program the surgeon often assumes a leadership role, the collaboration of all is essential to its success. Indeed, the necessary diagnostic modalities, such as echocardiography, angiography, computerized tomography, or magnetic resonance imaging are often difficult to evaluate and require the analytical and judgment skills of specifically trained physicians. The same is true for the intra-operative management of the patients. Indeed, cardiac anesthesiologists and perfusionists with specialized training in the care of children with congenital cardiac disease carry the utmost importance. This concept carries over to the intensive care unit with the post-operative care of the patients. The treatment of CHD is very complex and necessitates the work of many highly skilled individuals, a high level of organization and logistics and appropriate financial support

CHALLENGES TO IMPROVEMENT OF CARDIAC CARE FOR CONGENITAL HEART DISEASE ACROSS THE WORLD

For an obvious reason of lack of resources, the development of pediatric and congenital heart surgery around the world has been late, slow and erratic in most developing countries. Competing priorities, poor structural organizations, lack of financial resources, lack of trained personnel and absence of stable training and educational infrastructure are among the many reasons for this unfortunate situation. While some countries have succeeded in developing surgical programs to treat CHD, most children born with a cardiac malformation still do not have access to

appropriate medical and surgical care.

To palliate to this complete or relative absence of access to cardiac surgical care in many countries, different projects have emerged. This help takes many forms and it is safe to say that the perfect model does not exist yet. Most of this work is funded by charitable organizations and helps children with CHD on a small scale. Some groups bring children in need to North America or Europe so that they can undergo surgery and then return to their country of origin. This has been largely inefficient due to the great cost and effort required and has only helped very few children. Humanitarian surgical missions consisting of cardiac surgeons, cardiologists, intensivists, anesthesiologists, perfusionists, and nurses visit countries for a few weeks at a time with the goals to operate children in need of surgery as well as to form surgical teams and hopefully launch congenital cardiac surgery programs which can flourish and progress in a sustainable fashion. Finally, some areas have seen the establishment of cardiac centres after the local training of their healthcare professionals or their return from instruction abroad. Surgeons, cardiologists, anaesthesiologists, intensivists and other professionals trained internationally infinitely enrich their countries upon their return. However, a serious problem is the lack of retention due to the poor local infrastructure and critical mass of health care professionals, which further exacerbates the vicious circle. By and large these efforts have so far had a minimal impact in the numbers of children treated compared to the overall needs.

All the efforts described above have to be concerted and the various groups interested in globally improving congenital cardiac care around the world have to meet and organize themselves to reach their goal in a sustainable fashion. The World Society for Pediatric and Congenital Heart Surgery aims to provide this forum. It is of paramount importance to identify the most profitable, practical, and cost-efficient way to help the children of the world with CHD.

Indeed, while we do intensive research and strive to decrease our mortality rates by fractions of percentage points in the western world, the vast majority of children born with CHD still have an unacceptably high risk of mortality. The progress of the last decades has been largely limited to the developed world. Consequently, every year approximately 90 % of more than 1 000 000 children born with CHD across the world receive either suboptimal care or are totally denied care.

Although CHD has not been on the radar screen of most global health agencies and humanitarian organizations so far and since there has been little focus on the global epidemiology of pediatric and congenital cardiac disease, considerable work remains to be done if one is to try to significantly improve cardiac care around the globe.

WORLD SOCIETY FOR PEDIATRIC AND CONGENITAL HEART SURGERY: LEADING THE WAY IN A NEW PARADIGM SHIFT FOR THE GLOBAL IMPROVEMENT OF CARE

The idea for a global organization was first discussed in 2004 in Montreal during an international meeting of pediatric and congenital heart surgeons scheduled during the Centennial Celebrations of the Montreal Children's Hospital under the leadership of Christo I. Tchervenkov, Professor of Surgery at McGill University. The World Society for Pediatric and Congenital Heart Surgery was then established in 2006.

During his Presidential Address at the Inaugural Meeting of Washington DC in May 2007, the World Society President, Christo I. Tchervenkov from Montreal, Canada, presented his vision for the role of the World Society and talked about the key elements for the global improvement of care. President Tchervenkov coined the phrase "Medicine of RESPECT" or "Medicine of Responsible Education Sustained through Partnership, Empowerment, Care and Commitment, and Teamwork and Trust" as the basis of the necessary paradigm shift required for the global improvement of care in the 21st century [5].

The World Society for Pediatric and Congenital Heart Surgery is in an exceptional position to truly improve care for pediatric and congenital cardiac disease across the world. Being the largest society for pediatric and congenital heart surgery in the world with more than 500 members from close to 70 countries, its potential for playing a defining role in the global improvement of care is significant. The vision of the World Society is that every child born anywhere in the world with a congenital heart defect should have access to appropriate medical and surgical care. Its mission is to promote the highest quality comprehensive cardiac care to all patients with pediatric and/or congenital heart disease, from the fetus to the adult, regardless of the patient's economic means, with an emphasis on excellence in education, research and community service. The vision and mission of the World Society are being pursued by working towards clearly defined objectives in the following domains: patient care, training and education, research, and community service. In the area of patient care, the World Society hopes to promote the professional and educational development of surgeons specializing and practicing pediatric and congenital heart surgery across the world, as well as the dissemination of informational support to patients, parents of patients, families of patients, and

health care professionals, working in collaboration with societies such as the International Society for Nomenclature of Pediatric and Congenital Heart Disease. It also wants to develop global standards for the training and education of pediatric and congenital heart surgeons and for the practice of pediatric and congenital heart surgery. Finally, its members originating from all areas of the globe will form a forum for the respectful exchange of knowledge in the form of scientific meetings and publications across the world

Finally, and maybe most importantly, the World Society aims to foster collaboration across medical and surgical subspecialties and is working toward the establishment of a multi-societal Global Organization for Pediatric and Congenital Heart Disease. This Organization has seen birth in June 2008, in Montreal, with the proclamation of a resolution for its establishment at the World Summit on Pediatric and Congenital Heart Surgery Services, Education and Cardiac Care in Children and Adults with Congenital Heart Disease taking place in Montreal from June 19-22, 2008. Composed of multiple professional associations of surgeons, cardiologists, intensivists, anaesthesiologists, nurses, and perfusionists, this Global Organization will be the cornerstone of the large-scale improvement of congenital cardiac care around the world.

CONCLUSION

It is our hope that this article will give a good overview of the nature of CHD, of its global impact and of the challenges that inevitably need to be addressed in order to truly impact on the future on innumerable children around the world. Every speciality concerned by CHD need to be empowered and embark on this journey to globally improve our services to children of countless developing countries.

Congenital cardiac surgery has evolved enormously over the last 60 years since the pioneering work of Abbott, Blalock, Taussig, Gibbons, Lillehei, Kirklin, Castaneda and others. It has matured to a point where it enjoys unprecedented successes with results barely conceivable only a few decades ago. However, only a small proportion of the children born yearly with CHD benefit from those successes. The world needs a major paradigm shift in the care for pediatric and congenital cardiac disease. The field of congenital cardiac surgery does not need any new major scientific discovery. There is rather a need to share with the rest of the world what has already been discovered and implemented over the last half-century. A hand needs to be extended to those in the developing world. Such major improvement in care can only result from the systematic organization of all health care providers across the world, based on the concept of a Medicine of RESPECT, or the Respectful Education Sustained through Partnership, Empowerment, Care, Commitment, Teamwork, and Trust [5].

Medical students, being where they are in their training, should hopefully be influenced and enlightened by the facts previously described. Their open-mindedness, optimistic view of the world, and indefectible enthusiasm represent perhaps what is needed to truly advance this agenda. The objectives that the World Society for Pediatric and Congenital Heart Surgery has given itself are numerous and broad and will likely have a real impact on the remaining 90% of children born with CHD who are not offered treatment. However, the process we have embarked on will be long and arduous and may be filled with many frustrations. It will not be a sprint, or even a marathon, but perhaps more of a long arduous triathlon. Nevertheless, we have taken the first few steps on this challenging and exciting journey. The World Society for Pediatric and Congenital Heart Surgery and the soon to be established Global Organization for Pediatric and Congenital Heart Disease are in a unique position to lead the way in this seemingly daunting task. We sincerely welcome the input of all medical students and strongly encourage all of those interested to participate, in one way or another, in their upcoming careers or academic projects, to the furthering of this somewhat grandiose, but, in our opinion, noble and realistic endeavour.

REFERENCES

1. Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? Lancet 2005; 365: 891–900.
2. Kirklin JW, Barratt-Boyes BG. Cardiac Surgery, 2nd edition. New York: Churchill-Livingstone, 1993.
3. Abbott ME. Atlas of Congenital Cardiac Disease, (re-edition). McGill-Queen's University Press 2006. 62 pages.
4. Jacobs ML, Mavroudis C, Jacobs JP, Tchervenkov CI, Pelletier GJ. Report of the 2005 STS Congenital Heart Surgery Practice and Manpower Survey. Ann Thorac Surg. 2006 Sep;82(3):1152-8.
5. Tchervenkov CI. Presidential Address: Hearts for Life across the World. The World Society News 2007. Volume 1, Issue 1, pages 6-8.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Managing the Psychology of Health Care: What it means and what it is worth

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BACKGROUND

Health care is perhaps the most complicated of services. While most services in the business world are challenged by the diversity of clients and variability in their needs, health care must face this challenge with tremendous pressure from other factors. On the one hand, the stakes are extremely high, and the demand for excellence is unmatched by those placed on other service providers. On the other hand, the whole activity takes place not only in the tangible world of wards and beds, but also in the abstract world of psychological and sociological forces that guide all stakeholders, from those holding the scalpel to those holding the chequebook.

While every issue in health care has its own shadow of debate and controversy, there are certainly moments of ephemeral consensus. The role of the patient in clinical decision making has been revisited along with the social and environmental changes in Western society over the past century. These include the acceleration of information exchange, increased awareness of rights and a steady erosion of physicians' perceived omnipotence, partly a result of the two previous developments. What we have today is the Partnership model, an acceptable model of the patient-provider relationship, whereby the patient is not a passive recipient of a series of health-related procedures, but rather an active participant who holds the final word on clinical decisions.

This arrangement raises some very interesting questions. The first wave is superficial, asking what the evidence is for it, against it, and what we can expect from this model from the perspective of patients and providers. The second wave asks about the hidden dynamics. Is an increased role for a patient really a dilution of expertise? Regardless of the answer, what happens to this current model in practice? Do the heightened emotional states and psychological distortions affect the patient's view of the situation to the point where they may not be acting in their best interests? This introduces the ethical question of determining best interests and delegating the authority to pursue them. With all these issues to be sorted out, how can health care managers plan to remove the impurities from the patient-provider relationship to optimize health outcomes?

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PATIENT EMPOWERMENT

The term "patient empowerment" has been described by the World Health Organization as "a process through which people gain greater control over decisions and actions affecting their health" (1). Considering that health is a function of a multitude of variables and factors, this remains vague. For the purposes of this paper on clinical decision-making, empowerment can be understood by its primary function: to uphold the values and principles underlying declarations of patients' rights.

Patient Rights

In 1994, the WHO issued a declaration of patients' rights, and in 2002, the Active Citizen Network proposed a European Charter of Patients' Rights (2)(3). The most pertinent ones related to the patient's role in clinical decision making are as follows:

- Right to information, which includes personal as well as biomedical information, both of which should form the basis of any sound decision-making.
- Right to free choice between different treatment options.

Although these rights cannot be refuted, they must be exercised with caution in some particular contexts in

order to avoid harm to the patients. Some examples of this will be discussed shortly.

Access to information

The big enabler of patient empowerment has been the ease with which patients can access and understand medical information. The biggest leap in the availability of information has come with the internet. Websites directed at patients such as webmd.com and familydoctor.org have shattered the health professional's monopoly on the distribution of information and corroded their power. While the knowledge of a competent physician will never be surpassed by that of the most avid reader of WebMD, informed patients have changed the dynamics of healthcare. A patient now has a basis for discussion, and with discussion comes doubt, challenge and in some cases, near-autonomous care on the part of the patient. The physician's aura of omnipotence has faded, or even, in some cases, disappeared, and new models of patient-physician relationship have arisen.

PATIENT-HEALTH PROFESSIONALS INTERACTION MODELS

The generic process of health care has several steps, beginning with detecting a problem or symptoms, continuing with information gathering, diagnosis, treatment and monitoring. Some of these steps involve decisions, the most significant one being the evaluation and selection of treatment options. There are six general models for health care delivery with defined roles for both the patient and health care provider in each step of the health care process (Table 1) (4). The two most extreme models are the Autonomous model and the Unilateral health care provider (HCP) model. The latter is likely rare in its pure form, and violates the basic principles that underlie patient-centered care. The more practical version of the Unilateral HCP model is the Paternalistic model, in which the most significant feature is that the chosen treatment is selected by the HCP.

The Partnership model is the intermediate between the two ends of the spectrum and is the one that seems most reasonable. In this model, every step is carried out with cooperation between the patient and the HCP. This model allows for several desirable practices to be put in place:

- The care process incorporates the knowledge and professionalism of HCPs
- The patient's involvement in gathering information about the condition and treatment options introduces a second competent voice to the discussion on their health
- The patient's involvement in the generation and selection of treatment options requires a level of knowledge shown to improve adherence and outcomes (4)
- The communication required by the Partnership model has been shown to improve patient satisfaction (5)
- The patient's values regarding health are strong decision inputs

From a theoretical perspective, it seems that this partnership model is ideal, based on the notion that a patient should be informed of their health situation with the HCP as only one of multiple sources and that they should be participants in the clinical decision regarding treatment, a decision made with respect to their values.

Activities	(A) Autonomous patient	(B) Autonomous health care system patient	(C) Partnership	(D) Propose – Dispose Model	(E) Paternalistic model	(F) Unilateral HCP model
HEALTHCARE PROVIDER (HCP) ROLE	None	Prescription writer	Partner	Expert	Authority	« God »
(1) Problem detection (signs & symptoms)	Patient	Patient	Patient + HCP	Patient + HCP	Patient + HCP	HCP
(2) Additional patient information required for diagnosis	Patient	Patient	Patient + HCP (e.g., medical record)	Patient + HCP (e.g., medical record)	Patient + HCP (e.g., medical record)	HCP
(3) Diagnosis & Prognosis	Patient	Patient	Patient + HCP	HCP	HCP	HCP
(4) Define health goals	Patient	Patient	Patient + HCP	HCP	HCP	HCP
(5) Generate treatment options	Patient	Patient	Patient + HCP	HCP	HCP	HCP
(6) Generate general information about options	Patient	Patient	Patient + HCP	HCP	HCP	HCP
(7) Generate patient information needed to assess option suitability for patient (contraindications, etc.)	Patient	Patient	Patient + HCP	Patient + HCP	HCP + Patient	HCP
(8) Evaluate options	Patient	Patient	Patient + HCP	HCP	HCP	HCP
(9) Decide on treatment option	Patient	Patient	Patient + HCP	Patient	HCP	HCP
(10) Implement treatment	Patient	Patient	Patient + HCP	Patient	Patient	HCP
(11) Monitor and evaluate	Patient	Patient	Patient + HCP	Patient + HCP	HCP	HCP

Table 1. Models of patient-physician treatment involvement (4; reproduced with permission)

HEALTH OUTCOMES AND PATIENT EMPOWERMENT IN THE PARTNERSHIP MODEL

In healthcare, a process, strategy or practice is only as good as the health outcomes associated with its implementation. In this case, there are many studies that confirm the value of some element or form of a partnership model.

Communication

In a study sponsored by the Austrian Ministry of Health, outcomes were compared for patients undergoing cardiac surgery before and after HCPs underwent communication training for admissions, pre-surgery and discharge discussions (5). The differences are significant. Patients in the intervention group were discharged 1.1 days earlier, were transferred quicker to less intense treatment, and experienced an 11% increase in overall satisfaction, as well as improvement in several communication and pain-based measures of satisfaction. These outcomes can be attributed to the enhanced communication similar to the patient-centric principle that motivates the partnership model.

Information

Smith et al carried out a cluster randomized trial testing the effectiveness of mailed communications in increasing adherence to beta-blocker therapy in patients with recent myocardial infarctions (6). Patients received two mailings spaced two months apart, containing similar information. Written in lay language after extensive consultations with patient focus groups, the mailings addressed the importance of beta-blocker therapy, the risks of non-compliance and handling of adverse effects and information on alternative and complementary therapies such as statins, ACE-inhibitors and aspirin. Defining adherence as a percent-of-days covered greater than 80, 17% more patients were adherent in the intervention group than the controlled group. The intervention here includes information that should be part of a healthy HCP-patient relationship based on the partnership model.

HCP disposition

The Centre for Studies in Family Medicine at the University of Western Ontario carried out a study whereby medical consultations were taped and assessed by a research assistant as well as patient post-encounter survey for various measures of patient-centeredness (7). Patients were followed up for two months and observed for health outcomes as well as consumption of health care services. Patients perceiving that a consultation was patient-centered were less likely to receive diagnostic tests (14.6% vs. 24.3%) and be referred (8% vs. 16%) in the following two months than patients who did not perceive that the consultation was patient-centered. Differences were even more pronounced with respect to patients reporting that they found common ground with their physician, defined as "when the physician clearly described the problem and the management plan, answered questions about them, and discussed and agreed on them with the patient". Of patients perceiving that they found common ground with their physician, only 4.1% received diagnostic tests and 6.1% received referrals in the next two months compared to 25.4% receiving diagnostic tests and 14.9% being referred for patients who did not perceive that common ground was established. Perceived patient-centeredness was associated with lower post-encounter levels of discomfort and concern using a visual analog scale and the mental health dimension of the medical outcomes study short form 36 surveys. Perceived finding of common ground was associated with a lower post-encounter level of concern.

This study shows that the interaction between patients and their physician is very influential towards patients' health-related anxieties as well as consumption of health services. The more sympathetic, open communication between physicians and patients favored by the partnership model is a powerful force in health care delivery.

With this evidence from research into physician-patient communication, information transfer and relationship-building, it is clear that there are benefits to be had form implementing the Partnership model as measured by health outcomes.

THE DOWNSIDE TO PATIENT EMPOWERMENT

While patient-empowerment within the context of a well-executed Partnership model has clear benefits, there are also downsides which may surface in cases of both partial and full implementation, pertaining specifically to increased costs, reduced health outcomes and more inefficiency in the delivery of care.

Direct to consumer advertising (DTCA) for pharmaceuticals is a form of patient empowerment and is consistent with the Partnership model because it informs patients regarding their condition and treatment options. The DTCA practice is controversial because it may lead to overuse even though it prevents underuse. A study published by Kravitz et al. tested the prescription rate for patients diagnosed with depression or adjustment disorder who asked their HCP either for a specific drug by brand name or generic name, or did not ask for a specific drug treatment (8). Prescription rates for patients with depression were 53%, 76% and 31% respectively, and 55%, 39% and 10% for patients with

adjustment disorder. The fact that patients who did not ask for a specific drug were given pharmacological treatment about half the time, or less, than patients who asked for a drug by name is an illustration of the influence of patient empowerment. This power is not necessarily beneficial, as it could be argued that the results of this study are evidence of patient empowerment leading to unnecessary treatment, which can lead to decreased healthcare outcomes and increased costs.

The partnership model is rarely implemented in its ideal form. A study carried out by Stevenson et al. in the UK that recorded conversations between physicians and patients found that in most cases, communication was poor and patient-centered bedside manner, inadequate (9). This lead the researchers to conclude that they "found little evidence that doctors and patients both participate in the [partnership model]" (9).

The attitude of physicians seems to be the main factor in the low use of the partnership model, as evidenced in the oft-quoted article by Rebecca Say and Richard Thompson (10). What they found was that doctors had a hard time handling the heterogeneity of patients' expectations with regards to the level of involvement between the two parties. In some cases, physicians reported that the discussion of treatment options lead to anxiety in patients if they felt that their physician was unsure of the proper course of treatment. This discussion is however central to the partnership model and should be modified if it is causing more harm than good. Another difficult scenario occurs when doctors must respond to information obtained from the internet, either or low quality or misinterpreted by the patients. While well-executed communication and education interventions led to benefits, poor execution of those same endeavors leads to frustration and potential inefficiency. These issues have discouraged some physicians and patients from seeking the ideal Partnership model. However, these same issues should be addressed by health managers in order to exact the benefits of the interaction model. As physicians and patients become more accustomed to the partnership model and the expectations it holds for each party, the problems cited in the report should be less prevalent and less prohibitive as barriers to good care.

THE VERDICT SO FAR

The Partnership model has won favor in theory among academics and policy-makers. Studies with and without intervention components have shown that there are many benefits to be had from a well-executed partnership model, be it in the form of reduced costs, improved health outcomes or improved satisfaction. It has also been shown that such a model may introduce challenges such as over treatment, decreased timeliness, increased costs, and frustration on the part of both physicians and patients. The Partnership model is still in its developmental stages in practice, but the consensus is that it is the most appropriate way to proceed going forward.

WHAT MAKES THE PARTNERSHIP MODEL BETTER?

When comparing the Partnership model to its alternatives that differ by patient-HCP dynamics, it is reasonable to conclude that improvements in health outcomes are rooted in those dynamics. These can be direct in that improved communication leads to better diagnoses and the selection of more appropriate treatment options. They can also be indirect in that the dynamics enable the emotive care associated with improved patient satisfaction and clinical outcomes. By either route, the effect is primarily psychological. Health managers should want to know where they can harness psychology to their advantage, and where a poor understanding of patient psychology will ultimately lead to worse health outcomes and a less satisfying experience for both patient and HCP.

PSYCHOLOGICAL DETERMINANTS IN PATIENT BEHAVIOUR

A patient is constantly making decisions with regards to care. It begins with how they interpret symptoms such as whether that persistent pain is circumstantial or worthy of medical attention. In deciding treatment options, a patient makes the most explicit choice based on information they have gathered. Finally, there is the treatment phase where a patient must be committed to treatment. This means that there are three characteristic situations where a patient must make decisions: observation of state of health before presenting to a HCP, discussion and decision during the medical interview, and the treatment phase.

Observation

During the observation phase, the patient passively observes their health, noting any points of concern, monitoring them and choosing between seeking medical attention or not. The first patient decision relates to symptom observation. Cognitive psychology defines a confirmation bias as "a tendency to search for information that confirms one's preconceptions" (11). A hypochondriac patient is subject to this bias when they interpret benign symptoms to be caused by a serious disease. Working in the other direction, another patient may look for days when they feel good to confirm that they are healthy. This bias towards desirable outcomes is consistent with the desirability bias, a form of

"wishful thinking" (12). Another form of bias is the denial bias. A study by Phelan et al. showed that there was "widespread denial" among women who were late to seek medical attention for breast cancer (13). While these psychological phenomena are challenges at the micro level, they are also challenges that must be met at the population level. Much of the observation takes place with no physician involvement whatsoever. This is a growing problem in countries like Canada where it is estimated that 15% of Canadians do not have a general practitioner (14). Because this observation phase is often free of physician involvement, these biases must not only be confronted during face-to-face contact with HCPs, but at every point in the interface between the health care body and the general public.

To counter these biases, health managers must focus on communication that manipulates another bias of cognitive psychology, known as the framing bias. A frame is defined as "a psychological device that offers a perspective and manipulates salience in order to influence subsequent judgment" (15). In a landmark study by Beth Meyerowitz and Shelly Cheiken, it was shown that framing - manipulated through language – significantly affected the intentions of young women to perform breast self-examinations (BSE) (16). They distributed three different pamphlets about BSE, loss-frame, gain-frame and no-arguments, where the frame type is defined by whether the negative consequences of not performing BSEs (loss frame), the positive benefits of performing BSEs (gain frame) or neither (no-arguments) were stressed. After four months, 57% of subjects in the loss-frame pool increased the frequency of BSE compared to that prior to reading the pamphlet, while 38% and 39% reported the same for the gain-frame and no-arguments pamphlet. This shows that health managers must be especially mindful of the psychological implications of the conversations they are having with the patients, at both the micro and macro levels.

Medical Interview

This clinical phase involves two components. In the first, a patient and their HCPs discuss the medical elements of the condition, as well as treatment options and risks. This phase can be considered one of information gathering in essence and similar to the observation phase, though ideally it is less autonomous as it is a process done in partnership with the guidance of an HCP. The same cast of biases can apply here too, as a patient may have confirmation, desirability, and other similar biases that will direct their focus to and from certain bits of information.

The decision-making process can be influenced by several biases.

Focusing Effect – In decision making, it is defined as "not taking into account alternatives to an option that has been initially proposed or generated" (17). With increased access to information, patients may be more inclined to choose a treatment on their own prior to discussion with an HCP. This is dangerous in that the option may not be the best option for them, but is favored because of this bias. While not deterministic, "this initial focus on a given option may also make the subsequent retrieval of information about known alternatives more difficult" (18). To counter this, the exploration of alternative options must be facilitated under the guidance of HCPs. This will encourage both an understanding and consideration of alternative options where a focusing effect in a patient-driven education process would discourage both.

Loss Aversion – This concept is part of prospect theory, put forward by Kahneman and Tversky in 1979 which revisited the traditional theory of utilitarianism (19). It says that people are more motivated to avoid losses than pursue equal gains. In the context of health, this could be present when considering serious risks from surgery. It may explain why so many men with prostate cancer initially choose "watchful waiting" to avoid associated risks even though 50% of them will proceed to treatment within three years due to disease progression or anxiety (20). This is problematic, as it can delay treatment where the outcomes are time-sensitive. It is difficult to counteract this phenomenon *a priori* because the neutrality of an HCP as a counselor is likely compromised, presenting an ethical issue. Instead, HCPs should be trained to recognize loss-aversion stemming from emotionally-charged thoughts and steer the patients towards a more balanced view, especially where the patient may be misinformed about certain risks.

Availability Heuristic – Another theory by Tversky and Kahneman proposes that the availability heuristic is employed when a person "estimates frequency or probability by the ease with which instances or associations could be brought to mind" (21). Patients' conceptions of illness are generally most influenced by experiences of family and their immediate circle. It is therefore based on a very small, statistically insignificant yet emotionally and psychologically charged sample. Patients may draw on what they hear anecdotally to generate their own probability distribution of outcomes that is more vivid and therefore likely dominant over the outcome probabilities accepted by the medical community.

As with loss aversion, it remains the responsibility of HCPs to notice these heuristics and manage them. This takes time and will likely cause tensions in the patient-HCP relationship, but it is nonetheless a necessary

component of good patient-centered health care.

Treatment

The compliance of patients to the treatments prescribed is an often-discussed topic; it is unfortunately often very low. In the case of many infectious diseases, such as tuberculosis, patients are more prone to being non-compliant once they reach the asymptomatic stage, as they mistakenly equate well being with cure (22). While this non-compliance is brought about by poor education regarding the disease and its treatment timeline, it is made worse by the fact that patients may deny that they are sick or be overconfident regarding their health. These are HCP-independent processes, and are a good argument for increasing the frequency of HCP-patient interactions, discussions about patients' concerns and beliefs, and patient education. For treatments that take place over extended periods of time, particularly those that include asymptomatic phases, patients must be closely monitored to facilitate discussion with HCPs. Unfortunately, many of these thoughts and emotions are tied to external perceptions and stigma, meaning that the scope of the education efforts is widened from being patient-specific to community-wide.

PATIENT DECISION AIDS: ON THE PSYCHOLOGICAL FRONT LINES

For the most part, all these biases and psychological challenges to good health care decision-making and outcomes share two characteristics. Their genesis occurs outside the health care system, and they are information-based. Therefore the antidote, though not deterministic, must address those two concerns.

In her editorial published in Evidence Based Medicine in 2001, Annette O'Connor gives an overview of what a patient decision aid (PDA) is, what it does, as well as the characteristics of the best ones (23). PDAs have the following elements:

1. Information regarding the patient's condition: Coming from a reputable source, PDAs should inform patients of the medical background, treatment options and risks, as well as make reference to other credible sources of information.
2. Values classification: Using questionnaires to guide patients to a resolution on their values and health-related priorities simplifies the experience for patients and HCPs.
3. Examples of other patients: This has a therapeutic effect when patients are being expected to make a very important decision regarding their health.
4. A guide to shared decision making: Some patients may be intimidated by the medical environment and not exercise their full patient rights as partners in the delivery of their care.

These aids are very patient-centric, and truly abide by the principles of the Partnership model, patient rights and patient education. With the ubiquity of the internet, PDAs are easily distributed and shared among institutions. They are clearly relevant to this paper's discussion in that they are both information based and delivered under the guidance of HCPs. PDAs are an appropriate tool to counter the psychological biases that challenge health care outcomes. Education seems to be the universal antidote, but it is a specific type of education – HCP endorsed and guided – that will truly help patients. The effects of the emotions-driven availability heuristic are mitigated by a sound discussion on risks and outcomes, as well as the examples of other patients. The patient framework as a whole is guided by their values. It is important that these be brought about and discussed with the HCP, as one of the motivations for patient-centric care and the Partnership model is that patients' values be respected.

It is easy to suggest that all health providers should begin to distribute PDAs, focus on patient education and train their HCP to navigate the psychological labyrinth of a patient's mind. It is far harder to predict how great an effect it will have on health outcomes.

PUTTING THE PSYCHOLOGICAL DISCUSSION INTO PERSPECTIVE

The patient-centered Partnership model has been shown to be beneficial in many cases.. It may be hard to believe that just talking to Austrian cardiac surgery patients should lessen their pain, increase their recovery speed and discharge them over a day sooner from the hospital (5). Considered from a financial perspective, this leads to a significant reduction in costs as the patient flow rate increases, effectively increasing capacity through conversation. Even a simple thing such as loss-frame pamphlets has been shown to increase the frequency with which women perform BSEs 20% more than gain-frame and no-arguments pamphlets do. This leads to earlier detection of breast cancer, and better health outcomes.

One can extrapolate these findings to other cancers, procedures and interactions with the health system to guess the magnitude of improvement. One also has to wonder how much improvement can be made if a systematic effort was launched, aimed at harnessing the psychological forces that drive these improvements in health outcomes. While estimating the impacts would require an amount of research that goes beyond the scope of this paper, it would not be surprising if it were of the same magnitude as medical errors, now the focus of health managers worldwide. The Canadian Institute for Health Information estimated that medical errors kill

up to 24,000 Canadians each year (24). The Institute of Medicine's seminal report titled "To Err is Human: Building a Safer Health System" estimated that this figure lies between 44,000 and 98,000 in the United States, and that the cost associated with medical error is 17-29 billion dollars (25). These figures were once seen as a revelation. It is therefore plausible that mismanagement of health care psychology comes at a human and financial cost similar in magnitude to that of medical error that was once unknown as well. Health managers now understand the cost of process neglect, of not being vigilant in what they do. Now they need to understand the cost of neglecting the psychological side of health care delivery, not only in avoiding harm, but in enhancing care above expectations through what they say and how they say it.

If proper management of the psychology of health care can have such effects, the benefits will far exceed the costs of the implementation and management. This must be explicitly addressed by the health care management community.

CONCLUSION

Changes in the principles that guide health care, as well as the technological and sociological environment surrounding it have lead to a patient-centered care model, called the Partnership model. In this model, all steps of the care pathway are done by patients and HCP in partnership, particularly when it comes to therapeutic decisions. This model necessitates that a patient be well-informed and clear about their values and priorities, and that HCPs are able to serve that need. There is much evidence to show that this model is indeed a positive intervention for health outcomes. The analysis of the evidence points to psychology as a driving force. This paper outlined some of the psychological biases that may act against health interests and presented strategies to mitigate those risks, led primarily through patient decision aids. PDAs embody the informational, value guidance and support needs of patients to be positive contributors and active participants in their health. Properly executing these strategies could undo harm and unleash the positive benefits of this very unconventional force in health care. The magnitude of significance may be in the order of that of medical error.

This paper has focused on the patient. However, HCPs are equally human, and equally susceptible to psychological biases, though they can be educated to be self-aware of those biases in order to provide better care for their patients. Health care managers must be mindful of these forces in patients, their professional staff, and even support staff. Instilling a psychologically positive environment cannot be an effort focused on one stakeholder in health care, but on all stakeholders.

Just as a house is as good as its design, foundation and materials, health care is as good as its own homologues to those elements: the processes put in place, the biomedical knowledge, and the social and psychological forces that contribute and influence each interaction. A second look at the Partnership model and the evidence surrounding it will show how much of a role psychology plays. With minds come emotions, biases and moments of cloudy thoughts. The big challenge for health care providers will be to manage these as threats. The biggest opportunity will be to harness these as forces that can be manipulated to achieve improved health outcomes for all.

REFERENCES

1. World Health Organization (WHO) - Division of Health Promotion, Education and Communications. Health Promotion Glossary. 1998:1-36. http://www.who.int/healthpromotion/about/HPR%20Glossary%201998.pdf
2. WHO. Principles of the Rights of Patients in Europe: A common framework. 1994 Jun:1-15. http://www.who.int/genomics/public/eu_declaration1994.pdf
3. Active Citizen Network. European Charter of Patients' Rights. 2002 Nov:1-12. http://www.activecitizenship.net/index2.php?option=com_docman&task=doc_view&gid=19&Itemid=86
4. Angelmar R, Berman P. Patient Empowerment and Efficient Health Outcomes. 2007 Jan:139-162. http://www.sustainhealthcare.org/Report_3.pdf
5. Trummer U, Mueller U, Nowak P, Stidl T, Pelikan J. Does physician–patient communication that aims at empowering patients improve clinical outcome? a case study. Patient Education and Counselling. 2006 May;61(2):299–306.
6. Smith DH, Kramer JM, Perrin N, Platt R, Roblin DW, Lane K, Goodman M, Nelson WW, Yang X, Soumerai SB. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. Archives of Internal Medicine. 2008 Mar 10;168(5):477-83.
7. Stewart MA, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, Jordan J. The impact of patient-centered care on outcomes. The Journal of Family Practice. 2000 Sept;49(9):796-804.
8. Kravitz RL, Epstein RM, Feldman MD, Franz CE, Azari R, Wilkes MS, Hinton L, Franks P. (2005). Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants: An Randomized Controlled Trial. JAMA. 2005 Apr 27;293(16):1995-2002.
9. Stevenson FA, Barry CA, Britten N, Barber N, Bradley CP. Doctor-Patient Communication About Drugs: The Evidence for Shared Decision Making. Social Science & Medicine. 2000 Mar;50(6):829-840.
10. Say R, Thompson R. The importance of patient preferences in treatment decisions—challenges for doctors. BMJ. 2003 Sept 6;327:542-5.
11. Myers, D. Social Psychology. 7th ed. New York: McGraw-Hill; 2001.
12. Krizan Z, Windschitl P. The Influence of Outcome Desirability on Optimism, Psychological Bulletin. 2007;133(1):95-121.
13. Phelan M, Dobbs M, David AS. "I thought it would go away": patient denial in breast cancer. Journal of the Royal Society of Medicine. 1992;85:206-207.
14. Statistics Canada. Canadian Community Health Survey. The

Daily. 2008 Jun 18. http://www.statcan.ca/Daily/English/080618/d080618a.htm
15. Workingpsychology.com. Los Angeles: Kelton Rhoads, PhD.; c1997-2004. [cited on 2007 Apr 7] Framing IV; [about 2 screens]. Available from: http://www.workingpsychology.com/whatfram.html.
16. Meyerowitz B, Chaiken S. The Effect of Message Framing on Breast Self-Examination Attitudes, Intentions, and Behavior. Journal of Personality and Social Psychology. 1987 Mar;52(3):500-510.
17. Del Missier F, Ferrante D, Costantini E. (2006) Focusing Effects in Predecisional Information Acquisition, Acta Psychologica. 2007 Jun;125(2):155-174.
18. Sanbonmatsu DM, Posavac SS, Kardes FR, Mantel SP. Selective hypothesis testing. Psychonomic Bulletin & Review. 1998;5(2):197–220.
19. Kahneman D, Tversky A. Prospect Theory: An Analysis of Decision under Risk. Econometrica. 1979 Mar;47(2):263-291.
20. Klein, E. Treatment for Early Prostate Cancer, Uptodate.com. 2006.
21. Tverksy A, Kahneman D. Availability: A heuristic for judging frequency and probability. Cognitive Psychology. 1973;4:207-232.
22. Jaiswal A, Singh V, Odgen JA, Porter JDH, Sharma PP, Sarin R, Arora VK, Jain RC. Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. Tropical Medicine and International Health. 2003 July;8(7):625–633.
23. O'Connor A. Using patient decision aids to promote evidence-based decision making, Evidence-Based Medicine. 2001;6:100-102.
24. Canadian Institute for Health Information. Health Care in Canada 2004. Ottawa (Canada): Canadian Institute for Health Information; 2004.
25. Institute of Medicine. To Err is Human: Building a Safer Health System. 1st ed. Kohn LT, Corrigan JM, Donaldson MS, editors. Washington D.C. (USA): National Academy Press; 2000.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Saving the Empire: The politics of immigrant tuberculosis in Canada

Sylvia Reitmanova

"Yet in every continent, under every climate, and among men of every race, there are communities where tuberculosis is either completely absent or of little consequence; in fact, the disease has been practically wiped out from a few localities where it was once prevalent. Clearly, then, its destructive power is not the inevitable expression of geographic, climatic or racial factors."

-- René and Jean Dubos (1)

Through the lens of anthropology, health conditions are often embedded in diverse political and economic forces, interests, and discourses that powerfully shape our understanding of health, redefine the ways we think of disease, and challenge the boundaries of what we consider to be objective science (2). However, Western medical science rejects defining disease as a political or cultural construct since it assumes that the human body – which is often seen as a machine (3) – can be objectively described, measured, and evaluated. Disease is understood as a pure consequence of diverse biological, chemical, physical, and mechanical factors (or their combinations) that impact negatively on the human body at its macro- or micro-level. The role of a physician, then, is to take apart the broken machine and to fix or replace the damaged parts (4). As a result of such a conceptualization, disease is defined solely in biological, physical, and chemical terms that are usually neatly organized in the following categories: Definition, Basic Science (Pathogenesis), Epidemiology, Natural History (Spread and Clinical Manifestation), Diagnosis, Treatment, and Prognosis (5).

Following these concepts, tuberculosis (TB) is defined in medical books as an infectious disease caused by a bacillus, *Mycobacterium tuberculosis*, whose microbiological and chemical properties one can study in great detail. This definition is accompanied by a comprehensive description of the anatomic, pathophysiological, and immunological processes taking place when the TB bacillus settles in a human body, usually followed by the description of the clinical symptoms of TB and the scientifically established ways to diagnose and treat it. Finally, most medical books familiarize the reader with some medical and social conditions linked to immunodeficiency which are associated with the higher spread and development of TB within certain populations or among certain individuals. However, it needs to be noted here that with the advent of vaccination, antibiotics, and advanced technology during the first half of the twentieth century, TB was reconstructed as a medical disease with a social aspect from a previously held concept defining TB as a social disease with a medical aspect (6, 7). Consequently, the role of social factors in the conceptualizing of TB was de-emphasized.

Since modern medical science defines TB strictly as an infectious (not a social) disease, current TB management and control policies are guided by the three basic epidemiologic principles underlying the fight against infectious diseases: elimination of the sources of infection, disruption of the transmission process, and reduction of susceptibility in the unexposed population (8). According to current statistical data, immigrants from developing countries account for the highest ratio of TB cases in Canada (9) and are therefore considered the greatest source of infection. In order to eliminate this foreign source of infection and to disrupt further transmission, TB health management and control relies on two main

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interventions: preventing immigration to Canada of any who have active TB, and monitoring and treating those immigrants with latent TB who are already in the country (10). Taking into account the present conceptualizing of TB as an infectious medical disease, these two epidemiologic interventions seem to be scientifically well-justified.

However, interestingly, barring immigrants with TB from entering Canada in order to eliminate the source of infection was not always considered appropriate. Although objective science considers eliminating the source of infection as one of the main strategies in the modern fight against infectious diseases, documentation exists to show that TB once served as a reason to attract infected immigrants to Canada. In 1886, the Canadian Pacific Railway issued a brochure to attract new British immigrants (11). In this document, dozens of Canadian women maintained that their TB improved in Canada after a short time, due to the "exceedingly healthy climate" (12). These lay women's accounts were also officially supported by medical scientists of those times. For instance, Dr. William Hales Hingston of Montreal established that Canadian "dry air and cold winter… [were] decided recuperators of such diseases as consumption" (13). A British physician, Caleb Williams Saleeby, maintained that "the cold and sun of Canada, playing upon the well-fed, produce a splendour of physique, a low rate of disease [TB], an abundant energy of mind, a joie de vivre, or national euphoria" (13).

How could an infectious disease now perceived as a potential danger to the Canadian public and a burden to the Canadian healthcare system (10) play an important role in the country's immigration propaganda 120 years ago? This question cannot be answered by the simple assumption that, in Canada, TB was considered hereditary and Koch's confirmation of its contagiousness was not readily accepted. Attracting British immigrants with TB to Canada was nothing more than a desperate attempt by the British empire to build the new colony in the country that many considered to be the "White Man's Last Opportunity" (13). In this context, TB became conceptualized as a political means to fulfill a British nationalist dream about Canada as a new Saxondom, rather than a highly feared infectious disease that needed to be avoided and contained.

However, this situation changed dramatically at the beginning of the twentieth century when the rates of TB-related deaths and disabilities in Canada became alarmingly high. Moreover, between 1900-1920, the population in Canada grew by 64%, which created great problems such as overcrowding in unventilated and poorly-sanitated urban slums, labour unrest and distrust of immigrant's foreign attitudes and customs (6). In fact, immigrants were frequently suspected and feared "disease breeders," a belief that often led to "campaigns against immigrant-run street markets and fruit stalls, which were condemned as germ-ridden threats to the public health" (14).

These fears encouraged Canadian upper class politicians, physicians, businessmen, and suffragettes to protect the purity and healthiness of Saxondom from "racial poisons" such as TB, alcoholism, and venereal disease which were decimating their race and society (13). The term "racial poisons" was introduced by Saleeby who once, paradoxically, advocated the healing powers of Canadian skies. According to him, all racial poisons had to be eliminated from a society in order to preserve its quality. Saleeby, like other proponents of Galton's biological theory, believed that the predisposition to some diseases, including TB, was inherited along the lines of race and class (6, 13). The followers of this new school of thought, called eugenics, were convinced that the poor and immigrants, because their genes were considered to be inferior, suffered from TB and other diseases more readily than the white non-poor classes. Members of non-European races were often deemed infantilized, backward, and less evolved (13, 15). For these reasons, the owners of these supposedly inferior genes were exposed to specific measures to ensure that all defective, unassimilable, and unfit people would be eliminated from the "breeding stock" (6, 13). The measures applied to immigrants were thus intended to ensure that "Canada would forever remain white, Anglo-Saxon, and Protestant" (16).

The eugenics goal to eliminate TB was believed to be achievable through two means: controlled reproduction and controlled immigration. Eugenists considered that people with TB would bring "poor, feeble, miserable members into the world who would have no strength and vitality" and would fall easy victims to TB (6). For this reason, they opposed marriages of people with TB and pushed for the implementation of birth control. In 1928, their efforts resulted in the proclamation of the Sexual Sterilization Act of Alberta that justified the sterilization of mentally ill, Aboriginal, and immigrant women, all of whom were accused of decimating the desired stock (13). As a result, Canada "has continued to be profoundly and systematically exclusionary and oppressive for many Canadians" for the following four decades until the Act was finally repealed in 1972 (13).

In terms of controlled immigration, it was understood that, in order to protect existing healthy stock, it was necessary to avoid importing those who were unhealthy. This sentiment resonated in the question raised by Dr. John George Adami, former president of the Canadian

Association for the Prevention of TB and a delegate to the International Congress of Eugenics:

"Is it not better for us in Canada to increase our population by saving our own and making them strong and healthy rather than by spending our national money in bringing in Doukhobors, Galacians, Poles and the depressed peoples of Southern and Eastern Europe? " (17)

Others echoed this view. For instance, Dr. Helen MacMurchy, the first female intern at TorontoGeneral Hospital, stated in her influential third report on infant mortality in 1912:

"After ages will wonder at the stupidity of Government and a people which takes so much trouble to bring in immigrants from every corner of Europe and, for sheer lack of public thought, lets its own Canadian babies die in a quite unnecessary holocaust." (18)

The Canadian upper class believed the solution to these problems to be the improvement of the federal immigration policy; specifically, banning immigrants with TB from Canada. Yet, the facts – such as the lower rate of TB among immigrants compared to the higher rate of TB found among Quebec's factory workers returning home from the United States – continued to be overlooked (6). Bringing in immigrants with TB was no longer seen as a tool to save the Empire. On the contrary, in the first decade of the twentieth century, TB was perceived as an element destroying it. Consequently, immigrants with TB were barred from Canada along with those identified as "idiots, imbeciles, feeble-minded persons, epileptics, alcoholics, criminals, and anarchists" as well as persons who were "insane, dumb, blind, physically defective, and illiterate" (19). The routine chest X-ray examination of immigrants for TB was introduced in 1948 when Dr. George Clair Brink, the director of Ontario's Division of TB Control, inaugurated this program in England by bringing with him a Canadian X-ray machine (20). Around the same time, physicians called for repeated X-rays of immigrants already in Canada for a period of two to three years after their admission date (21).

Routine surveillance of immigrants with diagnosed latent TB infection is currently still required by Canada's immigration law (10). Its critics state, however, that "to date, there is no evidence that tuberculosis among the foreign-born population significantly affects the indigenous population" (22). For instance, a cross-sectional Montreal study has shown that there was no association between TB positivity of non-vaccinated Canadian-born children and neighbourhoods highly populated with immigrants from endemic countries (23). On the contrary, the risk of transmission to immigrant communities was greater since many immigrants had little protection from TB due to their poor living conditions (24). In addition, Fanning calculated that the screening for and prophylactic treatment of all latent infections among immigrants, which some policy makers recommend, would cost Canada about 35 million dollars each year (22).

It is true that immigrants account for 63% of TB cases in Canada, an increase of 28% since 1980 (9), but research rarely identifies the poverty of immigrants as the reason for such an unequal distribution of TB in western societies (25). Instead, many public health sources name the country of origin as the main factor associated with an immigrant's higher risk of developing TB (10, 26, 27). As a result of such an interpretation of risks associated with immigrant TB, these studies recommend that the effectiveness of TB control be enhanced by improving case reporting and adherence to drug therapy rather than by addressing the issue of immigrant poverty. Even the report about newly diagnosed TB cases that Canadian physicians are required to send to the public health authorities does not contain any detailed information on the social determinants of the sufferers' health such as their socioeconomic status, or their employment, life, and work circumstances (10).

Since TB is no longer seen as a social disease, the following facts are easily underrated in the explanation of immigrant TB: In the past two decades, the percentage of immigrant families living below the poverty line in Canada has increased. In 2000, about 20% of people residing in poor neighbourhoods (physically and economically underdeveloped places with high crime and few amenities) were immigrants (more than double the rates in the general population) and about 35% of immigrants had lower income in comparison with the general urban population (28). Immigrants, a substantial proportion of the "inner city" population which researchers defined as the "individuals who tend to be on the losing end of inequality issues," faced high unemployment and underemployment, fewer education opportunities, social dysfunction, homelessness, overcrowded or substandard housing, malnutrition, lack of access to health care and services, and substance abuse (28). As a result of these poverty-related conditions, the health status of immigrants has been compromised. They have been found to be at high risk of developing several infectious diseases (29) among which, not surprisingly, is TB (30).

Hay et al. concluded that "social issues appear to explain more about variations in health and well-being than do any combination of individual factors" (28). The concept of blaming people's biological endowment along with their personal health practices for their ill

health is outdated. The importance of social determinants of health has been recognized in public health for a long time (31). For instance, a Montreal study indicated that immigrants accounted for 77.3% of TB cases in Montreal between 1992 and 1995 and the majority of these people faced problems such as poverty, homelessness and substance abuse (32). However, public health authorities hesitate to acknowledge that what some immigrants find in this country is poverty, which fosters their vulnerability to TB. For instance, the current edition of Canadian TB Standards acknowledges that socioeconomic factors such as poverty, overcrowding and malnutrition play an important role in the development of TB and therefore they need to be taken into consideration in prevention strategies (10). However, the edition has applied this approach only to the problem of TB among Aboriginal people in Canada. The section on TB management within the immigrant population does not make any reference to immigrant poverty and its relevance to TB. Modern public health policies based on attributing the problem of immigrant TB to the country of origin while overlooking the real social causes that underlie immigrants' health are no better than older health policies that once associated TB with immigrants' "inferior" genes.

One can conclude that a historic account of TB in Canada clearly demonstrates how a disease can transcend its biologically-paved boundaries only to become a political construct in which nationality and ethnic origin interfer with the conceptualization of disease and minimize the role of scientific objectivity. If medical science wants to maintain its principles of objectivity, it needs to assume the responsibility of stopping disease from becoming a political issue. When both medical and non-medical interventions vary across lines of nationality and class, scientific definitions of diseases then become useless. Consequently our narrow-minded focus on geography and nationality as causes of TB in Canada poses a risk of unleashing the destructive power of diseases such as TB on a vulnerable population.

ACKNOWLEDGMENTS

The author would like to thank to Dr. Diana L. Gustafson and Dr. Mark Tate for their generous guidance in critical culture theory and Mrs. Irene Sheppard for her kind and patient editing help.

REFERENCES

1. Dubos RJ, Dubos J. The White Plague. Tuberculosis, Man and Society. London: Victor Gollancz Ltd.; 1953.
2. Good B. Medicine, rationality, and experience: an anthropological perspective. Cambridge; New York: Cambridge University Press; 1994.
3. McKeown T. Determinants of health. In: Lee PR, Estes CL, editors. The Nation's Health. 5th ed. Boston: Jones & Bartlett; 1999. p.9-17.
4. Clarke JN. Health, Illness and Medicine in Canada. 4th ed. Toronto, ON: Oxford University Press; 2004.
5. Avery ME, First LR, editors. Pediatric Medicine. 2nd ed. Baltimore, MD: Williams & Wilkins; 1994.
6. McCuaig K. The Weariness, the Fever, and the Fret. The Campaign against Tuberculosis in Canada 1900-1950. Montreal, Kingston: McGill-Queen's University Press; 1999.
7. Feldberg GD. Disease and class: tuberculosis and the shaping of modern North American society. New Brunswick, N.J.: Rutgers University Press; 1995.
8. Mausner JS, Kramer S. Epidemiology – An Introductory Text. 2nd ed. Philadephia, PA: W.B. Saunders Company; 1985.
9. Public Health Agency Canada. Tuberculosis in Canada 2005 [monograph on the Internet]. Public Health Agency Canada; 2005 [cited 2007 Dec 11]. Available from: www.phac-aspc.gc.ca/publicat/tbcan-pre05/pdf/tbcan-pre2005_e.pdf.
10. Public Health Agency Canada. Canadian Tuberculosis Standards [monograph on the Internet]. 6th ed. Public Health Agency Canada; 2007 [cited 2008 Feb 8]. Available from: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf.
11. Hupfer M. Anything in Skirts Stands a Chance: Marketing the Canadian North-West to British Women, 1880-1914. J Macromarketing. 1998;18(1):41-9.
12. Canadian Pacific Railway. What women say of the Canadian North-West. In: Jackel S, editor. A flannel shirt and liberty: British emigrant gentlewomen in the Canadian West, 1880-1914. Vancouver: University of British Columbia Press; ([1886]. 1982). p. 32-65.
13. Devereux C. Growing a Race. Nellie L. McClung and the Fiction of Eugenic Feminism. Montreal, Kingston: McGill-Queen's University Press; 2005.
14. Tomes N. The Making of a Germ Panic, Then and Now. Am J Public Health. 2000;90(2): 191-8.
15. Fernando S. Cultural diversity, mental health and psychiatry. The struggle against racism. East Sussex, UK: Brunner – Routledge; 2003.
16. Chapman T. Early Eugenics Movement in Western Canada. Alberta History. 1977;25(4): 9-17.
17. Adami JG. The Modes of Treating Tuberculosis and Their Cost. CAPTAR. 1909;151.
18. Toronto the 'uncivilized' - Bad water, unclean milk and neglect killed many hundreds early in the century. The Toronto Star. 1999 Dec 31; Sect L1.
19. Government of Canada. Eastern Canada. Canada - The New Homeland. Ottawa: Ministry of Immigration and Colonization; 1924.
20. The Lung Association [homepage on the Internet]. Tuberculosis History in Canada. [cited 2007 Nov 28]. Available from: http://www.lung.ca/tb/tbhistory/index.html.
21. Adamson JD, Edmison JN. Immigration Tuberculosis. JCMA. 1947;57(5):432-34.
22. Fanning EA. The impact of global tuberculosis in Canada: We are our brothers' keepers. Can J Infect Dis. 1995;6(5):225-27.
23. Menzies D, Chan CH, Vissandjee B. Impact of immigration on tuberculosis infection among Canadian-born schoolchildren and young adults in Montreal. Am J Respir Crit Care Med. 1997,156(6):1915-21.
24. Carballo M, Divino JJ, Zeric D. Migration and health in the European Union. Trop Med Int Health. 1998;3(12):936-44.
25. Farmer P. Infections and Inequalities. Berkeley, Los Angeles: University of California Press; 1999.
26. Hyman I. Immigration and health. Ottawa: Health Canada;

2001.
27. Wobeser WL et al. Expanding the epidemiologic profile: risk factors for active tuberculosis in people immigrating to Ontario. CMAJ. 2000;163(7): 823-8.
28. Hay D, Varga-Toth J, Hines E. Frontline Health Care in Canada: Innovations in Delivering Services to Vulnerable Populations [monograph on the Internet]. Canadian Policy Research Networks; 2006 [cited 2007 Dec 5]. Available from: http://www.cprn.com/documents/45652_en.pdf.
29. Hyman I. Immigration and Health: Reviewing Evidence of the Healthy Immigrant Effect in Canada [monograph on the Internet]. CERIS Working Paper # 55. Joint Centre of Excellence for Research on Immigration and Settlement, Toronto; 2007 [cited 2008 Jul 19]. Available from: http://ceris.metropolis.net/Virtual%20Library/WKPP%20List/WKPP2007/CWP55.pdf
30. Ambrosio E, Baker D, Crowe C, Hardill K. The Street Health Report: A study of the health status and barriers to health care of homeless women and men in the City of Toronto; 1992.
31. Shah CP. Public Health and Preventive Medicine in Canada. 5th ed. Toronto, ON: Elsevier; 2003.
32. Rivest P, Tannenbaum T, and Bedard L. Epidemiology of tuberculosis in Montreal. CMAJ. 1998 Mar;158:605-9.

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FOCUS REVIEW

Placebos in Medicine: Knowledge, Beliefs, and Patterns of Use

Amir Raz*†, Eugene Raikhel†, and Ran D. Anbar‡

This special collection of papers on the topic of placebos features diverse contributions from leading researchers. We are privileged to benefit from the perspectives of John Kihlstrom, Elizabeth Loftus and James Fries, Pesach Lichtenberg, and Irving Kirsch. In this commentary we contextualize the different accounts within an overarching whole.

While most contributors to this MJM Focus Reviews section are non-physicians, placebo research is a field of great importance to any health care professional. Although scholarly definitions abound (1), most practitioners loosely regard the placebo effect as any treatment that improves a symptom or disease but lacks specific effectiveness for the condition being treated (2). As we demonstrate below, the placebo effect is both powerful and inherent in any clinical interaction (3). In addition, the patient-practitioner relationship is a significant component of the psychosocial context of treatment, because health care workers communicate important information to the patient through their words, attitudes and demeanor (4). Use of placebos, therefore, presents a didactic, philosophical, ethical, and practical challenge for most physicians.

PLACEBOS AND PSYCHOSOCIAL FACTORS IN MEDICINE

Placebos exemplify the link between psychosocial factors and physiological processes. They bind psychology to the techniques of neuroscience and medicine (5, 6) and are beginning to connect physiology to the social sciences (7-9). Outlining the current inadequacies of medicoscientific reductionism in relation to the relative merits of social science, Kihlstrom's piece nicely complements that of Raz & Guindi on "Placebos and Medical Education." Individuals under the influence of a charismatic authority can have bodily experiences that many professionals would consider "all in the head." Such phenomena form an important element of many of the world's healing traditions, ranging from shamanism and possession cults to Christian healing practices (10, 11). The King's Touch (KT), for example, refers to a medieval belief that illness could be cured by the touch of a divinely anointed monarch (12). Following the introduction of the practice to Western Europe by Edward the Confessor, kings in both France and England healed patients by the laying on of hands, with specific diseases (e.g., tuberculosis of the neck) reportedly being especially amenable to their touch (13). By the 17th century, KT had extended well beyond the throne. Irish healer Valentine Greatrakes – aka "The Stroker" – was able to amass thousands of clients, with "his barns and outhouses crammed with innumerable specimens of suffering humanity" (14). While Greatrakes probably practiced a layman's form of psychotherapy that had previously been restricted to members of the ruling class (15), modern science speciously dismisses KT as preposterous. One Nobel Laureate, for example, claimed that chicken soup might be a more credible source of healing than KT because ingesting soup may have chemical effects while it seems impossible for the symbolic act of KT to exert influence on the body (16). However, suggestion can indeed bring about veridical physiological changes (17-19).

Kihlstrom's prominent investigations into hypnosis, cognitive, clinical and personality psychology, and health research put him in a unique position to comment

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on the social science of placebos. His piece is the backbone of this special issue and establishes the milieu for the other papers.

PLACEBOS IN MEDICAL PRACTICE

While commonly used by physicians in the clinical setting prior to the 19th century, placebos fell out of favor with the emergence of modern medicine (20). Over the past decade, however, our knowledge of the neural correlates of placebo mechanisms has greatly increased, rekindling the placebo "flame" anew (21). While bioethical issues shroud the use of placebos in evidence-based medicine (2), some clinicians, mostly academic physicians, appreciate the relative merits of placebos and capitalize on their mind-body therapeutics (22).

In his piece, Lichtenberg provides a glimpse into the use of placebos in clinical settings. Many readers may repudiate the use of inert treatments outside of research, but such practices abound in medical care. Placebos have been around for many years and are likely to persist at least a while longer. Modern physicians will do well to appreciate their foibles and virtues.

Studies, including recent research efforts, provide evidence for the use of placebos in clinical contexts. A survey of head nurses in a Connecticut health district evaluated the status of placebos within the hospital setting and found that 44% of respondents reported that placebos were currently being used in their unit or that placebos had been used within the past six months (23). In another study aiming to determine knowledge and patterns of placebo use, researchers sent surveys to house officers and registered nurses (RNs) working in two university teaching hospitals in the U.S. (24). Seventy-eight percent of physicians who responded had ordered at least one placebo as a painkiller, while 82% of RNs had administered at least one placebo as a painkiller. In Canada, researchers surveyed doctors and nurses from the Victoria General Hospital in Halifax to assess their knowledge of and attitudes towards placebo, as well as their patterns of placebo use (25). Eighty percent of both the RNs and physicians reported having administered a placebo during their time at the hospital, with 91% of the placebos consisting of saline injections. In yet another study examining the frequency of placebo use within nursing clinical practice, researchers found that among 263 respondents, 178 (68%) had administered a placebo to patients; however, only 12% had done so within the last year (26). In Denmark, a survey of 772 physicians found that among the 503 respondents, 86% of the general practitioners, 54% of the hospital doctors, and 41% of the private specialists reported using placebo interventions at least once within the last year (27). In a separate study probing the frequency of placebo administration among physicians and nurses in Israel, researchers found that 53 out of 89 respondents reported prescribing placebos, 33 of whom said they had prescribed them as often as once a month (28). Finally, a more recent study found that academic physicians in the Chicago area used placebos in everyday clinical practice (22). Forty five percent of these physicians surveyed reported administering placebos, though 96% believed that placebos have a therapeutic effect. Despite this evidence that physicians are prescribing placebos (22, 28), no specific protocol currently governs their clinical use.

Following up on recently published efforts (22, 27, 28), we have put together a web-based questionnaire aiming to survey knowledge, beliefs, patterns of use, and attitudes among health care professionals concerning placebos. With this tool we hope to probe the way clinicians and medical students construe placebos and the extent to which these individuals use placebos in clinical practice. We expect that our findings will elucidate the prevalence and impact of placebos in medical practice. We encourage you to visit http://tinyurl.com/PlaceboSurvey and fill out a short anonymous questionnaire to assess beliefs, patterns of use, and attitudes concerning placebos. We hope to provide results of our survey before long.

PLACEBOS AND THE CONSENT FORM

Even if clinical use of placebos remains relatively widespread, a dramatic change over the past decades makes this practice increasingly difficult to discuss or acknowledge. With the rapid growth of legal and administrative regulations affecting medical practice and decision-making since the 1960s, as well as the enshrinement of patient autonomy as an ethical norm in medicine, the therapeutic use of placebos has become something of a dirty secret (29, 30). At the heart of this bureaucratic management of clinical ethics is the idea of informed consent. Early proponents of clinical and research ethics questioned whether complete consent was ever realizable, and argued that responsible clinicians and investigators represent a "far more dependable safeguard than consent" (31-33). However, the recent tendency is to ensure consent by exposing patients to ever-more compendious accounts of possible side-effects and risks, however minor or unlikely. This trend takes on a particularly extreme form in the United States, where a notably litigious culture fosters a strong risk-aversion tactic among institutions providing medical care. Thus, the consent form has turned into the virtual opposite of the placebo.

If consent forms represent the apogee of transparency and rational choice, placebos seem to be an apparently

inevitable prelude to deceit. As Loftus and Fries argue, however, even with increased reliance on bureaucratic tools such as consent forms, the purview of suggestion and expectation – core placebo components – continues to thrive. In fact, the insistence on full disclosure introduces a new, generally unappreciated variant of suggestion into our midst. In their unpublished pilot study, Loftus and Fries show that patients who sign consent forms describing side effects (some of which are invented by the researchers) do in fact experience those side effects in response to placebo. Such negative responses (i.e., "nocebo effects") overlap with certain placebo phenomena (34, 35). Moreover, that the act of reading and signing a form is a source of suggestion underscores the range of factors which can produce physiological effects without physical or chemical intervention.

In the minds of many contemporary practitioners who thrive on the ideals of patient autonomy and self-realization, placebos belong to an era when paternalism and beneficence characterized the therapeutic relationship. Two opposing stances, however, seem to guide even the beneficial effects of modern placebos: a passive current of "being cared for" and an active one of "caring for oneself" (36). It is likely that both have physiological effects. After all, mere observation often induces behavioral changes in patients, even in the absence of active clinical interventions – the "Hawthorne effect" (37).

SHOULD WE DEVELOP PLACEBOS FOR MEDICAL PRACTICE?

Sometimes, when clinical trials demonstrate that an experimental treatment is comparable to a placebo, clinicians conclude that the treatment is unsuitable for prescription. Such a conclusion, however, is incongruous with the notion that receiving nothing is appropriate or preferable. For example, in several randomized double-blind trials, non-prescription cough suppressants and expectorants have failed to show increased effectiveness over placebo (38). Many pediatricians refuse to recommend over-the-counter cough therapy because they think it is ineffective and potentially harmful (39). Such practice, however, disregards the placebo effect. In other words, non-prescription cough therapy probably is helpful for some individuals because of its placebo effect. For this reason, the medical community may wish to consider identifying therapies that work as a result of placebos. Such interventions should have minimal side-effects and be inexpensive; yet should be unusual and costly enough to raise patients' expectations regarding effectiveness (40).

On the other hand, some clinicians continue to prescribe certain medications even if their effects are comparable to placebos. Typically, the reluctance to stop prescribing medication is due to force of habit, a desire to please the patient, or the belief that anecdotal experience provides sufficient evidence for its efficacy. For example, as Kirsch reports in this issue, despite ample evidence that anti-depressants provide scant benefit beyond a placebo effect, many clinicians insist on continuing their use.

PLACEBOS AND MEDICAL EDUCATION

Western medicine follows largely in the footsteps of Descartes, whose mind-body dualism allowed physicians to treat the body without worrying about the potential effect of their interventions on the soul and made the practice of medicine more acceptable to theologians of the time (41). Modern students often learn to construe the body as an isolated entity, unaffected by the mind or social environment (42). Thus our medical system continues to operate from the point of view that we can understand and treat disease in biological terms, largely neglecting the effects of the mind on the body or vice versa.

Even if some medical students and physicians acknowledge that psychology might matter to clinical practice, few view psychology as a science on par with biology. Instead, they consider psychology and the other social sciences to be "soft" while regarding themselves as operating in the domain of "real," hard science (43). Whereas a reduction from biology to chemistry to physics may seem viable to many individuals, a reduction from psychology is knottier. Nonetheless, one can understand psychosocial factors only by stepping outside the exclusively biological paradigm of contemporary medicine and taking a serious look at psychology and other social sciences.

Raz and Guindi explore placebos from the vantage point of current medical education. Fortunately, medical students who appreciate the notion of placebo in therapy may be able to build their careers on a foundation that encompasses mind-body interactions. Thus, future medical practitioners will greatly expand their knowledge base and clinical applications involving placebos.

OTHER ASPECTS

Placebos currently occupy a paradoxical position in both lay and scientific discourse, as a renewed interest in the mechanisms underlying various body-mind phenomena vies uneasily with skepticism of non-biological explanations in medicine (1). An example of this tension was the powerful and conflicting set of reactions to a meta-analysis of clinical trials claiming that placebo effects are minimal or non-existent (44).

Multiple researchers have critiqued many aspects of this controversial meta-analysis (45-48), and re-analyses of the data yielded findings of a "robust" placebo effect (49) setting off a flurry of rebuttals and debates (50-52).

Criticisms aside, this contentious meta-analysis is extremely telling in that the assumptions it makes about placebos are similar to those made by much of mainstream medicine. For example, it confuses confirmatory with exploratory explanations and treats meta-analyses of data from randomized clinical trials as one of the most authoritative ways of demonstrating effectiveness while it ignores experiments which demonstrate the mechanisms underlying placebo responses (53, 54). Indeed, epistemological issues explain one important source of difficulty for contemporary medicine in acknowledging placebo responses (3).

Contemporary medicine elides most aspects of the physician-patient encounter in its explanations of cure, but it also fosters an ideal – a fantasy in which biological disease entities thrive without the messiness of psychology, meaning, or culture. In this regard, Kihlstrom's allusion to the Star Trek Feinberger is most appropriate. The field of psychiatry provides an excellent example of this tendency.

While psychiatry used to engage with the social sciences for much of the 20th century (55, 56), over the past twenty-five years a biological paradigm has become more dominant, reducing psychological and psychiatric explanations of behavior to neurobiology (57). Thus for many professional leaders, including the scientific directors of the Canadian and U.S. national institutes of mental health, the future of psychiatry lies in its becoming "a clinical neuroscience discipline" (58). Such reductionism, however, often makes it difficult for clinicians to acknowledge, understand and treat patients whose "non-specific" symptoms deviate from textbook characterizations. This issue is especially poignant as efforts to revise the Diagnostic and Statistical Manual of Mental Disorders (DSM) will soon result in DSM-V (59, 60). Recent findings from psychological experiments and neuroimaging studies reveal that differences in cultural background and language mirror divergent cognitive styles (61). In addition, numerous experimental, clinical and ethnographic accounts reveal that beliefs and expectations are likely to have effects on the ways that people experience bodily sensations and symptoms (62, 63). Culturally-specific attributions of symptoms may shape a person's expectations so as to amplify experiences of particular somatic or psychological sensations, and it therefore seems that culture can frame symptoms (64).

We can illustrate how culture can shape biology. Lactase, the enzyme necessary to digest milk, provides a good example into this process. While the majority of adult humans rarely produce lactase, descendants of populations which domesticated cattle and used milk as a central food source are more likely to carry a genetic variation allowing lactase to persist into adulthood (65, 66). Similarly, among Vietnamese and Cambodian patients in the U.S., researchers have described culturally-specific forms of panic (67, 68). Another example from Japanese culture draws on the societal value of aging females: menopausal women in Japan, are less likely to experience the hot flashes and night sweats that are widespread among older women in North America (69, 70). (Anthropologists have ruled out the possibility that these differences are due to eating more soy (i.e., ingesting chemicals that closely mimic the action of estrogen). Thus it is at least possible that this difference may have to do with the fact that Japanese culture promotes a different understanding of what it means to be an older woman and that the body is complying with this cultural expectation). A final example of cultural suggestion comes from the history of hypnosis which have changed in ways that reflect changing social expectations and mores (71): while the 18th century patients of Anton Mesmer convulsed violently as they felt animal magnetism racing through their bodies; those hypnotized by the Marquis de Puysegur entered a "sleep-walking" state; and Jean-Martin Charcot's patients were and behaved as hysterics.

Indeed, the effect that culture has on behavior is consistent with our modern concept of suggestion – a powerful, psychological influence that affects individuals through their subjective beliefs and experiences. Our bodies seem to have a culture and a history (64). If we want to develop a medicine that is adequate to the needs of patients, we must acknowledge that beyond physiology, biology is a co-construct of cultural phenomena. Thus, our understanding of illness and cure must draw on the social as well as the life sciences.

REFERENCES:

1. Harrington A. The many meanings of the placebo effect: Where they came from, why they matter. Biosocieties. 2006;1:181-93.
2. Shapiro AK, Shapiro E. The Powerful Placebo: From Ancient Priest to Modern Physician. Baltimore, MD: Johns Hopkins University Press; 1997.
3. Harrington A. The placebo effect : an interdisciplinary exploration. Cambridge, Mass.: Harvard University Press; 1997.
4. Benedetti F. How the doctor's words affect the patient's brain. Evaluation & the Health Professions. 2002 Dec;25(4):369-86.
5. Wager TD, Scott DJ, Zubieta J-K. Placebo effects on human {micro}-opioid activity during pain. Proceedings of the National Academy of Sciences. 2007 June 26, 2007;104(26):11056-61.
6. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL,

Davidson RJ, et al. Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. Science. 2004 February 20, 2004;303(5661):1162-7.
7. Kaptchuk TJ. The Placebo Effect in Alternative Medicine: Can the Performance of a Healing Ritual Have Clinical Significance? Annals of Internal Medicine. 2002;136:817.
8. Moerman DE, Jonas WB. Deconstructing the Placebo Effect and Finding the Meaning Response. Annals of Internal Medicine. 2002;136(6):471-6.
9. Wilce J, editor. Social and Cultural Lives of Immune Systems. New York: Routledge; 2003.
10. Csordas TJ. Elements of Charismatic Persuasion and Healing. Medical Anthropology Quarterly. 1988;2:121-42.
11. Kirmayer LJ. The cultural diversity of healing: meaning, metaphor and mechanism. Br Med Bull. 2004;69:33-48.
12. Jacob JR. Robert Boyle and Subversive Religion in the Early Restoration. Albion: A Quarterly Journal Concerned with British Studies. 1974;6(4):275-93.
13. Alexander F, Selesnick S. The History of Psychiatry: An Evaluation of Psychiatric Thought and Practice from Prehistoric Time to the Present. New York: Harper & Row Publishers; 1966.
14. Laurence RM. Primitive Psychotherapy and Quackery. Boston: Houghton Mifflin; 1910.
15. Bromberg W. Man above Humanity : A History of Psychotherapy. Philadelphia: Lippincott; 1954.
16. Weinberg S. Dreams of a Final Theory: The Search for the Fundamental Laws of Nature. New York: Pantheon Books; 1992.
17. Raz A, Fan J, Posner MI. Hypnotic suggestion reduces conflict in the human brain. Proc Natl Acad Sci U S A. 2005 Jul 12;102(28):9978-83.
18. Raz A, Shapiro T. Hypnosis and Neuroscience: A Cross Talk Between Clinical and Cognitive Research. Arch Gen Psychiatry. 2002 January 1, 2002;59(1):85-90.
19. Raz A, Shapiro T, Fan J, Posner MI. Hypnotic Suggestion and the Modulation of Stroop Interference. Arch Gen Psychiatry. 2002 December 1, 2002;59(12):1155-61.
20. Moerman DE. Meaning, medicine, and the "placebo effect". Cambridge, U.K. ; New York: Cambridge University Press; 2002.
21. Price DD, Finniss DG, Benedetti F. A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. Annu Rev Psychol. 2007 Jun 5.
22. Sherman R, Hickner J. Academic physicians use placebos in clinical practice and believe in the mind-body connection. J Gen Intern Med. 2008 Jan;23(1):7-10.
23. Goldberg RJ, Leigh H, Quinlan D. The current status of placebo in hospital practice. General Hospital Psychiatry. 1979;1(3):196-201.
24. Goodwin JS, Goodwin JM, Vogel AV. Knowledge and Use of Placebos by House Officers and Nurses. Annals of Internal Medicine. 1979;91(1):106.
25. Gray G, Flynn P. A survey of placebo use in a general hospital. General Hospital Psychiatry. 1981;3(3):199-203.
26. Ernst E, Abbot NC. Placebos in clinical practice: results of a survey of nurses. Perfusion. 1997;10:128-30.
27. Hrobjartsson A, Norup M. The Use of Placebo Interventions in Medical Practice--A National Questionnaire Survey of Danish Clinicians. Eval Health Prof. 2003 June 1, 2003;26(2):153-65.
28. Nitzan U, Lichtenberg P. Questionnaire survey on use of placebo. BMJ. 2004 October 23, 2004;329(7472):944-6.
29. Rothman DJ. Strangers at the bedside: a history of how law and bioethics transformed medical decision making. New York: Aldine de Gruyter; 2003.
30. Spiro H. Clinical Reflections on the Placebo Phenomenon. In: Harrington A, editor. The Placebo Effect, An Interdisciplinary Exploration. Cambridge, MA: Harvard University Press; 1997.
31. Beecher HK. The powerful placebo. J Am Med Assoc. 1955;159(17):1602-6.
32. Beecher HK. Ethics and Clinical Research. New England Journal of Medicine. 1966;274:1354-60.
33. Kelly A. Research and the Subject: The Practice of Informed Consent.
34. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience. 2007;147:260-71.
35. Hahn RA. The Nocebo Phenomenon: Concept, Evidence, and Implications for Public Health. Preventive Medicine. 1997;26(5):607-11.
36. Barrett B, Muller D, Rakel D, Rabago D, Marchand L, Scheder J. Placebo, meaning, and health. Perspect Biol Med. 2006;49(2):178-98.
37. De Amici D, Klersy C, Ramajoli F, Brustia L, Politi P. Impact of the Hawthorne Effect in a Longitudinal Clinical Study The Case of Anesthesia. Controlled Clinical Trials. 2000;21(2):103-14.
38. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev. 2008(1):CD001831.
39. Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible role of pseudoephedrine and other over-the-counter cold medications in the deaths of very young children. J Forensic Sci. 2007;52(2):487-90.
40. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161(12):1140-6.
41. Anbar RD. Hypnosis: An important multifaceted therapy. The Journal of Pediatrics. 2006;149(4):438-9.
42. Good B. How medicine constructs its objects. Medicine, Rationality, and Experience: An Anthropological Perspective. Cambridge, UK: Cambridge University Press; 1994.
43. Luhrmann TM. Of two minds : the growing disorder in American psychiatry. New York: Knopf.; 2000.
44. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. New England Journal of Medicine. 2001 May 24;344(21):1594-602.
45. Greene PJ, Wayne PM, Kerr CE, Weiger WA, Jacobson E, Goldman P, et al. The powerful placebo: doubting the doubters. Adv Mind Body Med. 2001;17(4):298-307; discussion 12-8.
46. Kirsch I, Scoboria A. Apples, oranges, and placebos: heterogeneity in a meta-analysis of placebo effects. Adv Mind Body Med. 2001;17(4):307-9.
47. Spiegel D, Kraemer H, Carlson RW. Is the placebo powerless. N Engl J Med. 2001;345:1276.
48. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 2008;59:565-90.
49. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS. The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. J Clin Psychol. 2005;61(7):835-54.
50. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. Journal of Internal Medicine. 2004;256:91-100.
51. Hrobjartsson A, Gotzsche PC. Powerful spin in the conclusion of Wampold et al.'s re-analysis of placebo versus no-treatment trials despite similar results as in original review. J Clin Psychol. 2007;63(4):373-7.
52. Wampold BE, Imel ZE, Minami T. The placebo effect: "Relatively large" and "robust" enough to survive another

assault. Journal of Clinical Psychology. 2007;63(4):401-3.
53. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. British Medical Journal. 2008;336(7651):999.
54. Kaptchuk TJ, Stason WB, Davis RB, Legedza ART, Schnyer RN, Kerr CE, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. BMJ: British Medical Journal. 2006;332:391.
55. Luhrmann TM. Of two minds: the growing disorder in American psychiatry. New York: Knopf; 2000.
56. Shorter E. A History of Psychiatry : From the Era of the Asylum to the Age of Prozac. New York: Wiley; 1998.
57. Gold I, Stoljar D. A neuron doctrine in the philosophy of neuroscience. Behavioral and Brain Sciences. 1999;22(05):809-30.
58. Insel TR, Quirion R. Psychiatry as a Clinical Neuroscience Discipline. JAMA. 2005;294(17):2221.
59. Fink M, Taylor MA. Issues for DSM-V: the medical diagnostic model. Am J Psychiatry. 2008 Jul;165(7):799.
60. Krahn LE, Bostwick JM, Stonnington CM. Looking Toward DSM-V: Should Factitious Disorder Become a Subtype of Somatoform Disorder? Psychosomatics. 2008 Jul-Aug;49(4):277-82.
61. Han S, Northoff G. Culture-sensitive neural substrates of human cognition: a transcultural neuroimaging approach. Nat Rev Neurosci. 2008;9(8):646-54.
62. Kirmayer LJ, Sartorius N. Cultural Models and Somatic Syndromes. Psychosom Med. 2007;69:832-40.
63. Hinton DE, Howes D, Kirmayer LJ. Toward a medical anthropology of sensations: definitions and research agenda. Transcult Psychiatry. 2008;45(2):142-62.
64. Harrington A. The cure within : a history of mind-body medicine. 1st ed. New York: W.W. Norton; 2008.
65. Beja-Pereira A, Luikart G, England PR, Bradley DG, Jann OC, Bertorelle G, et al. Gene-culture coevolution between cattle milk protein genes and human lactase genes. Nature Genetics. 2003;35(4):311-3.
66. Durham WH. Coevolution: Genes, Culture, and Human Diversity. Stanford, CA: Stanford University Press; 1991.
67. Hinton D, Um K, Ba P. Kyol Goeu ('Wind Overload') Part I: A Cultural Syndrome of Orthostatic Panic among Khmer Refugees. Transcultural Psychiatry. 2001;38:403.
68. Hinton DE, Hinton L, Tran M, Nguyen M, Nguyen L, Hsia C, et al. Orthostatic panic attacks among Vietnamese refugees. Transcult Psychiatry. 2007;44(4):515-44.
69. Lock M, Kaufert P. Menopause, local biologies, and cultures of aging. American Journal of Human Biology. 2001;13(4):494-504.
70. Lock MM. Encounters with aging : mythologies of menopause in Japan and North America: University of California Press; 1993.
71. Gauld A. A History of Hypnotism. Cambridge, UK: Cambridge University Press; 1992.

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FOCUS REVIEW

Placebo: Feeling Better, Getting Better, and the Problems of Mind and Body

John F. Kihlstrom*

ABSTRACT: Over its history, medicine has vacillated between acknowledging placebo effects as important and trying to overcome them. Placebos are controversial, in part, because they appear to challenge a biocentric view of the scientific basis of medical practice. At the very least, research should distinguish between the effects of placebos on subjective and objective endpoints. Theoretically, placebos are of interest because they underscore the other side of the mind-body problem: how mental states can affect physical conditions.

Medicine, and the healthcare professions generally, has always had a vexed relationship with the placebo. Was it Hippocrates, or was it Galen, who enjoined physicians to use new medicines while they still had the power to heal – acknowledging that something other than the intrinsic properties of drugs was critical to their success? In any event, long before Pepper (1) and Beecher (2) drew professional attention to placebo effects, scientific physicians appreciated the importance of belief and suggestion in curing disease (for comprehensive coverage of placebo effects and related topics, see 3-7). It was not long ago that placebo pills, labeled as such, were listed in the *Physicians Desk Reference*. Norman Cousins (8) famously advocated placebo effects in medicine at roughly the same time that the randomized clinical trial – still the gold standard for evidence-based treatment – effectively consigned the placebo effect to the status of a nuisance variable which must be overcome, instead of a catalyst to be capitalized on. The *New York Times Magazine* announced on its cover (January 9, 2000) the "astonishing fact" that "placebos work". But only a year later, not content merely to show that effective treatments are better than placebo, Hrobjartsson and Gotzsche (9,10) concluded that placebos had virtually no practical effects on clinical outcome – leading the *Wall Street Journal*, in a May 30, 2001 commentary, to criticize the "Dale Carnegie school of medical thought". Nevertheless, the *New York Times* recently reported (May 27, 2008) that a Maryland-based company, Efficacy Brands, proposed to market a cherry-flavored placebo named Obecalp (read it backwards) over the counter to reduce the use of active medications for children with minor ills, hypochondriasis, and other forms of abnormal illness behavior.

Why are placebos so controversial? In part, I think, it is because they appear to challenge the biological basis of medical practice. Beginning with the microbe-hunting of Pasteur and Koch, through the pharmaceutical revolution, the development of laboratory diagnostics and imaging techniques, and pharmacogenomics, a major trend in the scientific revolution in medicine has been the development of diagnostic and therapeutic techniques that minimize human interaction between physician and patient. Elsewhere, I have cited the "feinberger", the hand-scanner used on Star Trek to diagnose and treat illness, as the apparent ideal for scientific medicine, because it obviates the need to take account of any psychosocial dimension of illness, prevention, or treatment (11). Scientific medicine, in this exclusively biocentric view, is simply a matter of treating germs with pills.

But the behavioral and social sciences are sciences too, and the placebo and related effects underscore the psychosocial dimensions of illness, prevention, and treatment: of the effect of the patient's (and the physician's) beliefs, attitudes, and expectations on the

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effects of those pills; on the role of human judgment in assessing symptoms, reading test results, making diagnoses, and choosing treatments; on the intrapersonal and interpersonal determinants of compliance, the importance of physician-patient communication and social support on treatment outcomes; the relationship between social class (and social status) and health. You can make a pill to treat an illness – that's a matter of understanding the biology, but then you've got to get the patient to take the pill – and that is a matter of psychology and social science.

The fact that Hrobjartsson and Gotszche, searching the entire medical literature, were able to find only 114 studies that compared placebo to a no-treatment control is powerful testimony to the widespread lack of interest in the placebo effect as an effect – an effect that can be added to the specific effects of prescription drugs or other biological treatments. In the treatment of pain, for example, big, dark-colored, bad-tasting placebos are more effective than small, brightly colored, good tasting ones; placebos delivered intravenously are more effective than placebos delivered intramuscularly, which in turn are more effective than placebos delivered orally (12). And it appears that the effect of a placebo was a constant proportion of that of the active agent to which it was compared: placebo believed to be aspirin is roughly 55% as effective as real aspirin, but placebo believed to be morphine is roughly 55% as effective as real morphine (12). More recently, we have learned that expensive placebos are more effective than cheap ones (13). At the very least, results such as these suggest how genuine medications ought to be marketed, if we are to maximize their effectiveness.

Wampold and his colleagues suggest that placebo effects will be greatest with psychological as opposed to physical disorders – that is, for disorders like depression rather than for cancer or heart disease; and, in the case of physical disorders, when the endpoint is psychological rather than in nature – that is, for anxiety, or depression or pain rather than for coronary cardiovascular disease or for cancer (14). The implication is that the placebo effect, being "psychological" in nature, will work only on the psychological dimensions of health and disease. Certainly, there seems to be a huge placebo component in the treatment of certain psychiatric disorders, such as depression (15, 16). But at the same time, the medical literature is littered with convincing demonstrations that patients' beliefs and expectations can moderate drug and other biological effects on objective as well as subjective endpoints. In one recent study, for example, Parkinson's disease patients experienced higher degrees of motor control when they were told they were receiving electrical stimulation of the subthalamic nucleus than when the stimulation was delivered without their knowledge (17). So much for the feinberger. Paraphrasing the advertisements for Nexium™, future research needs to distinguish between two types of endpoints: subjective endpoints –feeling better – and objective– getting better.

Placebo effects have been called the "crown jewel" of psychosomatic medicine, because they reveal the effects of mental states -- attitudes, beliefs, and expectations -- on physical outcomes. Psychosomatic effects, in turn, are in bad odor among some segments of the medical community for the same reason that placebo effects are: the proposition that psychosocial factors might play a causative role in physical illness is seen as compromising the basis of medicine on biological science. After Marshall & Warren (18) identified the role of *H. pylori* in gastritis and peptic ulcers (a discovery that earned them the Nobel Prize in 2005), a leading molecular neuropsychiatrist wrote a commentary entitled "Another One Bites the Dust" (19) celebrating the triumph of biomedicine over psychology. But as it turns out, while antibodies for *H. pylori* are found in over 90% of ulcer patients, they are also found in almost 80% of ulcer-free patients, indicating that "other factors in addition to *H. pylori* infection have an important role in the development of peptic ulcer" (20). Some of these factors are psychosocial: animal models clearly show a causal role for psychological stress in the origin of ulcers (21). If both stress and bacterial infection contribute to gastric disease, then both deserve appropriate diagnosis and treatment.

But beyond whatever advantage they can provide in the treatment of illness, placebos are of theoretical interest because of the light they can shed on the problems of mind and body. Usually, the mind-body problem is framed as unidirectional: how brain processes can produce conscious mental states. But placebos, and other psychosomatic effects, remind us that there is another mind-body problem: how mental states can affect bodily functioning. Documenting these effects, and understanding their underlying psychological and biological mechanisms, is the great challenge posed by placebos.

REFERENCES

1. Pepper, O. H. A note on the placebo. American J Pharmacology. 1994; 117; 409.
2. Beecher, H. K. The powerful placebo. JAMA. 1995;159, 1602-1606.
3. Benedetti, F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Ann Rev Pharm Tox. 2007; 48, 33-60.
4. Harrington, A. The placebo effect: An interdisciplinary exploration. Cambridge, Ma.: Harvard University Press. 1997

5. Harrington, A. The cure within: A history of mind-body medicine. New York: Norton.2008
6. Price, D. D., Finniss, D. G., & Benedetti, F. A comprehensive review of the placebo effect: recent advances and current thought. Annual Review of Psychology. 2008; 59: 565-590.
7. Shapiro, A. K., & Shapiro, E. The powerful placebo: From ancient priest to modern physician. Baltimore, Md.: Johns Hopkins University press. 1997
8. Cousins, N. Anatomy of an illness (as perceived by the patient). NEJM. 1976; 295, 1458-1463.
9. Hrobjartsson, A., & Gotzsche, P. C. Core belief in powerful effects of placebo interventions is in conflict with no evidence of important effects in a large systematic review. Advances in Mind-Body Medicine. 2001; 17: 312-318.
10. Hrobjartsson A, Gotzsche P.C. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. NEJM. 2001;344(21):1594-1602.
11. Kihlstrom, J. F. Expecting that a treatment will be given, when it won't, and knowing that a treatment is being given, when it is [Commentary on "Open versus hidden medical treatments: The patient's knowledge about a therapy affects therapy outcome" by F. Benedetti, G. Maggi, L. Lopiano, M. Lanotte, I. Rainero, S. Vighetti, & A Pollo]. Prevention & Treatment. 2003; 6: Article 4.
12. Evans, F. J The placebo response in pain reduction. In J. J. Bonica (Ed.), Advances in Neurology. New York: Raven. 1974; 289-296
13. Waber, R. L., & al. Commercial features of placebo and therapeutic efficacy. JAMA, 2008; 299: 1-16-1017.
14. Wampold, B. E., Minami, T., Tierney, S. C., Baskin, t. W., & Bhati, K. S. The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. J Clin Psych. 2005; 61; 835-854.
15. Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. The emperor's new drugs: An analysis of antidepressant medication data submitted to the US Food and Drug Administration. Prevention & Treatment. 2002; 5: Article 23.
16. Kirsch, I., & Sapirstein, G. Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. Prevention & Treatment. 1998; 1: Article 2a.
17. Benedetti, F., Maggi, G., Lopiano, L., Rainero, I., Vighetti, S., & Pollo, A. Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. Prevention & Treatment. 2003; 6.
18. Marshall, B. J., & Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984; 1: 1311.
19. Hyman, S. E. Another one bites the dust: An infectious origin for peptic ulcers. Harvard Review of Psychiatry. 1994; 1; 294-295.
20. Nomura, A., Stemmermann, G. N., Chyou, P.-H., Perez-Perez, G. I., & Blaser, M. J.. Helicobacter pylori infection and the risk for duodenal and gastric ulceration. Annals of Internal Medicine. 1994; 120: 977-981.
21. Overmier, J. B., & Murison, R. Animal models reveal the "psych" in the psychosomatics of ulcers. Current Directions in Psychological Science. 1997; 6(6): 180-184.

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FOCUS REVIEW

The Role of the Placebo in Clinical Practice

Pesach Lichtenberg*

The placebo is the most commonly-employed treatment across cultures and throughout history (1). Today's physician, resting on her evidence-based laurels, might have no trouble accepting this claim when considering the medical practice of yore. After all, what else can one make of the potions, herbs, leechings and rituals of our distant colleagues of an earlier age—medicine men, shamans, wizards—if not that they were, wittingly or ignorantly, purveyors of placebos? None of this ought to be relevant to our enlightened time, when we can exploit our understanding of physiology, pathology, pharmacology and the double-blind randomized placebo-controlled study to deliver scientifically-informed, empirically-validated, precisely-targeted therapeutic interventions.

Yet the placebo is here, a central item of our pharmacopeia, widespread and, certainly in the opinion of most clinicians, effective. This is the clear conclusion of a series of recent studies whose purpose was to gauge the extent of placebo use amongst physicians and to give some sense of how effective practitioners found them to be. Using decidedly low-tech methods (i.e. questionnaires), findings across disparate locales were impressively uniform. For over 500 Danish physicians who responded to a questionnaire, placebo use was as high as 86% amongst general practitioners, 54% amongst hospital-based physicians, and 41% of private specialists (2). In Chicago, 45% of 231 internists affiliated with three local medical schools admitted to using the placebo (3). In our own study in Israel, we questioned 90 physicians and nurses in primary and tertiary care and found that 60% used the placebo (4). In all locales, the placebo was administered in a variety of forms and for a variety of purposes, and was believed by most of its purveyors to be ethical and effective.

Some may be surprised by these findings. The local press even typically reports them ("Israeli Physicians Give Phony Meds" was one headline that I found particularly unsavory). Yet it is likely that these reports actually underestimate the extent of placebo use.

Allow me to justify this statement. The placebo is notoriously difficult to define (5). Indeed, even the surveys quoted above did not use a uniform definition. The Danish survey offered as a definition of placebo an intervention "not considered to have any 'specific' effect on the condition treated, but with a possible 'unspecific' effect." The Chicago questionnaire asked the physician to define placebo, the three possibilities including treatment with a non-specific effect (37%), an intervention not expected to have an effect through a known physiologic mechanism (51%), or treatment that is inert or innocuous (28%). The Israeli survey simply skirted the issue and started asking questions about placebo use. For all surveys, a placebo could take the form of vitamins, saline injections, sugar pills, antibiotics (for non-bacterial infections), and sub-therapeutic dosages of standard medication.

At the risk of reducing one ambiguity to another, it might help to think of the placebo as anything causing a therapeutic reaction, or "placebo effect", by psychological means, such as providing reassurance, assuaging anxiety, eliciting conditioned responses or arousing positive expectancy. (Some may object that I have here consigned psychotherapy to the status of a placebo; but I do not think that is a problem for one who appreciates the potential of placebo effects and the many ways of usefully producing them [6]. Ultimately, psychological effects are as real as any other.)

Thought of in this way, it becomes apparent that the placebo effect is part of every intervention. The inscrutable scrawl on the prescription pad, the reassuring smile, the limp stethoscope hung from the nape of the neck—these all contribute to the placebo effect. So, apparently, do the color of the pill (7), and even the number of pills swallowed by the patient (8,9). You just can't avoid the placebo effect (although, admittedly, comatose patients may be an exception). If you doubt this, just consider what happens if you

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artificially nullify the placebo effect. This has been tried, by concealing from the patient that he was receiving medication. The result was that morphine calmed pain less, diazepam did not calm anxiety at all, atropine only slightly increased heart rate, while propranolol only slightly decreased it (10,11). On the other hand, revealing that the pill to be provided is a placebo may not necessarily abolish its benefit (12, 13); apparently our reaction to treatment and all that it entails is too deeply conditioned to be reversed by mere full disclosure.

The placebo is at last being appreciated for its subversive potential. To ponder the placebo leads one to reconsider many of our presumptions about the gap between mind and body, about the untapped subtleties of medical treatment, and about what really heals when we administer our therapies.

People are often concerned about the ethics of the placebo. Certainly, giving a placebo where a more effective therapeutic alternative is available would be unethical. Similarly, providing a placebo in the futile hope of distinguishing “organic” from “supratentorial” maladies, or simply for the purpose of being done with an irksome patient, cannot be defended. Yet under certain circumstances, as I have described elsewhere (14), the placebo—whether an inert pill, a superfluous vitamin, or a miniscule, sub-therapeutic dose of medication—can be legitimately and ethically offered as treatment. If standard treatments have failed or caused intolerable side effects, a placebo may sometimes provide comfort.

Two case vignettes may help illustrate how the placebo can be usefully and ethically employed. A 62-year-old man suffering from post-operative pain was treated with repeated intramuscular injections of an opioid analgesic, but continued to complain of intense pain and to demand further injections. The staff, seeking to avoid an excessive dose, decided to alternate opioid analgesics with intramuscular saline. They explained to the patient that saline injections have often been found to alleviate pain, and they expressed optimism that it would help him as well. The patient responded well to the treatment, to everyone’s satisfaction.

A 38-year- old woman in psychotherapy for depression expressed her belief that her problem was "chemical", and the talk therapy was pointless. Insisting that she get "a prescription for a pill", the hesitant psychiatrist relented and provided 10 mg of imipramine, a medication that usually requires 100-200 mg and two-to-four weeks to achieve a therapeutic effect. The doctor explained that while higher doses are often used, they would wait to see her reaction to this dose, which can also be of benefit (15). The woman at her next weekly visit reported an immediate and significant improvement. She subsequently decided to leave psychotherapy, returning every 3-4 months to the psychiatrist to renew her prescription.

The ethical problem with the placebo, then, is deceit. The solution, we suggest, is honesty. The physician must convey to the patient the message that, "Though we don’t know exactly how this pill works, it can help you feel better.”

In fact, if we want to be completely frank with our patients, this sentence might have to accompany just about any treatment we might offer.

REFERENCES

1. Shapiro AK, Shapiro E. The powerful placebo: from ancient priest to modern physician. Baltimore and London: Johns Hopkins University Press, 1997.
2. Hróbjartsson A, Norup M. The use of placebo interventions in medical practice-a national questionnaire survey of Danish clinicians. Eval Health Prof. 2003;26(2):153-65.
3. Sherman R, Hickner J. Academic physicians use placebos in clinical practice and believe in the mind-body connection. J Gen Intern Med. 2008;23(1):7-10.
4. Nitzan U, Lichtenberg P. Questionnaire survey on use of placebo. BMJ. 2004 23;329(7472):944-6.
5. Gøtzsche PC. Is there logic in the placebo? Lancet 1994(344):925-6
6. Frank, J. D. & Frank, J. B. Persuasion and healing: A comparative study of psychotherapy (3rd ed.). Baltimore, MD: Johns Hopkins University. 1996
7. de Craen AJ, Roos PJ, Leonard de Vries A, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. BMJ 1996; 313(7072):1624-6
8. Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. Arch Intern Med 1993;153(16):1863-8
9. de Craen AJ, Moerman DE, Heisterkamp SH, Tytgat GN, Tijssen JG, Kleijnen J. Placebo effect in the treatment of duodenal ulcer. Br J Clin Pharmacol 1999;48(6):853-60
10. Benedetti F, Maggi G, Lopiano L, Lanotte M, Rainero I, Vighetti S, Pollo A. Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. Prevention & Treatment. 2003; 6(1)
11. Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol. 2004; 3(11):679-84.
12. Park LC, Covi L. Nonblind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. Arch Gen Psychiatry. 1965;12:36-45.
13. Vogel AV, Goodwin JS, Goodwin JM. The therapeutics of placebo. Am Fam Physician 1980;22(1):105-9.
14. Lichtenberg P, Heresco-Levy U, Nitzan U. The ethics of the placebo in clinical practice. J Med Ethics. 2004 Dec;30(6):551-4.
15. Brown WA. Placebo as a treatment for depression. Neuropsychopharmacology 1994; 10: 265-9

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FOCUS REVIEW

The Potential Perils of Informed Consent

Elizabeth F. Loftus* and James F. Fries

Informed consent is supposed to be a good thing, isn't it? Motherhood, apple pie, and informed consent. After all, we don't want the return of the bad old days when unwitting human guinea pigs were experimented upon without knowing what they were getting into. But there is another side to informed consent; in fact, there are perils to informed consent that ought to make the medical establishment think harder before continuing to uncritically accept it as a universal constant.

Some time ago, we wrote an editorial in *Science* entitled "Informed consent may be hazardous to your health" (1). There we pointed to the rather suggestible nature of the human mind. We know that plying people with certain kinds of information can make them believe that they experienced things that never happened. Studies on the malleability of human memory have shown that people can be led to believe that they saw stop signs instead of yield signs, that they got sick eating particular foods as children, and that they even had experiences that are highly implausible such as witnessing people being demonically possessed or being accosted by the Pluto character on a trip to a Disney resort (2).

Not only can people be led to believe that they experienced events that did not occur, but they can also be led to experience feelings and symptoms that they would not otherwise feel. That's what placebos are all about. When a physician tells a patient or experimental subject that the drug being taken might cause nausea or dizziness, how many people develop the symptoms who wouldn't do so from the drug or the medical procedure alone? We argued that simple inspection of informed consent documents reveals a purpose more directed at protecting the institution than protecting the experimental subject. We argued that perhaps these individuals would be better off if they got a description of the general level of risk, but detailed risk possibilities, or even very slight risks, ought to be reserved for those who request them. And if the detailed information is given, it ought to be accompanied by a discussion of placebo effects – why they occur, and how to guard against them.

Critics were quick to jump on these ideas, arguing that the "right to full information on matters which may affect our minds and bodies prevails" (3). They accused us of displaying a distressing failure to make a distinction between rights and benefits. We were astonished that our critics would so readily construe a statement intended to be made in favor of human rights as an attack upon such rights. Of course, people have the right to determine what is done to their minds and bodies, but this must extend to symptoms and illness actually caused by poorly executed disclosure. We question, informed by our knowledge of the power of placebos, whether the current legalistic ritual associated with informed consent is the best way to ensure that this human right is protected. We only ask that those whose task it is to formulate informed consent rituals pay some attention to the harm that may be caused by the ritual itself. One harm is the planting of suggested symptoms, some of which can be rather unpleasant, such as anxiety, or downright distressing, such as severe physiological reactions. Would the critics actually endorse the idea that those involved in formulating these rituals have a right to harm people? Patients and subjects might be far less damaged by smaller amounts of balanced information than by mammoth descriptions of remote possibilities. We always advocated supplying the information to those who choose to know all, but to include in the presentation of the "all" a discussion of placebo effects and their potential for adverse reactions.

At the time we were immersed in this issue, we

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conducted an unpublished pilot study with patients at Stanford University Medical School who had been diagnosed with scleroderma and were enrolled in an experiment testing the efficacy of a particular drug cocktail (propanolol and alpha-methyldopa). The known side effects of the drugs did include upset stomach, tearfulness, dizziness, and headache. Before beginning the clinical trial involving the drug or placebo, patients received either a standard informed consent message or a "special message." Both messages informed them of possible side effects of the drug, and listed the known side effects, plus some implausible made-up ones that had not been associated with the drug (e.g., ringing in ears, burning sensation in feet).

Some of our subjects received a "special message" as part of their "informed consent." It read as follows: "You should keep in mind one important point about these possible side effects. Research has shown that simply mentioning possible annoying symptoms causes some people to experience these symptoms – even when no drug is taken at all. This happens because mention of the symptoms causes some people to expect that they will experience them, and a person's expectations can then lead to the actual experience. Very few people will actually have these problems and you can help yourself guard against these sorts of discomfort by keeping yourself optimistic and stopping yourself from expecting that side effects are going to happen to you."

Our pilot study revealed, not surprisingly, that subjects experienced side effects, some of which were physiologically unlikely. The suggestion in the informed consent led even those given a placebo to this unpleasant fate. A special message that explained the powerful role that expectations can have in producing unlikely symptoms reduced the reported side effects, and also decreased somewhat the use of medications to treat those unlikely symptoms. Our hope is that future researchers will do a full scale study that tests the impact of variations in informed consent rituals. While our special message may not be the best message to accomplish these hoped-for benefits, and we did not study whether it will work with different kinds of drugs or patients, our preliminary result should pique the interest of future researchers in considering both the positive and negative impacts of information that they ply their subjects and patients with. One size is not likely to fit all. Flexibility in informed consent protocols might convey to patients and subjects their right to as little harm as possible.

REFERENCES

1. Loftus, EF & Fries, JF. Informed consent may be hazardous to your health. Science. 1979 April 6;204(4388):11.
2. Loftus EF. Planting misinformation in the human mind: a 30-year investigation of the malleability of memory. Learning & Memory. 2005 Jul-Aug;12(4):361-6.
3. Marcus RB. Kuklick B. Bercovitch S. Uninformed consent. Science. 1979 Aug 17;205(4407):644,646-7.

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FOCUS REVIEW

Challenging Received Wisdom: Antidepressants and the Placebo Effect

Irving Kirsch

ABSTRACT: This article explores the reaction when an article challenging received wisdom is published and covered extensively by the media (1). The article in question was a meta-analysis of antidepressant clinical trials indicating that for most patients, difference between drug and placebo was not clinically significant. Reactions ranged from denial that the effects of antidepressants are so small to criticisms of the clinical trials that were analyzed. Each of these reactions is explored and countered.

"Doctors and patients know what works and what does not."

(C. Vargas, February 27, 2008, PLoS Medicine)

"Clinical practice plus millions of content patients can't be that wrong."

(R. Werner, February 27, 2008, PLoS Medicine)

On February 26, 2008, PLoS Medicine published a meta-analysis that my colleagues and I had conducted on antidepressant medication (1). Most meta-analyses suffer from publication bias, which can happen when pharmaceutical companies withhold unsuccessful trials from publication (2, 3). To circumvent this, we used the Freedom of Information act in the U.S. to obtain the data on all clinical trials submitted to the Food and Drug Administration (FDA) for the licensing of the four new-generation antidepressants.

The results of our meta-analysis showed that people got better on medication, but they also got better on placebo, and the difference between the two was small. In fact, it was below the criterion for clinical significance established by the National Institute for Health and Clinical Excellence (NICE), which sets treatment guidelines for the National Health Service in the UK. Clinical significance was found only in a few relatively small studies conducted on patients with extremely severe levels of depression.

This study was the subject of widespread media attention, especially in the UK, where it was front page news in most of the national daily newspapers (4). Not surprisingly, it stirred considerable controversy. In this article, I examine some of the reactions to the meta-analysis.

"PLACEBOS COULD NOT PRODUCE EFFECTS LIKE THESE"

Placebo effects can be surprisingly strong. Placebos can reverse the effects of powerful medications. They can affect the body as well as the mind. They produce side effects as well as beneficial effects. They can produce symptoms and alleviate them. In this section, I look at the power of belief to produce profound changes in people's experience.

One of the earliest reports on the power of placebo was the seminal work of Stewart Wolf, who demonstrated the ability of placebos to block the effect of potent drugs (5). A pioneer in the investigation of placebo effects, Wolf reported three successful experimental attempts at reversing the effects of active medications that typically induce abdominal discomfort. In each case, the reversal was brought about by misinforming the subject about the nature of the drug being administered, and in each case the subjective changes were verified by physiological assessment. One of Wolf's subjects was a 28-year-old pregnant woman who was suffering from nausea and vomiting. Wolf gave her ipecac, a drug that interrupts normal gastric contractions, thereby inducing vomiting and nausea. Although ipecac is commonly used to induce vomiting when toxic substances have been swallowed, Wolf

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misinformed his patient that it was a medicine which would alleviate her nausea. Prior to taking ipecac, the patient displayed an absence of gastric contractions. Within 20 minutes of ingesting the drug, normal gastric contractions resumed and the nausea ended.

Placebos have been reported to produce some rather startling effects on skin conditions. The most impressive of these reports involves the suggestion-related production and inhibition of contact dermatitis (6). Contact dermatitis is a skin condition produced by chemical substances to which people have become sensitized. In the study reported by Ikemi and Nakagawa, 13 students were touched on one arm with leaves from a harmless tree, but were told that the leaves were from a lacquer or wax tree (Japanese trees that produce effects similar to poison ivy and to which the boys had reported being hypersensitive). On the other arm, the subjects were touched with poisonous leaves, which they were led to believe were from a harmless tree. All 13 subjects displayed a skin reaction to the harmless leaves (the placebo), but only two reacted to the poisonous leaves.

Although a meta-analysis published in the New England Journal of Medicine concluded that the placebo effect is not very powerful (7), Wampold and his colleagues have reanalyzed those data and calculated the number needed to treat (NNT) for placebo compared to no treatment at all (8). NNT is the number of patients that need to be treated to achieve one success by means of a particular treatment. So the smaller the NNT, the larger the effect. Compared to no-treatment, the NNT for placebo is 7. Although this is not a large effect, it is instructive to compare it to the NNT for various accepted medical treatments, as published in a growing database of published studies provided online (http://www.cebm.utoronto.ca/glossary/nntsPrint.htm) by the University of Toronto's Centre for Evidence-Based Medicine. The NNT for radiotherapy for breast cancer, for example, is shown on that database to be 8, that for beta-blockers for chronic heart failure is 24, the flu vaccine has an NNT of 12, and aspirin as a prophylactic for myocardial infarction has an NNT of 208.

The NNT of 7 for placebo treatment was calculated across studies of many different clinical conditions. But there is good reason to believe that the placebo effect should be even greater on depression. This is because hopelessness is a core feature of depression, and one of the presumed effects of a placebo is to instill hope (9). If you ask depressed patients what the worst thing in their life is, many will tell you that it is their depression. They feel stuck in an intolerable condition and they are hopeless about the possibility of getting better (10). So it stands to reason that a treatment promising relief would bring some relief, merely on the basis of hope-instilling promise. Indeed, a meta-analysis of the published antidepressant literature indicates that the placebo effect (placebo – no-treatment) is twice as large as the drug effect (drug – placebo) (11).

"ANTIDEPRESSANTS WORK IN CLINICAL PRACTICE"

Clinical experience shows that antidepressant drugs work, in the sense that patients get better when given medication. So do our meta-analyses. Patients given antidepressants in the clinical trials showed substantial and clinically significant improvement, as did those given placebo. Physicians do not generally prescribe placebos to their patients. Hence they have no way of comparing the effects of the drugs they prescribe to placebos. When they prescribe a treatment and it works, quite naturally they ascribe the cure to the treatment. But the history of medicine is replete with cures that were "known" to work by doctors and their patients. These apparently effective treatments, that we now consider to have been placebos, include dolphin's genitalia, lizard's blood, crocodile dung, pig's teeth, putrid meat, frog's sperm, powdered stone, human sweat, worms, and spiders. That is why placebo-controlled trials are required in order to demonstrate drug efficacy. When the administration of a drug is followed by improvement, the improvement might not be due to the drug's chemical composition. Placebo-controlled trials are used to separate the drug effect from such factors as the placebo effect, spontaneous remission, and regression towards the mean.

"YOU HAVEN'T PROVEN THAT ANTIDEPRESSANTS DON'T WORK"

This is absolutely true. In fact, our data show a small advantage for drug over placebo that is statistically significant, but not clinically significant. But I will extend this criticism. Not only haven't we proven that antidepressants don't work, but we also haven't proven that their effect is below the threshold of clinical significance. What we have shown is that the data upon which drug approval was based does not show clinical significance. But it is always possible that future studies, perhaps with better experimental methods or measures of depression, will show a greater effect.

Possibility is a long way from fact, however. The onus should not be on critics to demonstrate that a treatment is ineffective, but rather for proponents to demonstrate that it is. If all that is needed is an absence of proof that a treatment does not work, then perhaps we ought to resume using treatments crocodile dung and dolphin genitalia until well-enough designed clinical trials prove conclusively that they are not more effective than placebo.

"ANTIDEPRESSANTS DRUGS MIGHT WORK FOR SOME PEOPLE BUT NOT OTHERS"

This is indeed possible. In fact, we found evidence of greater drug effectiveness in a small subset of studies involving patients with exceptionally high levels of initial depression, although it seemed that they were less responsive to the placebo, rather than more responsive to the drug. We also found that the drug-placebo difference was zero for people who were moderately depressed. For this rather large group of sufferers, antidepressants seemed to have no drug effect at all.

It is feasible that there are other subgroups of patients for which antidepressants are more effective, but simply asserting this possibility is not enough. One must identify those subgroups and demonstrate the clinically-significant benefit they obtain from active medication over placebo. Some of the data for doing so have already been collected. For example, gender is most certainly identified in the data sets of most, if not all, clinical trials. It would be a simple matter, for example, to reanalyze these data to test whether women are in fact more responsive to SSRIs and men to tricylic medication, as has been suggested (12).

Note that if there are some groups of patients that respond better than the overall mean, then there must also be some that respond worse. Given how small the advantage is over placebo overall, this should be of considerable concern. If some are responding substantially better, then others must not be responding at all—or even being made worse by the active medication, compared to how they would have fared on placebo. If this is the case, it would be important to know it so that antidepressant medication could be prescribed more selectively.

Understandably, pharmaceutical companies might be reluctant to carry out analyses of this sort, as they have the potential to cut into sales substantially. One way around this is to require that raw data for all approved medications be available for researchers to reanalyze. This could easily be done with full protection of the anonymity of those who participated as subjects. Greater transparency and availability of the data would be in the best interests of patients, doctors, third-party payers, health researchers, and government agencies.

"THE CLINICAL TRIALS ARE FLAWED"

Defenders of antidepressants have noted a number of flaws in the clinical trials used to evaluate them. One is that the patients in these trials were not depressed enough. In fact, using the American Psychiatric Association classification scheme, the mean baseline severity was in the very severe range for all but one of the trials we analyzed. The one exception was a clinical trial involving moderately depressed patients, in which the response to drug was virtually identical to the response to placebo.

"Very severe" is the most severe category in the classification scheme. So how can it be asserted that the patients were not depressed enough? One possibility is that clinical trial researchers distort the data. According to a spokesperson for the FDA, patients may be rated as more severely depressed than they actually are so that they will qualify for the trial (4). Now if this is true, then the response of treatment is even less than the clinical trials indicate, unless of course the researchers also inflate scores at the end of the trial. Equally troubling is the idea that researchers are intentionally distorting the data in any way. These trials are the basis for drug approval. If the data have been distorted, then perhaps the drugs should not have been approved in the first place.

Whereas some critics have complained that the patients in the clinical trials we assessed were not depressed enough, others have argued that they were too depressed. An editorial in Nature Reviews Drug Discovery, for example, complained that "All but one trial analyzed involved groups with mean initial depression scores in the 'very severe' range, limiting the strength of extrapolations" (13). Of the two contradictory criticisms, this is the more cogent. The drug companies did not conduct any trials on patients between the very severely depressed and moderately depressed categories. But here too, the evidence should be on the companies to demonstrate efficacy for the severely—but not *very* severely—depressed patients.

There may be many flaws in clinical trials, including relatively short durations, unrepresentativeness of the sample, and the breaking of blind by patients and doctors on the basis of side effects (14). But these trials are the data on the basis of which the drugs were approved. If they are flawed, then we have no evidence of drug effectiveness, and the drugs should not have been approved in the first place.

"DON'T ASK; DON'T TELL"

Finally, some have argued that even if the drugs don't work, it was wrong of my colleagues and me to publish our studies. We shouldn't tell patients that the drugs don't work because it will undermine their faith in treatment. I disagree. Without accurate knowledge, patients and physicians cannot make informed treatment decisions, researchers will be asking the wrong questions, and policymakers will be implementing misinformed policies. If the antidepressant effect is largely a placebo effect, it is important that we know this. It means that improvement can be obtained without reliance on addictive drugs with potentially serious side effects (15, 16).

REFERENCES

1. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, et al. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. PLoS Med 2008; 5(2): e45 doi:10.1371/journal.pmed.0050045
2. Turner, E.H. et al., Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. New England Journal of Medicine 2008; 358: 252-260.
3. Melander, H., et al., Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. British Medical Journal. 2003; 326: 1171-1173.
4. Elias, M., Study: Antidepressant barely better than placebo, in USA Today. 2002.
5. Wolf, S., Effects of suggestion and conditioning on the action of chemical agents in human subjects the pharmacology of placebos. Journal of Clinical Investigation. 1950; 29:100-109.
6. Ikemi, Y. and S. Nakagawa, A psychosomatic study of contagious dermatitis. Kyushu Journal of Medical Science. 1962; 13: 335-350.
7. Hróbjartsson, A. and P.C. Gøtzsche, An analysis of clinical trials comparing placebo with no treatment. New England Journal of Medicine. 2001; 344:1594-1602.
8. Wampold, B.E., Z.E. Imel, and T. Minami, The placebo effect: "Relatively large" and "robust" enough to survive another assault. Journal of Clinical Psychology. 2007; 63(4):401–403.
9. Frank, J.D., Persuasion and healing. Revised ed. 1973, Baltimore: Johns Hopkins.
10. Teasdale, J.D., Psychological treatments for depression: How do they work? Behaviour Research and Therapy. 1985; 23:157-165.
11. Kirsch, I. and G. Sapirstein, Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. Prevention and Treatment. 1998; 1: Article 2a.
12. Kornstein, S.G., et al., Gender differences in treatment response to sertraline versus imipramine in chronic depression. American Journal of Psychiatry. 2000; 157:1445-1452.
13. Editorial, A double-edged sword. Nature Reviews Drug Discovery. 2008; 7:275.
14. Rabkin, J.G., et al., How blind is blind? Assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. Psychiatry Research. 1986; 19:75-86.
15. Ferguson, J.M., SSRI Antidepressant Medications: Adverse Effects and Tolerability Prim Care Companion J Clin Psychiatry. 2001; 3(1):22-27.
16. Warner, C.H., et al., Antidepressant Discontinuation Syndrome. American Family Physician. 2006; 74(3):449-456.

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FOCUS REVIEW

Placebos and Medical Education

Amir Raz*, Daniella Guindi

THE PLACEBO CHALLENGE

Placebos are ubiquitous, counterintuitive, topical, and germane to medical science (1). Current scientific understanding about placebos, however, is sparse, fraught with debates and even explicit confusion (2-4). Whether one subscribes to placebo phobia or placebo mania (5), the domain of placebos draws on definitions, concepts, and paradigms that often baffle not just the general public, but the greater medical community (3). Thus, many modern physicians find placebos difficult to swallow or prescribe for others (6). As we discuss separately in this issue, ethical considerations complicate administration of placebos in clinical settings (7-9). Ethics aside, however, practitioners seem unclear even about fundamental concepts in the science of placebos, including the difference between placebo effect and placebo response (10). The platitudes health care professionals utter about placebos in personal communications and over cocktails provide ample evidence for this trend. The bright McGill University fourth-year medical students who attended my Placebos in Medicine class were products of this dynamic. (McGill Medical School offers Placebos in Medicine as an elective component to a Medicine and Society core course).

Medical students receive little education about placebos. This lacuna may well explain why the medical community continues to entertain an incoherent understanding of the placebo effect, largely considering it a sham effect, albeit one coupled with a powerful physiology (11). Furthermore, most contemporary medical students obfuscate the little they know of placebos with what they learn in "physicianship" (i.e., courses focusing on the "softer" issues of medicine, such as bed-side manner). Speciously, they seem to view placebos through the narrow lens of grooming and dressing well for the clinic, smiling at patients, and maintaining a cheerful attitude. Consequently, tomorrow's clinicians expect placebos to wield a minor effect, if any. Medical students draw their inspiration from today's physicians, who themselves often maintain erroneous conceptions about placebos (12). As a senior physician-colleague recently put it to me, most placebos are inert, yet to do something (e.g., cause changes) they need to be anything but "inert." As a matter of fact, most placebos are inert, yet changes do occur (13, 14). Historically, physicians have been keenly aware that sick people get better after taking inert drugs (11). It is less evident, however, that physicians were then, as they are now, largely ambivalent about placebos (15-17).

From the outset, the road to a medical career seems congruent with reductionist science but incongruent with social science. For example, scoring highly on the Medical College Admission Test (MCAT) may make understanding placebos more difficult. The 260-minute MCAT comprises 60 minutes of "verbal reasoning," an hour-long "writing sample" and a 70-minute (54%) even split between "physical sciences" and "biological sciences." It is apparently vital that future physicians are conversant with 17th-century physics. In the biological sciences, biochemistry aside, the MCAT favors a knowledge of "things" (e.g., the details of prokaryotic cell transcription and translation) over an understanding of "relationships" (e.g., among predators, prey, plants, insects, and climate). Subsequently, medical education scantily draws on core issues in the social sciences and seldom addresses the complexities and subtleties of emotion, ritual, or culture. Such medical education may be advantageous for understanding causal relationships (e.g., penicillin kills bacteria), but may be less helpful when cause and effect

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Text Box 1: Excerpts from Student Comments

Below is a compilation of a few short excerpts from Placebos in Medicine students who completed the course:

"Due to its central role in medicine, not appreciating the value of placebos imposes an unfortunate limitation on both physicians and their patients. Dr. Raz's course sheds light on the how and why, while empowering students to leverage this knowledge for the ultimate well being of patients, [providing] a compelling means to achieve higher standards of care."

"I have always wondered about the art of medicine, the true fusion between science, disease knowledge, patient interaction and cure. After taking the placebo course, I [am beginning to understand] some of the complexities behind this art."

"The universality of placebos and the power of placebo effects became explicit [during the course]. I quickly realized its utility in our profession, no matter which specialty any of us would choose."

"The most important thing I have learned is that the placebo effect is everywhere; it's in the way I interact with my patients, the route of administration of the medication [I am providing], and even in the number of times I tell them to take a pill every day."

"After attending the placebo class, I changed my approach to my everyday medical interactions."

"[This elective] emphasized the importance [of] physicians having a deep understanding of the power of communication and suggestion."

"[We] learned about the complex issues of how to define the placebo effect, why some people can be more affected than others, and how placebos are significant [outside] placebo-controlled trials."

are more subtle. For example, why would a drug work twice as well in one country than in another? Why would a pill work better when it is blue than when it is red? And why do more placebos work better than few?

A CHECKERED HISTORY

Most people still construe the Latin word "placebo," as "I shall please" although this designation probably stems from a misattribution. In medieval English the term placebo took on a different meaning, referring to a sycophant who endears others with trickery rather than with substance. By the early nineteenth century a placebo referred to any medicine designed more to please than benefit the patient. Consequently, by the mid-nineteenth century it was common for people to refer to such treatments not just as "placebos" but as "mere placebos." At that time, reports described water as more effective medicine than placebos (12).

While early placebos were inert substances administered primarily to please the patients, the biological revolution of the twentieth century imbued the meaning of placebos with an unexpected twist. Considering them effective treatments, practitioners had been prescribing roborants to patients, only to learn from subsequent scientific research that their drugs were placebos (18). In more ways than one, such drugs had been prescribed not to please patients but to please doctors (16).

While anecdotal clinical trial reports comparing placebo and no-treatment groups found little evidence for placebo effects (19, 20), such claims have been widely critiqued (21-23), and the history of medicine is replete with placebos and abundant accounts document their therapeutic potential (11). The rise of evidence-based medicine, however, seems to have resulted in amnesia among many modern clinicians. Whereas even doctors from historical fiction know that their patients' attitudes toward medical treatment comprise a fundamental part of the healing process (24), the majority of present-day physicians are neither savvy nor conversant with research findings regarding placebos (16). Forging an interaction between biology and psychology, however, placebos elucidate many fascinating aspects of human culture and physiology (25, 26). They are integral to medicine and should have an important place in contemporary medical education.

A PROMISING PROSPECT

Outside of clinical trials, some physicians exclusively associate placebos with non-specific approaches such as psychotherapy and complementary and alternative medicine (CAM) (27). Many professionals, for example, inaccurately construe placebos as inevitably leading to the promotion of therapies that fall short of normal scientific standards of evaluation (28, 29). Whereas most CAM practices – ranging from the

preposterous to the somewhat-plausible-but-as-yet-unproven – are incongruent with scientific standards (30), placebo research is the apotheosis of marrying the sensibilities of experimental psychology with the applied value of clinical science (25).

What we think, say, and know about the world can have a dramatic influence on our physiology because culture and biology interrelate in powerful ways. Current medical education, however, may be more an impediment than an aid for grasping and leveraging placebos in medicine. Cause and effect are undeniably more tenuous in the social sciences relative to the dynamics of levers and pulleys, but to suggest a physics model of causality to our future physicians is to mislead them in ways far worse than placebos may mislead their patients.

Adding a full course on the clinical science of placebos to an overburdened medical school curriculum is a logistic challenge. It is feasible, however, to provide medical students with insights from social and cognitive psychology, medical anthropology, and other relevant social science disciplines. Placebos in Medicine was my effort to lead by example and offer interested medical students a peek into the science of placebos. It was my hope that such brief exposure would whet their research appetite, pique their intellectual curiosity and, most importantly, make them into better physicians. The students' reviews and enthusiastic response to the course's material suggest that placebo education may be sorely lacking from current medical pedagogy (see Text Box 1 for a few brief excerpts).

While medical schools have emphasized traditionally that the most important aspect of any medical experience is its content, the role of psychosocial factors and their influence on treatment is looming increasingly large. It is now evident, albeit strange and counterintuitive, that receiving – rather than the actual content of – medical treatment can initiate a healing process (31, 32). The medical community should engage in an open discussion regarding the relative merits and shortcomings of placebos in medicine because physicians must draw on relevant insights from the entire spectrum of science, including social science, to better heal and cure. An effective training program, therefore, must introduce future physicians to the science of placebos.

REFERENCES:

1. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. Journal of the American Medical Association. 2008 March 5, 2008;299(9):1016-7.
2. Ernst E. Placebo: new insights into an old enigma. Drug Discovery Today. 2007;12(9-10):413-8.
3. Harrington A. The many meanings of the placebo effect: Where they came from, why they matter. Biosocieties. 2006;1:181-93.
4. Kaptchuk TJ. Powerful placebo: the dark side of the randomised controlled trial. Lancet. 1998 Jun 6;351(9117):1722-5.
5. Rothman KJ. Placebo mania. British Medical Journal. 1996 Jul 6;313(7048):3-4.
6. Shapiro AK, Shapiro E. The powerful placebo: from ancient priest to modern physician. Baltimore: Johns Hopkins University Press; 1997.
7. Ehni HJ, Wiesing U. International ethical regulations on placebo-use in clinical trials: a comparative analysis. Bioethics. 2008 Jan;22(1):64-74.
8. Miller FG, Kaptchuk TJ. Sham procedures and the ethics of clinical trials. Journal of the Royal Society of Medicine. 2004 December 1, 2004;97(12):576-8.
9. Thompson WG. The placebo effect and health: combining science and compassionate care. Amherst, N.Y.: Prometheus Books; 2005.
10. Kirsch I. Hidden administration as ethical alternatives to the balanced placebo design. Prevention & Treatment. 2003 Jun;6(1): No Pagination Specified.
11. Harrington A. The placebo effect: an interdisciplinary exploration. Cambridge, Mass.: Harvard University Press; 1997.
12. Moerman DE. Meaning, medicine, and the "placebo effect". Cambridge, U.K. ; New York: Cambridge University Press; 2002.
13. Moerman DE, Jonas WB. Toward a research agenda on placebo. Advances in Mind-Body Medicine. 2000 Winter2000;16(1):33.
14. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. Annals of Internal Medicine. 2002 Mar 19;136(6):471-6.
15. Moerman D. Doctors and patients: the role of clinicians in the placebo effect. Advances in Mind-Body Medicine. 2003 Spring;19(1):14-22.
16. Harrington A. The cure within: a history of mind-body medicine. 1st ed. New York: W.W. Norton; 2008.
17. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annual Review of Pharmacology and Toxicology. 2007 Jul 31.
18. Houston WR. The doctor himself as a therapeutic agent. Annals of Internal Medicine. 1938 Feb;11(8):1416-25.
19. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. New England Journal of Medicine. 2001 May 24;344(21):1594-602.
20. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. Journal of Internal Medicine. 2004 Aug;256(2):91-100.
21. Wampold BE, Imel ZE, Minami T. The story of placebo effects in medicine: Evidence in context. Journal of Clinical Psychology. 2007;63(4):379-90.
22. Wampold BE, Imel ZE, Minami T. The placebo effect: "Relatively large" and "robust" enough to survive another assault. Journal of Clinical Psychology. 2007 Apr;63(4):401-3.
23. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS. The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. Journal of Clinical Psychology. 2005;61(7):835-54.
24. O'Brian P. Master and commander. New York: W.W. Norton; 1990.
25. Raz A. Genetics and neuroimaging of attention and hypnotizability may elucidate placebo. International Journal of Clinical and Experimental Hypnosis. 2008;56(1):99 - 116.
26. Raz A. Hypnobo: perspectives on hypnosis and placebo. The American Journal of Clinical Hypnosis. 2007 Jul;50(1):29-36.
27. Raz A, Michels R. Contextualizing specificity: specific and non-specific effects of treatment. The American Journal of Clinical Hypnosis. 2007 Oct;50(2):177-82.

28. Beyerstein B. Alternative medicine: Where's the evidence? Canadian Journal of Public Health. 1997 May-Jun;88(3):149-50.
29. Beyerstein BL. Alternative medicine and common errors of reasoning. Academic Medicine. 2001 Mar;76(3):230-7.
30. Colquhoun D. Science degrees without the science. Nature. 2007 Mar 22;446(7134):373-4.
31. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Annals of Internal Medicine. 2002 Jun 4;136(11):817-25.
32. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? Journal of Clinical Epidemiology. 2000 Aug;53(8):786-92.

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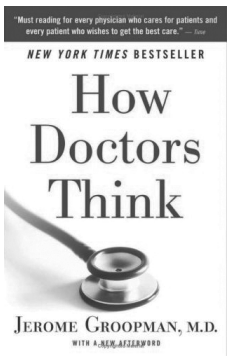
BOOK REVIEW



Book Review by Chenjie Xia, McGill University,
by Dr. Jerome Groopman

Mariner Books; 1st edition
(Feb 13 2008)
ISBN-10: 0547053649
ISBN-13: 978-0547053646
Price: $17.95

In his latest book, How Doctors Think, Dr. Groopman, a haematologist affiliated with Harvard Medical School, takes the readers on a tour of a wide range of medical fields while jumping swiftly back-and-forth between the physician and the patient's perspective. Most chapters open with the story of an individual patient and his doctor, whose interactions introduce us to an aspect of problem-solving in medicine. The author then further expands upon the subject in an essay form by weaving into the story-telling opinions from experts of cognitive thinking in medicine as well as evidence from recent research work on the topic. The stories, although slightly melodramatic at times with their predictable climax followed by a happily-ever-after resolution, do provide an accurate and helpful glimpse of the complex infrastructures of health care to those unfamiliar with the field. Dr. Groopman possesses a quite impressive ability for stripping medical facts of their jargon and rendering them accessible to laymen. Each story directs his lens onto particular "cognitive errors" in the practice of medicine, a term he uses to describe flaws in the thinking of physicians that result in misdiagnosis and/or mismanagement of illnesses. Then, deftly alternating the focus between the analysis and the story, he intertwines theory and practice to demonstrate how these mental traps can be averted.

A common belief among the general public, fuelled by popular entertainment media, unreservedly equates advanced technology with better medical care. Although health care providers attempt to show a bit more discernment toward the magnetic attraction of technology, we nevertheless find ourselves engulfed by this tornado of armamentarium that allows us to see deeper and smaller into the human body. Certainly, new technology is not portent of the downfall of medicine, on the contrary. But Dr. Groopman guards us against the looming danger of relegating to the back row the time-old skills of speaking and listening to the patient in favour of simply relying on faster and easier tests in making a diagnosis. Example after example, he highlights the risk of overlooking important subtleties, nuances and ambiguities in a patient's illness if we are not tuned in to their speech, their body language, their personal background. In a similar argument, he calls upon our caution in facing the increasingly influential presence of algorithms and guidelines in clinical practice. He asserts that these recipe-like approaches lead to cognitive errors in hindering creativity and flexibility of our thinking. He concedes that medicine is dominated by uncertainty and practiced with trial-and-error, and it is thus by no hazard that an atmosphere of conformity in medical practice is required to provide a certain structure. However, he urges us to never become passive followers of orthodoxy, to always challenge the rigor and validity of what we are taught and what we believe to be the truth. To those who assert doctors will no longer be needed with the increasing widespread access to information and the technological advancement of diagnosis and treatment modalities, How Doctors Think provides a resounding counterargument to their preposterous claim.

Through his vivid story-telling, where individual doctors, the pediatrician, the endocrinologist, the plastic surgeon or the radiologist, come to life each with their own distinct personality and emotional profile, Dr. Groopman reminds us that the most neglected and thus most threatening source of cognitive error is the physician himself. As fallible individuals, our own past experiences and current state of mind can greatly colour and sometimes cloud our judgement. For example, faced with a "difficult" patient who is failing treatment for a chronic illness because of non-compliance to medication, many physicians will feel annoyed or perhaps even disgusted. Dr. Groopman asserts that these are quite natural reactions from a physician; it would be ludicrous to demand complete emotional detachment from physicians, who are also human beings. The danger lies not within the existence of these emotions per se, but rather with the ignoring of them as potential sources of cognitive errors. He further argues that because each physician's particular temperament precludes him from being compatible with all types of patients, when choosing a physician, one should always keep in mind that a "good doctor" for your neighbour might not turn out to be a "good doctor" for you.

This book primarily targets the general public, but it is

also of tremendous value to medical practitioners of all levels, especially for those on the giving and receiving ends of medical education. For example, we are taught as beginner medical students to pose diagnoses through a step-wise, logical approach. However, shortcuts and pattern recognition easily find their way into our daily work with patients, most often subconsciously. Again, Dr. Groopman argues that the use of gestalt in clinical practice need not be frowned upon, in fact, it is often necessary in situations of time-restraint. What needs to be amended in the curriculum is the explicit acknowledgment of pattern recognition in clinical practice in order to empower novice medical students to use it consciously and with full awareness of its pitfalls. Medical students are taught many skills to avoid technical errors; it is now time for cognitive errors to share some of the spotlight as well. And this new focus does not only apply to medical students, but to the entire medical community. In How Doctors Think, numerous examples are offered of individual physicians or teams of medical care providers openly discussing cognitive errors and reflecting on changes both at their own individual and institution levels to avoid similar future occurrences. In that respect, Dr. Groopman's book is more than a candid reflection of our mistakes, it is also a celebration of those who, through creativity, open-mindedness and dedication, have been and will be learning from these mistakes to provide better patient care.

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