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EDITORIAL

IMPACTING THE PRACTICE OF MEDICINE BY INDUSTRY

Steven Lin, BMSc

The practice of medicine has dramatically changed over the last several decades. Many important factors have led to this evolution, which include the advent and accessibility of medical-related information from the Internet. This facilitated the evolution of the patient-physician relationship from one of paternalism and unquestionable authority to one of cooperation and compromise. Some believe that this new relationship has been responsible in part for the medicalization of society. Medicalization occurs when previously non-medical problems are treated as medical problems, which tend to be classified as illnesses or disorders. Although it is not the purpose of this editorial to address the controversy of treating disorders such as erectile dysfunction and attention-deficit hyperactivity disorder as medical problems, it will examine the influence of medicalization on the creation of new markets and its impact on the practice of medicine.

There has been a growing public demand for medical solutions. Some have suggested that the public's tolerance for mild symptoms and benign diseases has decreased, which has led to the redefinition of uncomfortable body states and isolated symptoms as medical diseases (1). Furthermore, patients have become more knowledgeable, more demanding, and more critical of the medical profession. The Internet has allowed easy access to health-related information and has acted as a forum for open communication between people with similar views. This has spurred the development of medical markets in which the pharmaceutical industry plays a large and active role.

For decades, drug manufacturers have directed their promotion at the medical profession. This was most reasonable considering the paternalistic patient-physician relationship of the time. However, it was not until 1985, when the industry proposed to and was approved by the Food and Drug Administration (FDA) to advertise, although with some restrictions, to consumers on the basis that it would be of educational benefit and facilitate consumer empowerment over personal health care. In 1997, the FDA issued new guidelines and revisions for broadcast direct-to-consumer (DTC) advertising, which included fewer restrictions on providing drug names and medical conditions, and on disclosing product risks (2). Accordingly, the pharmaceutical industry increased its DTC advertising expenditure from under 800 million to almost 2.5 billion dollars from 1996 to 2000 (3).

The effects of DTC advertising by the pharmaceutical industry can be better appreciated by examining the marketing history of paroxetine, better known as Paxil. In 1996, Paxil was approved for the treatment of depression, a market that was quickly saturated with other selective serotonin reuptake inhibitors (SSRI). It was not long before the manufacturers of Paxil, now called GlaxoSmithKline, sought FDA approval for other uses, particularly for anxiety. Paxil became the first drug approved for the treatment of social anxiety disorder (SAD) and generalized anxiety disorder (GAD) in 1999 and 2001, respectively. The multimillion dollar marketing and advertising campaigns helped redefine people's views on common emotions such as worry and shyness. Numerous broadcast advertisements that included both personal accounts and "expert" advice appeared on television and radio. There were even bus stop posters with slogans such as "Imagine being allergic to people". Soon after, consumers were even offered "self-tests" at www.paxil.com to help assess the likelihood of suffering from SAD and GAD. Dr. Edna Foa, Director of the Center for the Treatment and Study of Anxiety and Professor of psychology at the University of Pennsylvania, commented, "One gets the impression from the ads that if you are shy and you have some difficulties and you want to be outgoing, then take Paxil. You are promoting medication when it is unnecessary" (4). The disease awareness campaigns that focused on individual's fears in specific social situations, especially when public speaking, helped redefine and medicalize emotional states, and by doing so, created an expansive medical market. Barry Brand, Paxil's product director, told the journal Advertising Age, "Every marketer's dream is to find an unidentified or unknown market and develop it. That's what we were able to do with social anxiety disorder" (4).

DTC advertising can affect the patient-physician dynamic positively by increasing the dialogue about diagnoses and treatment options. At best, it has the potential of helping patients become better informed and of accelerating the trend toward patient autonomy. However, pharmaceutical companies are primarily responsible to their shareholders and not to patients. This presents an obvious conflict of interest when “educational” DTC advertisements are used to market brand-name drugs and to increase drug sales. Physicians' attitudes toward DTC advertising are often

negative. In a survey of family physicians, about 80% thought negatively of DTC advertising citing that the advertisements were promoting a misleading and biased view (5). This type of advertising can lead to more frequent discussions that digress from meaningful issues of diagnoses and treatments to more trivial matters such as brand-specific drugs. DTC advertising also has the potential of creating a society of aggressive, distrustful and ill-informed patients.

The influence of industry continues to change the practice of medicine, particularly the patient-physician relationship. As health care professionals, we must remind patients that although DTC advertising can inform them, it should not be confused with medical advice. This is a new role for physicians to act as a learned intermediary between patients and the advertisements from industry.

In the midst of these changing times, this *MJM* issue includes several articles that recognize the impact of industry on other facets of medicine, including my contribution reviewing the recent concerns over the safety of selective cyclooxygenase-2 (COX-2) inhibitors.

It is important to recognize that there are closer ties between industry and medicine than ever before--even in medical education. For example, the American Academy of Dermatology announced the initiative of a pilot program that would fund 10 new dermatology residency positions for the 2006 US match from donations made by the academy, pharmaceutical companies and other interested parties (6). Not surprisingly, the program has met with resistance over concerns about protecting residents from industry influence during their training. It is unclear to what extent will the practice of medicine change from the influence of industry. But it is more than likely that we will continue to see more examples of this growing relationship.

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LETTERS TO THE MJM

NEGLECTED DISEASES: WHY DO SOME MAJOR DISEASES RECEIVE LESS ATTENTION THAN OTHERS?

Dear *MJM*,

Infectious diseases pose serious threats to healthcare in developing countries. The list of these diseases is endless. They are all damaging and they are all serious. However, a few of them receive most of the public attention. The media is always after 'juicy' stuff. It likes to focus on murderers who kill in a 'stylish' way like HIV which attacks the patients' immune system leaving them vulnerable to other opportunistic infections or like Ebola and other hemorrhagic fevers that makes patients bleed from every body orifice they have (1). There are many movies about AIDS victims (2). Ebola has inspired a few best-selling novels and at least one Hollywood movie (Outbreak, Directed by Wolfgang Petersen) (3). But, as far as I know, there are no movies, except for documentaries, featuring malaria (300 million acute illnesses annually)(4), Bilharziasis (200 million people infected, 600 million at risk) (5), tuberculosis (one third of the world's population infected) (6) or Onchocercial river-blindness (17.7 million people infected) (7). In 2004 about 40 million people were living with HIV/AIDS and 3.1 millions died of it (8) however, the WHO stresses the fact that while tropical infectious diseases permanently disable millions of people each year, they cause comparatively few deaths and it is this low mortality that makes it harder to draw international attention to their grave toll (9).

This trend is dangerous because it steals public interest and consequently resources from legitimate efforts against many other killers (10). Probably malaria, tuberculosis and Bilharziasis are not as 'photogenic' or as slick as HIV or Ebola but they still claim millions of people every year (4-9). These are not diseases that can be overlooked. In the context of their chronicity the word 'lives' gains another sense; it stands for the miserable tens of years patients live after they catch any of these debilitating diseases multiplied by the millions of individuals affected. If we look at things this way we will realize the impact of such "unlucky" infections on those unfortunate patients.

Blaming the media is probably the more good-natured explanation; the other one carries the more selfish face of the drug industry in rich countries. Of the 1233 new drugs identified as reaching the market between 1975 and 1997, only 13 were approved for neglected tropical diseases (11,12). This has given rise to a global 'drug gap' (13), in which the drug companies invest almost exclusively in drugs for the developed world that will be marketable and profitable (14,15). Funds and resources mostly come from developed nations, which are primarily interested in targeting diseases that affect their citizens (like AIDS), the people who can pay for the drugs (14,15). Patients who contract the same infection in poor countries may indirectly share some of the benefits of such programs, such as the development of new antiretroviral drugs just because they are 'lucky' enough to be infected with a disease that receives interest from the rich drug companies. In such cases the pharmaceutical industry sees a potential market in patients from developed countries infected with the same disease, for example a poor African patient might not be able to afford antiretroviral treatment but many patients from the US or Europe with HIV/AIDS will have medical insurance to pay for the drug thus making the whole deal profitable (14). Not all patients are that 'lucky'. Many have infections confined to developing, poor countries that present no market prospects for the pharmaceutical industry (14,15), thus making infections like sleeping sickness and Chaga's disease the world's 'most neglected diseases' (14)

It has been estimated that less than 10% of global spending on health research is devoted to diseases or conditions that account for 90% of the global disease burden (15,16), a disparity known as the 10/90 gap (16).

What we need now are initiatives to provide equal opportunities for patients with different diseases; that is, some sort of "affirmative action" to reverse the ill-effects of a long lasting discrimination between diseases. Médecins sans Frontières believes that the best hope of controlling the world's most neglected diseases is for the public to accept responsibility for drug development (14). Highlighting neglected diseases in the media would be a very effective tool to move the public. Medical students can play a vital part in that. They should learn about diseases not common in their locality, especially major global infections that do not receive due attention from the media or medical school curricula, and transmit their knowledge to other healthcare workers and to the public. We should strive to bring the suffering of millions of patients with these diseases into focus. The increasing awareness will hopefully help to direct more resources and funds into interventions and research projects to alleviate suffering.

Sincerely,

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Faculty of Medicine, Assiut University, Egypt

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PRIMUM NON LUCRIFACERE: THE INTRODUCTION OF NO FREE LUNCH AT MCGILL

Dear *MJM*,

In this era of exponential advances in medicine and biomedical technology public resources to fund this explosion of research are becoming increasingly strained. It is a result of this that researchers are forced to rely or seek private funding in basic science and clinical research, with as many as 66% of therapeutic trials receiving some form of pharmaceutical industry funding.

This leads toward a situation which lends itself to an ethical dilemma, and a conflict-of-interest: a pharmaceutical company's primary obligation is toward its shareholders, a clinician-researcher is expected to be both a scientist and a physician - they must hold themselves to the standards of the scientific process, and above all, to the care of the patient.

The breach of the social obligation of the pharmaceutical company and the researcher toward the ethical and evidence-based care of the patient, and the introduction of systematic bias into clinical research, has been widely documented (1). Research articles with findings non-favourable to industry goals are often delayed or suppressed, principal investigators with principled objections are removed from publication or threatened, and in one study it was demonstrated that eleven percent of articles were "ghostwritten", and nearly twenty percent of articles named authors who did not sufficiently contribute to their writing (2).

Research is certainly not the only area of medical practice into which the influence of the pharmaceutical industry has crept. Pharmaceutical representatives are omnipresent in primary-care practices, at CME or all kinds, including hospital rounds and medical conferences, and in private offices or private events. Exposure to pharmaceutical representatives and pharmaceutical advertising has been adequately studied and repeatedly demonstrated to adversely influence appropriate prescribing and educational practices, and cost of prescriptions (3). The benefits of extricating medical education and medical practice from the influence of the drug industry are well known; up to 75% of Canadian family medicine residency programs thus far have implemented some form of guidelines regulating the interactions between their residents and the pharmaceutical industry, however less than a quarter of residents in family practice have actually read the national guidelines, and 60% to 90% (4,5) of residents polled agree that more teaching about industry-physician interactions is warranted. Pharmaceutical advertising is effective, though few physicians have the

insight admit that they themselves are affected by it. In a telling survey of resident attitudes toward pharmaceutical advertising, 61% of residents felt their clinical decision-making to be unaffected by pharmaceutical advertising, whereas only 16% felt their peers to be similarly uninfluenced (6).

Even those not in direct and frequent contact with pharmaceutical detailing or advertising are at risk of being misled: Choudhry and colleagues surveyed 192 authors of clinical practice guidelines (CPGs) for common adult diseases; they found that nearly 60% of the respondents noted a prior financial relationship with a pharmaceutical company whose drug was being considered in the CPG (7).

The lists of offenses against ethical medical practice continue: the distribution of false and even downright dangerous advertising material in the name of profit(3); disseminating false or inappropriate information in educational settings (3); engaging in advertising practices targeting the general public shown to create strain in the patient-physician relationship (8).

Perhaps the most frightening evidence of the unsuspecting nature of the physician toward this covert, and overt, manipulation of their policies and practices is the surgical precision with which the pharmaceutical industry has analyzed the cost-benefit ratio of advertising. They know down to the dollar how much advertising is required to bend the doctors far enough to maximize their profits. A recent publication in the Journal of Marketing has even come to the statistical conclusion that doctors are under-saturated with pharmaceutical representative visits and colourful journal advertisements (9). The same author published another recent article on how to best manipulate the public to persuade their physician to prescribe a particular company's medication (10).

For those readers who still do not believe the dangers of the intimacy between pharmaceutical companies and medicine at all of its levels have simply to answer one question - why else would the pharmaceutical companies, who are profit-driven, spend well over $11 billion per year in advertising to physicians in the United States alone (3)? To quote an economic analysis by the non-profit health policy NGO, FamiliesUSA.org:

"U.S. drug companies that market the 50 most often prescribed drugs to seniors spent almost two-and-one-half times as much on marketing, advertising, and administration as they spent on research and development (R&D) in 2001".

The solution rests in the hands of the medical profession. The pharmaceutical companies are not to blame: they do what they are meant to do, which is to appease their share holders, and they do it very well. The solution must begin on an individual level - it is up to each physician to improve their standards of ethical behaviour. There have been several guidelines written by national organizations to this effect (11), but the bottom line is self-awareness. It is for this reason that a group of medical students at McGill University have decided take an active stance on this critical issue, and to create a local chapter of No Free Lunch at McGill.

Sincerely,

Adam Hofmann, MD,CM
Founder and Co-Leader of "No Free Lunch McGill"

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ORIGINAL ARTICLE

Female Sexual Dysfunction in Married Medical Students

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ABSTRACT:

Background: Sexuality and its manifestation constitute some of the most complex of human behavior. Sexual dysfunction is more prevalent in women than in men. Prevalence of the subgroups of female sexual disorders is: desire disorder in 5-46%, arousal disorders in 7-10% and orgasmic disorders in 7-10%. The objective of our study was to measure the prevalence of female sexual dysfunction in female medical students. Materials and Methods: Thirty two medical students participated in the study. The mean age was 24.30± 1.29 years. Duration of marriage was 2.68±1.5 years. Their husbands' education ranges from secondary school diploma to PhD. Persian version of Sexual Function Questionnaire (SFQ) was piloted among medical students with and without chief complaint of female sexual dysfunction. Results: Prevalence of an abnormal score in each subgroup of SFQ was as follows: 20.0% in desire, 56.7% in arousal sensation, 33.3% in arousal lubrication, 36.7% in orgasm, 6.7% in pain and 20.0% in enjoyment. In our study 40.0% had sexual problems at least in one subgroup and 6.7% had problems in all subgroups. Only 2 participants were unsatisfied with their sexual life and seeking for any treatment. Discussion: In this study, prevalence of Female Sexual Dysfunction (FSD) ranges from 6.7% to 56.7% in subgroups of the disorder. Solving social problems have critical effect on quality of life. Evaluation of FSD is important in total and especially in women who are university educated and will be occupied in essential positions.

KEY WORDS: female sexual dysfunction, medical student, sexual function questionnaire

BACKGROUND

Sexuality and its manifestations constitute some of the most complex of human behavior. The expression of sexuality and intimacy remains important throughout the life span (1). We know that female genital sexual response is a combination of vaso-congestive and neuromuscular events in the genital tract and pelvic floor which are controlled in part, by specific neurotransmitters (2). Female sexual response begins with desire (libido) for sexual interaction. Masters and Johnson (3) in 1966 described four component of the sexual response: excitement, plateau, orgasm and resolution. But the act of sex includes a woman's sexual self and self-image, intimate relationships, family, society and culture. The complexities of her environment, sexual and partner history, past relationships, mental health status, current medical problems and hormonal status all play a role (4).

Sexual dysfunction is defined as "disturbances in sexual desire and the psycho-physiological changes that characterize the sexual response and cause marked distress and interpersonal difficulty"(5). It is a

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combination of problems that has both biologic and psychosocial components and is multi-factorial in etiology. Until recently, the diagnosis of female sexual dysfunction (FSD) has relied on the classification system of the American Psychiatric Association's Diagnosis and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). This classification was expanded to include psychogenic and organic cause of desire, arousal, orgasm and sexual pain disorders. (4,6) New questionnaire such as Sexual Function Questionnaire (SFQ) was designed to respond to this need.

Hypoactive sexual desire disorder is the persistent or recurrent deficiency of sexual fantasies, thoughts and/or desire for or receptivity to sexual activity which cause personal distress. Female sexual arousal disorders (FSAD) include the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress. An orgasmic disorder is the persistent or recurrent difficulty, delay in or inability to attain orgasm following sufficient sexual stimulation and arousal causing personal distress. Sexual pain disorders include dyspareunia, vaginismus and non-coital sexual pain disorders (4).

Most studies suggest that sexual dysfunction is more prevalent in women than in men. A comprehensive literature review by Simons and Carey (7) notes an overall prevalence of the following disorders: desire disorders 5-46%; arousal disorders 7-10% and orgasmic disorders 7-10%. A study by Shokrollahoi et al in Iran was done and revealed the prevalence of inhibited desire 15%, inhibited orgasm 26%, lack of lubrication 15%, vaginismus 8% and dyspareunia 10%; 38% of the women had at least one sexual dysfunction. The most common sexual difficulties reported were "too little foreplay before intercourse" and" partner chooses inconvenient time" (8% each) (8).

Several measurements have recently been published and include the Female Sexual Function Index (FSFI) (9), the Female Sexual Questionnaire (SFQ) (6), and the Female Sexual Distress Scale (FSDS) (10).The FSFI was supported by Zonagen, Inc. and Bayer AG. It is 19-item questionnaire assessing six domains including desire, subjective arousal, lubrication, orgasm, satisfaction and pain. The SFQ, developed by Pfizer for clinical trials, is a 31-item survey that measures seven domains of female sexual function (desire, enjoyment, orgasm, arousal-sensation, arousal-lubrication, pain and partner satisfaction) (4). The FSDS was supported by Derogatis, et al. The original version has 20-item and a "polished" version has 12-item questionnaire assessing frequency or intensity of female sexual distress. It is important to remember that the prevalence data is dependent on the assessment techniques and these have been highly variable (7). SFQ is a multidimensional questionnaire which is utilized in many studies and clinical trials all over the world. SFQ was incorporated in four European, multi-center, phase II clinics and in USA (6).

The objective of our study was to determine prevalence of FSD among married medical students. We chose this group due to omit the effect of age, disease, and level of education as confounding factors.

MATERIALS AND METHODS

In this pilot study during spring 2004, 32 married medical students at Tehran University of Medical Sciences from different sociocultural levels were enrolled. Women in this study were aged 21-26 years (mean age ± SD: 24.30±1.29, range: 21-29).

We devised a questionnaire including: demographic data: female age, husband's age, husband's education, duration of marriage, past obstetrical history, past medical history, drug history during past 6 months, hirsutism, acne, pattern of menses, contraception method used, body mass index (BMI) and complaints of FSD (by clinical interview) (Table 1). Subsequently, SFQ-V1 questionnaire was completed by each subject.

Subjects with a history of ingesting drugs for more than 3 months in the past 6 months, endocrinologic diseases and psychiatric problems were excluded. Two were excluded because of past history of Diabetes mellitus and antidepressant use.

SFQ-V1 has 6 domains and 26 items. These 6 domains included desire, arousal-sensation, arousal-lubrication, orgasm, enjoyment and pain (6) (Table 2). For providing Persian version of SFQ -V1, a translation was produced and back-translated to English, to ensure that the original meaning of each item was maintained. Persian version of SFQ was circulated among married medical students. The prevalence of sexual dysfunction was calculated for each domain. The congruence of scores and demographic data were estimated.

This study was approved by the ethics committee of Tehran University of Medical Sciences. Data were evaluated with the statistical software package SPSS (release 10; Chicago, IL). Significant level sets at $P<0.05$.

RESULTS

Our subjects were medical students from the first to seventh levels. Husband's education ranges from secondary school diploma to PhD. All of the subjects were nulliparous. Four (13.3%) of subjects had acne. Hirsutism was found in 3 (10%). Hormonal assays were normal in these patients. In 40.0% the contraception method utilized was condom, 16.7% used oral contraceptives and 43.30% didn't use any contraception (Table 1).

Only 2 (6.6%) participants were unsatisfied about their sexual life in clinical interview and sought treatment.

Table 3 shows the frequency of sexual dysfunction detected by SFQ in each subgroup of sexual dysfunction. In our study 40.0% had sexual problems at least in one subgroup and 6.7% had problems in all subgroups.

To investigate various factors that may cause female sexual dysfunction, in a multivariate regression analysis, no significant relation was detected between female ages, male age, duration of marriage, male education, irregular menses, contraception methods used, BMI, hirsutism, and acne with FSD.

Table 1. Characteristics of female medical students who filled the Sexual Function Questionnaire

	Mean ± SD (minimum-maximum)
Female age (y)	24.30 ± 1.29 (21-29)
Husband's age (y)	27.03 ± 2.94 (22-34)
Duration of marriage (y)	2.68 ± 1.5 (1-6)
BMI (kg/m²)	22.76 ± 2.99 (17.85- 30.04)
	Number (%)
Husband education	
Diploma	2 (6.7%)
University education	28 (93.3%)
Contraception method used	
Hormonal	5 (16.7%)
Non-hormonal	12 (40%)
Nothing	13 (43.3%)
Menses	
Irregular	7 (23.3%)
Regular	23 (76.7%)

DISCUSSION

The major factors that determine a female's sexuality are as follows: genetic and hormonal factors, learning of sexual components early in adulthood, suggestion of parents about the sexual function of children, religion, cultural factors, depression, physical disease and aging (4).

It is difficult to select a group that is unique for this type of study. We chose medical students as a match case group because age, health, and education are important factors in determining female sexual function. The group that we chose was in the third decade of life. The age shows its effects on sexual function in older subjects (11). So the bias of age effect is omitted in this way. Level of education affects the complaint of FSD in the same way. Well educated persons can understand items of the SFQ more readily and answer to questions without shame.

In 1999, the National Health and Social Life survey reported that 43% of American women reported sexual problems including: lack of desire, decreased vaginal lubrication, pain and discomfort with intercourse, or decreased pleasure and difficulty achieving orgasm (12). One study in 2004 revealed that 55% of the evaluated women were satisfied with their sexual life in the last month, 20% were fairly satisfied and 21% were unsatisfied (13). In a German study on female medical students, prevalence of sexual dysfunction was 25% (13). According to our research only 6.6% of women complained about sexual problems. The low prevalence of seeking medical care for sexual dysfunction is related to cultural issues in Iran.

After completing SFQ, we showed that 40.0% had sexual problems at least in one subgroup and 6.7% had problems in all subgroups. In comparison with nations with similar socio-cultural factors, Cayan et al reported a prevalence of 46.9% in Turkish women. Prevalence of FSD was 21.7% in the ages of 18-27 years in the same study (11). Lower prevalence in young Turkish women and German medical students can be explained by difference in cultures. Shokrollahi et al studied the prevalence of sexual dysfunction in women seeking services at family planning centers in Tehran (8). There was at least one sexual dysfunction in 38% of women. Abnormality of desire, orgasm, lubrication and pain were found in 15%, 26%, 15% and 18% respectively. However in our study, these abnormalities were 20%, 36.7%, 33.3% and 6.7% respectively. It seems that having more knowledge about the physiology of orgasm and lubrication in well-educated subjects can explain the higher prevalence of reporting abnormality in these two categories. Subjects with higher levels of education can explain some degrees of their pain as physiologic event, however any pain in general population may interpret and reported as pathologic.

In this pilot study we found no relation between demographic factors (female age, husband's age, husband's education, duration of marriage, hirsutism, acne, pattern of menses, contraception method utilized and BMI) and FSD, however it is postulated that many factors including age, knowledge, sexual knowledge, body image, partner dissatisfaction, and life stress (such as unemployment), chronic diseases, culture and … have some effects on the prevalence of this disease. Shokrollahi et al reported that a positive correlation was found between sexual knowledge and the experience of orgasm ($r = 0.1990$, $p = 0.001$). Cayan et al reported that sexual dysfunction was observed as significantly higher in the presence of older age ($p=0.001$), lower educational level ($p= 0.012$), chronic disease ($p= 0.032$)

Table 2. Guidelines to SFQ scores: SFQ score ranges indicative of likelihood of sexual dysfunction and normal function

Domain	High probability of female sexual dysfunction	Borderline probability of normal sexual function	High probability of normal sexual function
Desire	5-16	17-22	23-31
Arousal-sensation	4-10	11-13	14-20
Arousal-lubrication	2-5	6-7	8-10
Orgasm	3-8	9-11	12-15
Pain	2-8	9-11	12-15
Enjoyment	6-16	17-22	23-30

Table 3. Prevalence of sexual dysfunction in relation to subgroups of sexual function

Domain	Mean ± SD	High probability of female sexual dysfunction	Borderline probability of normal sexual function	High probability of normal sexual function
Desire	18.44 ± 3.54	6 (20.0%)	18 (60.0%)	3 (10.0%)
Arousal-sensation	9.89 ± 3.89	17 (56.7%)	5 (16.7%)	7 (23.3%)
Arousal-lubrication	6.20 ± 2.32	10 (33.3%)	9 (30.3%)	9 (30.3%)
Orgasm	8.57 ± 3.63	11 (36.7%)	10 (33.3%)	7 (23.3%)
Pain	9.96 ± 2.22	2 (6.7%)	26 (86.7%)	0
Enjoyment	15.57 ± 3.95	6 (20.0%)	14 (46.7%)	8 (26.7%)

(8, 11). It seems that the sample size in this study is too little to find these correlations. However the characteristics of this group are similar to the general population and by increasing the sample size valuable data will be obtained. For example in our research the incidence of hirsutism was 10% and acne 13.3%. The incidence of acne is about 40% among girls under 17 and it decreases when they grow older. The incidence of hirsutism is 10% (14).

There is a wide variety of sexual problems with a high prevalence of different disorders in this selected population. It would be important to bring up the point that female medical students are involved in an emotionally-charged and physically-demanding program, which may affect their level of sexual dysfunction. Depending on how their living situation is, and whether they receive help in household chores, the pressure that hospital work and household work together entailed can have a toll on one's emotional state, and this is important to consider in light of the high prevalence of sexual dysfunction among female medical students. The continued quest to understand female sexual dysfunction requires more research on underlying medical and non-medical conditions.

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ORIGINAL ARTICLE

Obstetric complications in children with Attention Deficit/Hyperactivity Disorder and Learning Disability

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ABSTRACT: This study aims to determine whether children with ADHD and learning disabilities (LD) have a significant history of obstetrical complications when compared to children with ADHD but without LD. Methods: Sixty-four children aged 6 to 12 years diagnosed with ADHD were assessed for a history of obstetrical complications using the Kinney medical and gynecological questionnaire. Learning ability was appraised using the Wide-Range Achievement Test (WRAT-R) for anglophone students and the "Test de Rendement Français" for francophone students. Results: Children with ADHD and a learning disability in mathematics had a higher rate of neonatal complications of great severity ($p = 0.01$) than children with ADHD and no disability in mathematics. Children with ADHD and a learning disability in reading also had a preponderance of neonatal complications of high severity ($p = 0.02$) compared to their peers with ADHD and no learning disability in reading.

Children with ADHD and learning disability tend to have a significant history of neonatal complications, which validates the theory that complications in early life could adversely affect a child's academic ability later in life. This further confirms the importance of the perinatal and postnatal periods in CNS development of brain regions essential for mathematics and reading ability.

KEY WORDS: ADHD, learning disabilities, obstetric complications

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a widespread psychiatric disorder in the pediatric population, affecting 6% to 9% of elementary school students (1). The cardinal features of ADHD are hyperactivity, impulsivity and inattention. Hyperactivity manifests as "a child who cannot sit still, climbs around when others are seated, and talks when others are talking" (1).

The etiology of ADHD is unclear at the present; however, it is known that ADHD has strong genetic determinants as indicated by family (2) and adoption (3) studies. Of special importance are twin studies (4) showing that ADHD heritability is high, ranging from 75 to 90%. The above studies state that non-shared environmental factors i.e., factors/events that are unique to one member of the family, account for the rest of the variance in ADHD phenotype (10-25%). In many cases, non-shared environmental effects have been found to out-weigh shared environmental effects. Thus, shared environmental effects that are typically thought to be life-shaping (such as family life) have less of an impact than non-shared effects on ADHD phenotype (5). Non-shared effects include events in pre-natal development and random variations in the genetic program of a child.

Case-control studies have shown that there is an increased risk of ADHD in children who have suffered pregnancy, labour/delivery and neonatal complications (6), a finding further supported by Ben-Amor et al (7).

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Learning disability (LD) encompasses problems with reading, spelling, vocabulary and arithmetic. Mathematics is mainly represented in regions of the parietal and frontal lobes. Disruption of neural circuits in these areas result in difficulties with number concepts, counting skills, arithmetic skills, procedural calculations, memory and visual-spatial skills (8). Broca's area, Wernicke's area, visual cortex and angular gyrus are parts of the brain involved in reading. Lesions in these areas can lead to deficiencies in vocabulary storage, reasoning, concept formation, and interpretation (9).

LD, as does ADHD, affects 6 to 9% of the pediatric population (10). Although the degree to which these two populations overlap could be as high as 45% (11), genetic epidemiological studies suggest that these two disorders are independently transmitted in families (12).

Although the neurocognitive mechanisms underlying these two disorders may be different (13), it has been suggested that children with ADHD and LD may have common frontal lobe dysfunction (14). Such disruption in areas involved in learning ability and sustaining attention is likely due to a combination of factors, including genetic and non-shared factors. Obstetric complications falling under the category of non-shared environmental factors have been found to be significantly greater among children with ADHD when compared to their siblings with no ADHD (7).

The goal of our study is to determine whether children with ADHD and comorbid learning disability tend to have had a greater history of obstetric complications when compared to children with ADHD only. Thus, it aims to look at whether obstetric complications are a factor in the etiology of ADHD and learning disability as an entity.

METHODS

Setting

All children participating in this study were recruited from the Disruptive Behavior Disorders Program (DBDP) and from the outpatient clinics at the Douglas Hospital, a psychiatric teaching hospital of McGill University in Montreal, Canada.

Subjects

Inclusion criteria:

Sixty-four children aged between 6 and 12 years diagnosed with ADHD were included in the study. The children and their parents were given a detailed explanation of the research protocol. Parents signed informed consent and children also gave consent for participation.

The children in the study met DSM-IV diagnosis of ADHD based on detailed clinical assessment, school reports, and reports from referring agencies, parents and pediatricians. A panel of two experienced child psychiatrists substantiated the DSM-IV diagnosis of ADHD based on a clinical interview with the child and parents, information collected from the different sources, and a structured interview using the Diagnostic Interview Schedule for Children DISC-IV (15).

Exclusion criteria:

Children with an IQ less than 70 on the Wechsler Intelligence scale for Children-III (16), history of Tourette syndrome, Pervasive Developmental Disorder or psychosis were excluded from the study. 53% of the subjects were anglophone and the rest were francophone. With respect to race, 8.4% of the subjects were black, 1.1% were aboriginal, 1% were half-Asian, 3.2% were half-black and half-Caucasian, 1% were half-Hispanic and half-Caucasian, and 85.3% were Caucasian.

Evaluation of learning disabilities

To evaluate learning disability, subjects wrote the Wide-Range Achievement Test-Revised (17) or Test de Rendement pour Francophones (18) according to their mother tongue.

The WRAT assessed academic performance, and consisted of reading, spelling and arithmetic subtests. The standard scores obtained in these subtests were ascribed a grade level. The WRAT was designed such that comprehension is not a factor in achieved test scores, and is widely used to assess a child's scholastic ability (17).

The TRF measures the scholastic abilities of subjects whose primary language is French. There are different tests with level of difficulty corresponding to the three stages of schooling from grades 1 to 12. The student is given the test appropriate to his/her grade level. The student's scores in the vocabulary, written comprehension and arithmetic subsections are also translated into grade equivalents.

Table 1. Neonatal complications of severity 6 in ADHD children with MD compared to ADHD children without MD

		Number of Neonatal complications of severity 6+		
		0	1	Total
Mathematics	Disabled*	15	3	18
	Not disabled*	46	0	46
Total		61	3	64

MD = Disability in mathematics
*Including children with and without reading disabilities

Table 2. Labour and Delivery complications in ADHD children with RD compared to ADHD children without RD

		Number of Labour & Delivery complications of severity 6+		
		0	1	Total
Mathematics	Disabled*	22	2	24
	Not disabled*	40	0	40
Total		62	2	64

RD = disability in reading
*Including children with and without mathematics disability

If there was a difference in reading or mathematics grade levels greater than or equal to two years with respect to expected grade level given the age of the child, the child was deemed to have a learning disability in the subject.

Assessment of obstetric complications

The Kinney medical and gynecological questionnaire (19) was used to interview mothers with respect to pre-, peri- or post-natal complications that may have occurred during their pregnancy as well as during labour and delivery. This questionnaire was also used to collect information on neonatal conditions. This questionnaire was complemented with medical files when available (60% of cases).

The McNeil-Sjostrom scale for obstetric complications (20) was used to score this questionnaire. These complications were classified into the following categories: prenatal (1st, 2nd and 3rd trimesters), labour/delivery, and neonatal (within the first 8 weeks of birth) complications, and total obstetrical risk.

Prenatal complications included vaginal spotting, absence of fetal movements. Labour and delivery complications included placental abnormalities, antepartum hemorrhages, drug toxic side effects (because of alcohol, tobacco and illicit substances), and fetal distress (assessed by abnormalities of fetal heart rate or meconium staining). Neonatal complications comprised suboptimal 5-minute Apgar scores, low birth weight, small head circumference (below 10th percentile), congenital defects such as patent ductus arteriosus, and medical complications such as pneumonia in the first 8 weeks of life.

Table 3. Neonatal complications in ADHD children with RD compared to ADHD children without RD

		Number of Neonatal complications of severity 6+		
		0	1	Total
Mathematics	Disabled*	21	3	24
	Not disabled*	40	0	40
Total		61	3	64

RD = disability in reading
*Including children with and without mathematics disability

The McNeil-Sjostrom scale allows for weighting of several hundred specific complications of pregnancy, labor and delivery and the neonatal period. These complications were assigned one of six severity levels corresponding to the ordinal degree of potential harm to the baby's central nervous system:

Level 1 - Not harmful or relevant;
Level 2 - Not likely harmful/relevant;
Level 3 - Possibly but not clearly harmful or relevant;
Level 4 - Clearly potentially harmful or relevant;
Level 5 - Clearly potentially greatly harmful/relevant;
Level 6 - Great harm to the offspring

Statistical Analysis

Clinical and demographic characteristics of children with ADHD and learning disability in reading or mathematics were compared to those of children with ADHD only using repeated measure ANOVA. Using the two-tailed paired t-test, we checked for correlations between reading disability and each of the obstetric complication subcategories. The same analysis was done with respect to disability in mathematics.

RESULTS

Children with ADHD and a disability in mathematics (MD) were found to have a higher rate of neonatal complications of severity 6+ ($p = 0.004$) than those without a disability in mathematics.

We noted that ADHD children with a reading disability (RD) had a greater preponderance of labour and delivery complications of severity 6+ ($p = 0.065$), neonatal complications of severity 6+ ($p=0.02$) than those with no reading disability.

All variables were similar across the different study groups, except for IQ and age. The children with ADHD and MD tended to be significantly older than those without MD ($p=0.001$) although this was not the case for children with ADHD and RD compared with those without RD ($p = 0.39$). The children with ADHD and MD had a significantly lower IQ than those with no MD ($p=0.016$) and those with RD had a significantly lower IQ than those with no RD ($p=0.002$).

DISCUSSION

A substantial proportion of children with ADHD have comorbid LD. Both disorders have causal

genetic as well as environmental risk factors. The results of the study have shown that a history of neonatal complications tends to be significantly more prevalent among ADHD children with a learning disability. Low birth weight (LBW), considered a neonatal complication and defined as a birth weight less than 2.5 kg, has been identified in past research studies as a risk factor in ADHD (21).

Stress during or following pregnancy is also a possible causal factor in learning disabilities (22). LBW children have been found to have delayed cognitive development (23) and subsequent RD and MD (24).

The main neonatal complications found to be prevalent among the children in our study were neonatal hospitalization, being in an incubator, requiring oxygen therapy, general anesthesia or surgery. These findings support earlier findings pointing to a higher prevalence of early-life stressful events among ADHD children (6). Such neonatal events have been shown to potentiate heightened locomotor activity later in life in animal models (25). A retrospective analysis of children who had been referred for ADHD found that many of them as infants had received Cardiff Bag Resuscitation and a 1-minute Apgar score below 7 or a 5-minute Apgar score below 9 (26). This further supports the relationship between neonatal complications and ADHD.

Environmental or psychosocial stress has been shown to impede neurogenesis, especially that of the hippocampus, the center of learning and memory (27).

Some human studies have proposed that hypoxic/ischemic brain damage secondary to perinatal asphyxia can lead to neurologic and intellectual dysfunction (28). In our study, the presence of severe (6+) neonatal complications among ADHD children with comorbid learning disabilities suggests that the global impact of the neonatal complication (such as hypoxia affecting brain development as a whole) leads to development of learning disability. Thus, greater severity of early-life stressful events tends to induce learning disability and ADHD, two disorders that have already individually been associated with neonatal complications.

Limitations

This study compared children with ADHD and learning disability to children with ADHD only; since it compared children of different families, it could not account for shared environmental factors.

In some other studies (14), a national standardized test was used to determine learning ability. This option was not available to us, as Canada does not administer such nationwide testing. When assessing learning disability, it is sometimes difficult to tell whether a child under the age of 8 has a learning disability for certain. In these cases, we assessed learning status using teachers' and psychiatric evaluations.

In addition, we did not address comorbidity of psychiatric disorders, although this may affect the degree of learning disability.

The major limitation is the low number of cases having neonatal complications of extreme severity (three cases in MD and two cases in RD).

Clinical Implications

Early insult on the fetal brain during crucial periods of development may have long-lasting effects on cognition and behaviour. The etiology of ADHD and learning disability is thought to be a combination of genetics and environmental stressors. This study indicates that a condition that affects half of the pediatric ADHD population may be linked to early-life stressful events when they are particularly severe. These results further support that which has already been shown for ADHD and learning disability individually; that the happenings in the early life of a child are crucial to brain development and have implications for a child's academic performance and functioning far into the future.

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ORIGINAL ARTICLE

Comparative DNA Flow Cytometric Study of Primary Intraocular and Central Nervous System Lymphomas

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ABSTRACT: Primary intraocular lymphoma is generally considered as a subset of primary CNS lymphoma. This study attempts to show that they may in fact represent distinct entities by comparing their respective proliferation rates using DNA flow cytometry. Four samples of primary intraocular lymphoma and seven samples of primary CNS lymphoma were analyzed, all from paraffin-embedded tissue. All tumors were of the large B-cell type. A normal human tonsil sample was used as a control. Tissue samples were analyzed by DNA flow cytometry, which is a precise and objective method to measure DNA content and cell proliferation of a tumor. S-phase fraction (SPF) and DNA content were measured for each sample. The average SPF for primary intraocular lymphoma was significantly higher than that of primary CNS lymphoma, 23.8 (range: 18.9 to 29.6) versus 15.1 (range: 1.1 to 25.1) respectively. Of the 11 tumors analyzed, 2 brain tumors were aneuploid and 1 eye tumor was peridiploid. All other tumors were diploid. Thus, no significant pattern was detected in the DNA content of the tumors. This lack of clinical significance of tumor aneuploidy is consistent with data reported in the literature. The results of this study indicate that primary intraocular lymphoma is more aggressive and of higher grade than primary CNS lymphoma. The different proliferation rates of intraocular and CNS lymphomas may be explained by either their different spatial location or a distinct genetic composition, the latter reinforcing the hypothesis that the two are fundamentally different entities

INTRODUCTION

Primary intraocular and central nervous system (CNS) lymphomas are defined as extranodal non-Hodgkin's lymphomas that are not associated with systemic involvement at the time of diagnosis (1,2,3,4). They are rare and lethal neoplasms that represent a challenge in terms of their diagnosis, treatment, and prognosis. Their terminology, classification, and pathogenesis are a source of continuous confusion. The research presented in this report attempts to elucidate the pathogenesis of primary intraocular and CNS lymphomas by comparing their DNA flow-cytometric profiles. Although intraocular lymphomas are generally considered as a subset of CNS lymphomas, this study attempts to show that they are actually different entities, of different genetic origin and pathogenesis.

Primary intraocular and CNS lymphomas combined represent about 2% (5) to 5% (6) of all lymphomas. Their incidence is higher in immunocompromised patients, notably those with AIDS, transplanted organs, and congenital immunodeficiencies (1,3,7). These neoplasms most often occur after 60 years of age (5,8).

Histopathologically, most primary intraocular and CNS lymphomas are high-grade large B-cell lymphomas (Figs 1A,B,C) (2,9,10). but T-cell lymphomas have also been reported (1). The malignant

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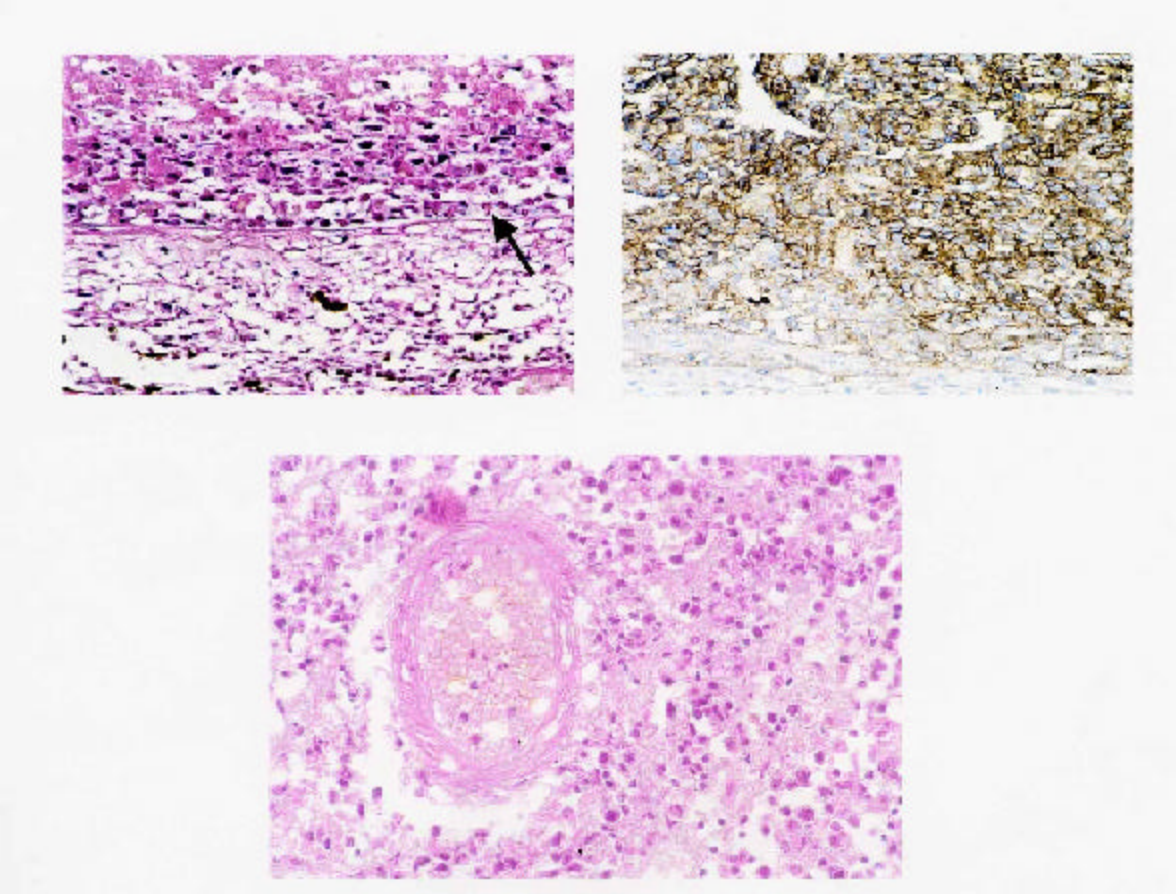
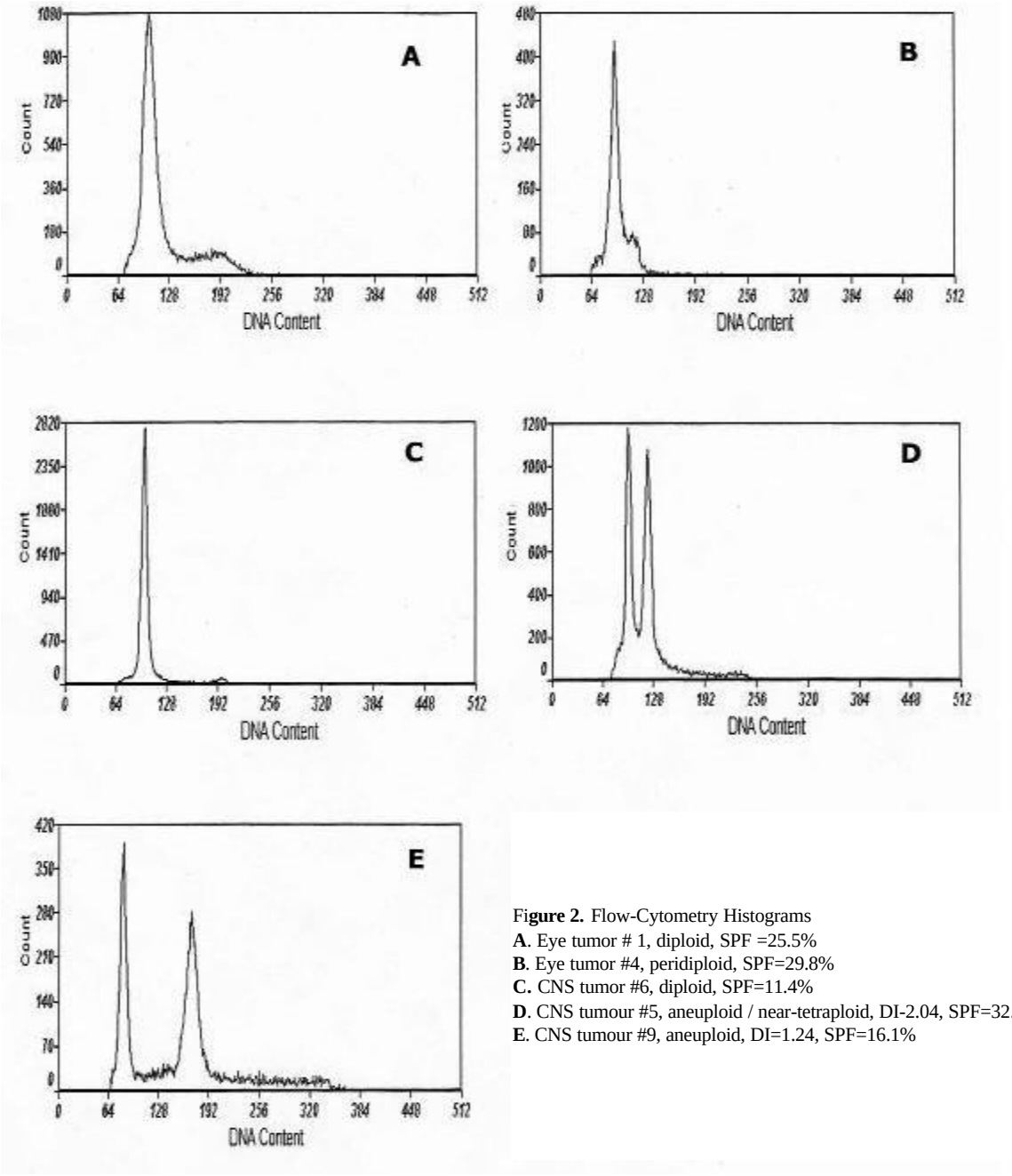


Figure 1. Histopathological and immunohistochemical features of primary large B-cell lymphoma of the retina and CNS.
A. H&E stain. Primary intraocular lymphoma showing large viable and necrotic neoplastic cells internal to the Bruch's membrane. Small reactive lymphocytes are present external to the Bruch's membrane.
B. L-26 monoclonal antibody marker. Primary intraocular lymphoma showing large B-cells in the retina.
C. H&E stain. Primary CNS lymphoma showing a blood vessel with neoplastic cells demonstrating a perivascular cuffing pattern.

cells of large B-cell lymphomas characteristically have abundant cytoplasm, round indented nuclei with large single or multiple nucleoli, and prominent nuclear membranes. Mitotic figures are common and extensive areas of central hemorrhagic necrosis are often apparent. Malignant cells are visible in the parenchyma, characteristically accumulated around blood vessels. Benign reactive T-lymphocytes often surround the neoplastic lesions (11,12).

Early intraocular lymphoma lesions occur characteristically between the retina and Bruch's membrane (2,9,12,13). Although it sometimes occurs as solely a malignancy of the eyes, 50% to 80% of patients who present with primary intraocular lymphoma exhibit CNS involvement later in their disease. Conversely, intraocular involvement is present in 12 to 18 of patients with primary CNS lymphoma (1,2,14). It is interesting to note that primary intraocular lymphoma is more likely to be followed by CNS involvement, rather than vice versa. The eyes are involved bilaterally in up to 75% of cases with or without concomitant brain involvement (2,8,9,10).

Primary intraocular lymphoma presents as corticosteroid-resistant uveitis, vitritis, or chorioretinitis, (2,7,10,15) with initial symptoms of blurred vision and floaters (13,14). Diagnostic techniques include vitrectomy, biopsy, or enucleation. Primary CNS lymphoma often presents with multiple lesions which can be located anywhere in the CNS, including the spine and leptomeninges, and which usually give rise to non-specific neurologic symptoms (1,14,16,17). It is diagnosed by imaging and biopsy. Primary CNS lymphoma is currently treated with chemotherapy and adjunctive cranial radiotherapy. Bilateral ocular and whole brain irradiation are used for intraocular involvement. With optimal treatment, the median survival has been reported to be 30 to 45 months in non-immunocompromised patients with primary



Fi**gure 2.** Flow-Cytometry Histograms
A. Eye tumor # 1, diploid, SPF =25.5%
B. Eye tumor #4, peridiploid, SPF=29.8%
C. CNS tumor #6, diploid, SPF=11.4%
D. CNS tumour #5, aneuploid / near-tetraploid, DI-2.04, SPF=32.6%
E. CNS tumour #9, aneuploid, DI=1.24, SPF=16.1%

CNS lymphoma (4).

The pathogenesis of primary intraocular and CNS lymphomas is a continuous source of controversy. First, the origin of the malignant cells is obscure. The retina and the CNS lack a lymphatic system and intrinsic lymphocytes. Furthermore, primary intraocular and CNS lymphomas are particular in their high specificity for the central nervous system, including the retina, which is an anatomical and functional extension of the brain; systemic spread has been reported in only 7-8 of autopsies (3,15). However, these systemic occurrences could represent second primaries, rather than metastases (6,17). There are several theories that attempt to explain the origin of the primary CNS lymphoma. The theory of malignant transformation within a lymphocytic reaction around a viral infection has been proposed (1). In AIDS patients, for example, involvement of the EBV virus in primary CNS lymphoma has been reported (1). Similarly, herpes virus involvement in immunocompetent patients has also been suggested (1,16). Another hypothesis is that B-lymphocytes are transformed elsewhere in the body and develop specific binding molecules for the CNS. Specific receptors for these molecules on the CNS endothelial cells may explain the "homing pattern" of this neoplasm (1,18). The relatively privileged sites of

Table 1. Clinical Data for Patients with Primary Intraocular Lymphoma

Patient	Age	Sex	HIV Status	Presenting Symptoms	Time from initial symptoms	Time from initial to diagnosis symptoms to death or to present	Diagnostic Procedure	Tumor site at ime of diagnosis
1	64	F	-ve	Uveitis	14 months	3 years	Ultrasound, enucleation	OD
2	40	M	-ve	Posterior Uveitis	10 months	2 years	Enucleation	OS
3	63	M	-ve	Blurred vision & floaters in R eye	25 months	9 years (A)	Ultrasound, enucleation	OD
4	39	M	+ve	Recurrent ocular infection not improving with treatment	30 months	1 year	Ultrasound, enucleation	OS

A= Alive at time of study

Table 2. Clinical Data for Patients with Primary CNS Lymphoma

Patient	Age	Sex	HIV Status	Presenting Symptoms	Time from initial symptoms	Time from initial to diagnosis symptoms to death or to present	Diagnostic Procedure	Tumor site at ime of diagnosis
5	70	M	-ve	Dizziness, visual distortion, headaches, acute convulsions	7 months	4 years (A)	CT, sterotactic surgery	R occipital lobe
6	71	M	-ve	Generalized seizure	< 1 day	3 years (A)	CT, excisional biopsy	L temporal parietal lobe
7	65	F	-ve	Back pain, numbness & weakness of lower extremeties	5 months	2 & ½ years (A)	CT, excisional biopsy	T10 epidural
8	53	F	-ve	Weight loss, ataxia, dysarthria, disorientation, mental deterioration	3 months	2 years	CT, sterotactic biopsy	L basal ganglia, L frontal lobe
9	44	F	-ve	Lower back pain, R knee pain, urinary retention	3 weeks	10 months	Imaging, excisional biopsy	T12-L2 epidural (+ bone marrow & liver)
10	63	F	-ve	Weight loss, myalgia, chills, vomiting, acute lethargy & confusion	5 weeks	6 months	CT, sterotactic biopsy	Peri-ventricular areas, L fronto- parietal lobe
11	36	M	+ve	Headache, CN 7 palsy, R eye protrusion and decreased vision	7 weeks	10 weeks	CT, sterotactic biopsy	L fronto-parietal lobe, OD

A= Alive at time of study

the CNS and retina, sequestered from the normal immune surveillance mechanisms, may further encourage the malignant growth (1,7,17). Another possibility is that these lymphomas in fact represent metastases from occult systemic lymphomas (19). Finally, completely different precursors for the malignant lymphocytes have also been proposed: reticulum cells, microglial, and glial cells (9,14,17).

Second, multifocal presentation of primary intraocular and CNS lymphomas is poorly understood; how does the tumor spread within the CNS without a communicating lymphatic system? Hematogenous spread is possible but, theoretically, it should lead to a higher occurrence of systemic metastases. Direct spread seems unlikely due to the large areas of normal brain tissue often located between lesions and the reported absence of brain involvement in bilateral intraocular lymphoma. Intraneural expansion is one possibility, although, to the best of our knowledge, the actual invasion of the optic nerve with neoplastic cells has never been demonstrated. Lastly, the choroidal circulation could be responsible for the retinal involvement (15).

To further elucidate the possible origin and mechanism of multifocal distribution of primary intraocular and CNS lymphomas, comparison of primary lymphoma of the retina with that of the CNS via DNA flow cytometry was performed.

DNA flow cytometry is an objective method for measurement of the DNA content (i.e. ploidy) and proliferative activity (determined by S-phase fraction or SPF) in normal and malignant cells. The advantage of this method is the ability to measure a multitude of parameters on thousands of individual cells in a short time. Furthermore, DNA flow cytometric studies are effective with both fresh tissue and formalin-fixed paraffinized tissue (20). Aneuploid and tetraploid populations have been described for non-Hodgkin's lymphomas, although abnormal DNA content appears to have very limited clinical or prognostic significance (21). In contrast, previous studies of non-Hodgkin's lymphoma have shown a good correlation between high proliferative activity, advanced histopathological grade, aggressive clinical behavior, and poor prognosis (21,22). Non-Hodgkin's lymphomas have been reported to have generally "intermediate" proliferative activities, defined by SPFs between 4% and 10% (21).

This study aims to compare the DNA flow cytometric results for primary diffuse large B-cell intraocular and CNS lymphomas and show that these neoplasms may be genetically different. To our best knowledge, flow cytometric analysis has never been applied specifically to primary intraocular or CNS lymphomas.

Table 3. DNA flow cytometric data for intraocular lymphoma

Patient	Ploidy	SPF (%)
1	Diploid	25.5
2	Diploid	18.9
3	Diploid	21.2
4	Peridiploid2	9.8
Average		23.9

PATIENTS, MATERIALS AND METHODS

Patients

Four paraffinized samples of primary intraocular lymphoma, with associated clinical information, were obtained from the Federal University of San Paulo, Brazil (3 samples) and from India (1 sample).

To obtain primary CNS lymphoma samples, computerized and manually filed data, as well as individual patient charts at the Cancer Registry of the Royal Victoria Hospital and the Montreal Neurological Institute Medical Records, Montreal, were analyzed. Data for all 18 patients registered as having primary CNS lymphoma between 1995 and 1999 was collected. The pathology reports and individual histopathological slides were reviewed with experienced CNS and ophthalmic pathologists in order to confirm the diagnoses. Seven patients with confirmed primary CNS lymphoma, whose paraffin blocks were prepared after 1995 and were available at the time of the present research, were identified and used for this study. Histolpathologically, all tumors included in this study were large B-cell lymphomas.

DNA Flow Cytometry

The following steps were performed on each of the 4 ocular and 7 CNS paraffin-embedded tissue samples, similar to the method described by Riley *et al.* (20).

Tissue deparaffinization: Two to five 50um sections of paraffin-embedded tissue were cut. Tissue sections were incubated twice for 10 minutes in 10ml ofxylene. Rehydration of the tissue was performed by 10 minute incubations in decreasing concentrations ofethanol: 100% twice, 95%, 70%, 50%. The tissue was then minced and left in 10ml of distilled water for 2-3 nights.

Tissue disaggregation and DNA staining: A fresh pepsin solution was prepared and brought to 37°C. Water was removed from each sample and 1 to 2 ml of pepsin was added to the tissue. Samples were vortexed and incubated for 30 minutes at 37°C. After incubation, each sample was diluted twice with cold PBS (phosphate buffered solution) and centrifuged at 900g for 10 minutes. The pellet was resuspended in 2 ml of Krishan DNA staining buffer (50mg/ml propidium iodide, Img/ml trisodium citrate, 350 units RNAse,

Table 4. DNA flow cytometric data for CNS lymphoma

Patient	Ploidy	SPF (%)
5	Aneuploid, near-tetraploid DNA content, DI=2.04	32.6
6	Diploid	11.4
7	Diploid	1.1
8	Diploid	25.1
9	Aneuploid DNA content, DI=1.24	16.1
10	Diploid	8.3
11	Diploid	11.0
Average		15.1

0.75ml/ml NP-40, in distilled water), vortexed, and incubated in the dark at 4°C overnight. The sample was then aspirated successively through 18, 20, and 22 gauge needles, and then filtered through a 53x37 mesh.

Flow cytometric analysis

An EPICS XL flow cytometer (Beckman Coulter® Corp., USA) was used for DNA measurements. Before each set of measurements, the instrument was adjusted by the use of normal human tonsil cells. An average of 28,000 nuclei (range, 13,595 to 38,625 nuclei) were analyzed for each sample. The coefficient of variation, defined as the standard deviation in percent of the mean DNA value of the diploid Gl/G0 peak, was 5.5 mean (range, 3.5 to 8.5). The DNA flow cytometry data was analyzed by MultiCycle for Windows, advanced DNA cell cycle analysis software. Phoenix flow systems (San Diego, California).

Definition of DNA index (DI), ploidy, and S-phase fraction

The DI of the diploid tumor cells was defined as 1.0. Tumors were defined as diploid by the presence of a single symmetrical G0/G1 peak in the histogram. A single broad asymmetrical G0/G1 peak was observed in one case of ocular lymphoma, a phenomenon most likely due to a minor degree of aneuploidy. According to other authors, we considered it appropriate to define such a tumor as "peridiploid" (22). Tumors with more than one discrete G0/G1 peak were considered aneuploid. The degree of aneuploidy was expressed as a DI, which was defined as the ratio of the channel position of the G0/G1 aneuploid peak to the channel position of the G0/G1 of the diploid peak. A DI of 2.0 corresponds to a tetraploid population. Cell cycle distribution, including the S-phase fraction, was estimated according to the Dean and Jett polynomial S-phase model.

RESULTS

Among patients with primary intraocular lymphoma (table 1), 3 were male and 1 was female. The mean age of patients was 51.5 years (range, 39-64). One patient was HIV positive at the time of diagnosis. Patients presented with symptoms such as uveitis, blurred vision, floaters, and recurrent eye infections. The average time from initial symptoms to diagnosis was approximately 19.75 months (range, 10 to 30). At the time of this study, 1 patient is still alive, 9 years after initial symptoms; 3 patients were dead. The average time from initial symptoms to death is 2 years (range, 1 to 3). All patients were diagnosed by ultrasound or enucleation. There is no reported brain or systemic involvement.

Regarding patients with primary CNS lymphoma (table 2), 3 were male and 4 female. The mean age was 57.43 years (range, 36-70). One patient was HIV positive at the time of diagnosis. Patients presented with symptoms such as weight loss, flu-like symptoms, headache, back pain, muscle pain, vague neurological symptoms, and focal neurological deficits. The average time from initial symptoms to diagnosis was approximately 2.5 months (range, 1 day to 7 months). At the time of this study, 3 patients are still alive, 4, 3, and 2.5 years after initial symptoms; 4 patients are dead. The average time from initial symptoms to death is 10.6 months (range, 10 weeks to 2 years). All patients were diagnosed by imaging (mostly by CT) and by biopsy. The tumor was located in different brain lobes in 5 patients. Among those, 4 patients had an additional site of tumor involvement, such as the basal ganglia, periventricular area, and right eye. Two patients had involvement of the meninges with epidural tumors of the spinal cord. Of the latter, 1 patient had reported systemic involvement of the bone marrow and the liver at the time of diagnosis.

The flow-cytometric histograms represent the number of cells on the y-axis plotted against the amount of DNA on the x-axis. The first, large peak corresponds to the G0/G1 phase of the DNA cycle. The second, much smaller peak represents the G2/M phase. The area below the curve between G0/G1 and G2/M is the S-phase. The ploidy and SPF of all 11 tumors was recorded (Table 3 and 4). The average SPF for primary intraocular tumors was 23.8% (range, 18.9 to 29.8). Three ocular tumors in cases 1, 2, and 3 had only diploid populations (Fig. 2A) and one eye tumor in case 4 had a near-diploid population (Fig. 2B). The average SPF for primary CNS tumors was 15.1% (range, 1.1 to 25.1). Five brain tumors had only diploid populations (Fig. 2C) and no abnormal DNA content. Brain tumors in cases 5 and 9 contained aneuploid populations (Figs. 2D & E).

DISCUSSION

In this study, DNA flow cytometry was performed on 4 primary large B-cell lymphomas of the eye and 7 primary large B-cell lymphomas of the CNS. The DNA content and S-phase fractions (SPF) were measured. Out of the 11 tumors analyzed, 2 brain tumors were aneuploid and 1 eye tumor was peridiploid. All the other tumors were diploid. These results involve too few samples to draw any significant conclusions based solely on DNA content. Furthermore, in the literature, aneuploidy has failed to provide any meaningful clinical significance (21,22).

Regarding tumor proliferation, the average SPF for primary intraocular lymphomas is significantly higher than that of primary CNS lymphomas. This apparent increase in tumor proliferation suggests that primary intraocular lymphoma may be more aggressive and of a higher grade than primary CNS lymphoma. This in turn may explain the clinical observation whereby patients with primary intraocular lymphoma have a higher rate of subsequent CNS involvement as opposed to a lower rate of intraocular involvement in primary CNS lymphoma (50%-80% vs. 12%-18%) (1,2,14). The primary intraocular lymphoma may thus be considered to have a higher malignant potential. The difference in grade and aggressivity between the two neoplasms could presumably be caused by either environmental or genetic factors.

The intraocular spatial location might be the causative factor stimulating proliferation due to a richer blood supply or the presence of different chemical growth factors. Moreover, the tumor location between the retina and the choroid leads to a unilateral T-cell reaction in which the retinal side of the tumor may be able to grow without immune interference.

Alternatively, the malignant cells of primary intraocular lymphoma might be genetically predisposed to higher proliferation rates. The data presented herein thus raises the possibility that primary CNS and intraocular lymphomas may arise from different progenitor cells. This hypothesis would explain why primary intraocular and CNS lymphomas do not behave like other extranodal non-Hodgkin's lymphomas and why there is no apparent spreading mechanism for neoplastic cells within the CNS and the retina. Support for this theory is found in a recent paper by Alizadeh et al., which demonstrates molecular heterogeneity within diffuse large B-cell lymphomas via gene expression profiling (23).

There are several factors that may have influenced the results of this study. First, the number of tissue samples [11] was small and interpatient variation might have played an important role. Second, although the cell viability is not considered as an important factor in DNA flow cytometric analysis and the usefulness of paraffin-embedded tissue has been demonstrated (20), fresh tissue samples still yield more accurate results; there is a smaller amount of debris resulting in sharper peaks on flow-histograms. Third, the statistical analysis was not adjusted for all possible interfering factors, such as patient age, gender, precise tumor location, HIV status, and treatment modality. Lastly, intrapatient circadian variation of cell proliferation in non-Hodgkin's lymphomas has been demonstrated and may bias the results as well (24).

In conclusion, the results presented in this report suggest that intraocular and CNS lymphoma have different proliferation rates and thus might represent genetically distinct types of neoplasms. Future studies will include DNA flow cytometry on a greater number of tissue samples and genetic profiling using PCR or complementary DNA microarrays (23). Such experiments would represent a further step in the understanding of the genetic identity and pathogenesis of these neoplasms.

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ORIGINAL ARTICLE

Examining Medical Student Attitudes Towards Physician-Assisted Suicide

Kevin Gabel*, Saul Miller*, Jeffrey So*, Andrew Suess*

ABSTRACT:

Physician-assisted suicide (PAS) is a highly debated issue. The Sue Rodriguez case highlighted the importance and the contentious nature of this issue in our society today. This study assessed attitudes towards PAS held by first and fourth year medical students at the University of Western Ontario via a 13 question anonymous survey. One hundred and twenty-four surveys were returned with a response rate of 53%. Respondents, especially those in fourth year, were unwilling to aid in PAS in the capacity of physicians (63% overall unwilling; P = 0.004). They wanted PAS to be an option, however, if they were patients themselves (64% overall; P = 0.002). A variety of factors were considered important in making decisions regarding PAS, especially a patient's clear understanding of medical management options. Most respondents welcomed (39%) or were neutral (45%) towards legalization of PAS. Opinions towards PAS tended not to change over the course of medical school (72% overall; P < 0.001). Students generally favoured the concept of PAS as long as they did not have to take part in it themselves. Although no differences between first and fourth year medical students were detected concerning their opinions towards PAS, willingness to participate may be affected by personal experience with patients.

KEY WORDS: physician assisted suicide, medical student, terminally ill, attitudes

INTRODUCTION

Decisions regarding end of life care are highly charged and of great importance, particularly in our aging society. Physician-assisted suicide (PAS) continues to generate significant controversy. It occurs when a physician facilitates a patient's death by providing the necessary means to enable a patient to perform the life-ending act (1). It has become more important in recent years; advances made in medicine and the ability to extend life longer than ever before raise questions surrounding the morality and ethics of PAS. One notable instance involving PAS is that of British Columbian Sue Rodriguez, an individual diagnosed with amyotrophic lateral sclerosis who wished to have the aid of a physician in ending her life. This sparked fierce debate from individuals who held differing views surrounding the topic. Ms. Rodriguez's attempts to strike down the law making PAS illegal in Canada found their way before the Supreme Court of Canada. There was a majority decision by the Court to uphold the law (2). Currently, PAS is not legal in Canada; Oregon, in 1994, was the first American state to legalize PAS.

Surveying medical students is instructive because it is likely that identities and attitudes as physicians are influenced by early experiences (3). In a recent American study, 20% of fourth year medical students said they received a request for a lethal drug prescription in the past year, indicating that exposure to this ethical dilemma is not uncommon (4).

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An American study by Warner et al. found that medical students did not wish to participate in the PAS process and generally opposed the idea of suffering patients prematurely ending their own lives (3). Social science students in Hungary, however, who had the least experience interacting with terminally ill patients when compared to other participants in the same study, were most in favour of legalizing PAS, while Hungarian nurses who cared for terminally ill patients on a regular basis were most opposed to PAS (5).

There is a dearth of data regarding medical student opinions in Canada on PAS. Furthermore, only a few studies have compared students in different years of medical school. A Puerto Rican study by Ramirez et al. found that medical students were more agreeable than medical residents to the idea of legalizing PAS (6). In a separate study, Ramirez et al. found first year medical students to be more accepting of PAS than third year medical students (7). In this study, we sought to determine and compare attitudes and opinions of first and fourth year medical students in a Canadian medical school towards PAS.

METHODS

Study Design

Attitudes were assessed via a survey administered to first and fourth year medical students at the University of Western Ontario (UWO) in London, Ontario, Canada. The surveys were given to students at the beginning of a lecture and collected at the end of the session. No incentive was offered for participation in the study. The survey was administered in March, 2004 when first year students had completed seven months of lecture-based training, while fourth year students had completed two years of lecture-based training, as well as nearly two years of clinical training in the hospital setting.

Survey Instrument

Thirteen questions were used to assess student attitudes towards PAS (see Appendix 1). Demographics collected included age bracket, gender and year of medical school. Attitudes were gauged via a four point Likert scale with choices ranging from strongly agree to strongly disagree; in two questions, options for neutrality or no opinion change were also included. The definition of PAS was provided at the top of the survey as stated above. The questions were chosen to determine students' attitudes towards PAS, and whether differences existed at the first and fourth levels of training. In addition, factors deemed important in making decisions regarding PAS were assessed. These included the age of the patient, persistence of the patient's request, obtaining more than one medical opinion, a clear understanding by the patient of medical management options, the patient's prospects for improvement, obeying the law, respecting patient autonomy, and alleviating suffering. Prior to administration, the survey was tested on five second year medical students who were not part of the sample populations; feedback was received regarding the clarity of the questions and the layout of the survey.

Approval for the study was granted by the Research Ethics Board of the Faculty of Medicine and Dentistry at UWO. The survey was anonymous, preserving student confidentiality. Participation in this study was optional.

Statistical Analysis

The results of the survey were tabulated and analyzed. A P-value of less than 0.05 was considered to be statistically significant. Two study groups were identified: first year medical students and fourth year medical students. These two groups were compared. Comparisons were also made based on age and gender. Where significant differences were found, results were identified. T tests were used to compare Likert score averages between years of study, and between genders. Single factor ANOVA was used for age based comparisons. The chi-squared test was used to assess the significance of agreement or disagreement based on a presumed equal distribution of responses.

RESULTS

Sample Characteristics

We administered the survey to a total of 236 students. We received responses from 72 students (54%) in the first year class and 52 students (51%) in the fourth year class. The final study group consisted of 124 students (overall response rate 53%), 53 (44%) of whom were male (Table 1).

Outcomes

Approximately half of all respondents entered medical school with a clearly defined opinion on PAS

Table 1. Demographics of the students surveyed

	First Year Students	Fourth Year Students
Number	72	52
Male	30 (42%)	23 (44%)
Female	40 (56%)	28 (54%)
Gender not specified	2 (3%)	1 (2%)
Age 20-22	25 (35%)	0
Age 23-25	45 (57%)	16(31%)
Age 26-28	5 (7%)	32 (61%)
Age 29+	1 (1%)	4 (8%)
Age not specified	1 (1%)	0

Table 2. Factors in making decisions about PAS

Factor	Students considering factor to be important			P-value (all)
	All	1st year	4th year	
Age of patient	51 (42%)	31 (44%)	20 (38%)	0.07
Persistence of request	80 (65%)	42 (58%)	38 (73%)	<0.001
Legality	108 (89%)	61 (87%)	47 (90%)	<0.001
Patient's prospects for improvement	110 (90%)	67 (93%)	43 (84%)	<0.001
Obtaining >1 medical opinion	114 (92%)	66 (92%)	48 (92%)	<0.001
Patient autonomy	118 (95%)	69 (96%)	49 (94%)	<0.001
Patient understanding of management options	119 (96%)	70 (97%)	49 (94%)	<0.001
Alleviating suffering	117 (96%)	69 (97%)	48 (94%)	<0.001

Apparent discrepancies between numbers and percentages are a result of some students not responding to all questions.

(57 respondents (46%)). Overall, respondents were unwilling to participate in PAS in the role of a physician (75 respondents (63%) unwilling to participate; P=0.004). There were significant differences related to year of study, with the fourth year class less willing to participate in PAS (35 first year students (51%), 9 fourth year students (17%) willing to participate; P<0.001). When asked whether they would want PAS to be an option as a patient, a significant proportion of respondents supported this notion (77 respondents (64%) support; P=0.002).

Participants considered most of the factors surveyed to be important in making decisions regarding PAS (Table 2). Students considered patient understanding of medical management options to be the most important of the factors assessed (85 respondents (69%) strongly agreed versus 62 respondents (51%) strongly agreed with the importance of alleviating suffering, the second most important factor; P=0.003). Males more strongly considered patient's prospects for improvement to be an important factor (50 males (94%), 57 females (85%) considered this important; P=0.01).

Most students' opinions towards PAS did not change over the course of medical school (89 respondents (72%) did not change; P<0.001). Of those students whose opinions did change, significantly more people became in favour of PAS (26 respondents (74%) became in favour, 9 respondents (26%) became opposed; P=0.004). Most students welcomed or felt neutral about the legalization of PAS (48 respondents (39%) welcomed, 55 respondents (45%) felt neutral). Males were more likely then females to welcome PAS legalization (28 males (53%), 18 females (27%) welcomed legalization; P=0.001).

DISCUSSION

This survey was designed to address medical student attitudes towards PAS and explore differences related to age, gender and year of study. Approximately half of the respondents entered medical training with a clearly defined opinion on PAS, the majority of whom did not change their opinions over the course of medical school. This was noted in both the first and fourth year classes, indicating that perhaps the clinical exposure in years 3 and 4 does not have a major impact on attitudes towards PAS. Where opinions did change, students became more in favour of PAS.

While nearly two thirds of the students surveyed stated they would want PAS to be an option as a patient, they would not be willing to participate in the process as physicians. In addition, it was noted that most students were not opposed to legalization. Taken together, these data suggest that most medical students were not opposed to the concept of PAS as long as they did not have to take part in it as physicians. In future studies, it may be useful to determine the reason behind the difference in the number of students supporting the legalization of PAS and the number willing to participate in the process themselves.

Fourth year students were significantly less willing to participate in PAS compared to first year students. This suggests that more senior medical students are less willing to actually participate as physicians in PAS, although their opinions about PAS itself do not change. Respondents considered most factors examined in the survey to be important in making decisions regarding PAS. This highlights the complexity of PAS and numerous considerations that need to be taken into account when making decisions about the issue.

Most of the current literature suggests that the majority of medical students support the legalization of PAS (4, 5, 6, 7). The data from this investigation are consistent with the aforementioned studies. Only the study by Warner et al., which showed medical students' opposition to PAS, indicated differently (3). In keeping with this study, previous research demonstrated that although medical students may be agreeable to the concept of PAS, few are willing to participate in the process themselves (4, 6). In contrast with the results of this study are prior investigations performed in other countries, which suggested that acceptance of the concept of PAS is inversely proportional to an individual's amount of clinical experience. That is, those who have the least experience with patients have more accepting attitudes towards PAS (5,6).

Limitations to this study include a low response rate, potential response bias, and the observational nature of the study. The latter suggests that differences between the two classes may be compounded by factors other

than the respondents' year of medical school. Inference methods employed rely on the assumptions that this is a simple, random sample and that the underlying population distribution is normal; this may not have been the case. Despite its limitations, the study provides significant insight into the attitudes of medical students at different stages of medical training, as well as the factors that help them form these opinions.

ACKNOWLEDGEMENTS

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APPENDIX 1. Survey instrument

Medical Student Attitudes Towards Physician Assisted Suicide

This survey is part of a second year bioethics research project regarding attitudes towards physician assisted suicide. For the purposes of the survey, physician assisted suicide occurs when a physician facilitates a patient's death by providing the necessary means to enable the patient to perform the life-ending act. For example, the physician prescribes pain killers and information about the potentially lethal dose, with the knowledge that the patient may commit suicide.

The survey is anonymous and participation is voluntary.

For each of the following statements, please circle whether you strongly agree, agree, disagree, or strongly disagree.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. I entered medical school with a clearly defined opinion on physician assisted suicide.	1	2	3	4
2. As a doctor, I would be willing to aid in physician assisted suicide.	1	2	3	4
3. As a patient, I would want physician assisted suicide to be one of my options.	1	2	3	4

The following eight statements concern decisions regarding physician assisted suicide. Indicate your level of agreement for each:

	Strongly Agree	Agree	Disagree	Strongly Disagree
4. The age of the patient is important.	1	2	3	4
5. The persistence of the patient's request is important.	1	2	3	4
6. Obtaining more than one medical opinion is important.	1	2	3	4
7. A clear understanding by the patient of medical management options is important.	1	2	3	4
8. The patient's prospects for improvement are important.	1	2	3	4
9. Obeying the law is important.	1	2	3	4
10. Respecting patient autonomy is important.	1	2	3	4
11. Alleviating suffering is important.	1	2	3	4

Please complete each of the following with the one phrase that best represents your opinion. Circle the letter of the response.

12. Over the course of medical school, I have:
    a. become much more in favour of physician assisted suicide.
    b. become somewhat more in favour of physician assisted suicide.
    c. not changed my opinion towards physician assisted suicide.
    d. become somewhat more opposed to physician assisted suicide.
    e. become much more opposed to physician assisted suicide.

13. If physician assisted suicide was legalized I would:
    a. strongly welcome the legislation.
    b. welcome the legislation.
    c. have neutral feelings towards the legislation.
    d. be opposed to the legislation.
    e. be strongly opposed to the legislation.

The following questions about you are needed for statistical purposes only:

14. In what year were you born?

15. What is your gender?

16. Please circle your year of medical school:

Meds 2007 Meds 2006 Meds 2005 Meds 2004

Thank you for your participation.

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CASE REPORT

Aortic Root Dilatation and Marfan's Syndrome: An Alternative Diagosis

Sheraz Younas*, MBChB, Michael Coupe†, MD, Shamyla Younas**

INTRODUCTION

In 1896, paediatrician, Dr Antoine Marfan, described a 5-year-old child with arachnodactyly to the Medical Society of the Paris Hospitals. Other features of Marfan's Syndrome were described over the subsequent years, including ectopia lentis in 1914, autosomal dominant inheritance, 1931, and thoracic aortic root dilatation in 1943.

Before composite graft-valve replacement was introduced as a viable prophylactic measure by Bentall and De Bono in 1968, many patients died from aortic aneurysm rupture.

Current diagnosis of a thoracic aortic aneurysm is based on echocardiographical evidence of root dilatation and aortic regurgitation at the sinuses of Valsalva with or without left heart abnormality. However, a clinical diagnosis of Marfan's Syndrome is more difficult due to ambiguity of the current clinical diagnosis criteria, its relatively sparse admissions in hospitals, and the inter-familial and intra-familial variance that the syndrome exhibits.

Accordingly, an inconspicuous Marfan's Syndrome patient, having an increased risk of aortic root aneurysm, dissection or rupture, may not be appreciated early enough to perform prophylactic valve replacement.

Increased awareness of Marfanoid signs amongst clinicians is imperative and should not be overlooked over commoner causes of aortic root regurgitation. Such surveillance will reduce the death rate associated with Marfan's Syndrome.

We discuss the diagnosis of Marfan's Syndrome in the context of a clinical scenario, which highlights this syndrome as an important cardiovascular differential diagnosis.

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CASE REPORT

A 43-year-old heavy-smoking gentleman was admitted to hospital with shortness-of-breath at rest, difficulty sleeping and a two-week history of a productive lower respiratory tract infection (LRTI). He did not show any overt Marfanoid signs albeit a height of six foot and BMI 17.96 kg/m2 (NR 20-25kg/m2).

He had never suffered from any significant illnesses and was not taking any regular medication. He lead an active life, playing squash and football.

He visited his doctor who prescribed a course of antibiotics. He failed to complete the course because he had not slept well for three weeks and felt very weak.

He later visited A&E and a diagnosis of LRTI and panic attacks was made. He was treated accordingly.

On discharge, the patient's condition deteriorated and he was admitted again to hospital with acute haemoptosis. On investigation, a decresendo diastolic murmur was found. A routine chest x-ray was reported to be normal. An echocardiogram followed and a gross aortic root dilatation was discovered. He had a trileaflet, non-stenotic aortic valve, torrential aortic valve regurgitation, mild mitral valve regurgitation with moderate dilatation and global hypokinesis of the left ventricle. His aortic root dilated to a massive 77.2mm (upper limit=1.9cm/m2 of body surface area). A left heart catheterisation confirmed these findings.

His LRTI resolved and he underwent a successful composite graft-valve replacement.

During his stay, it was understood that his 11 year-old daughter exhibited Marfanoid characteristics (her height, 5 foot 8 inches and suffered from a mild functional aortic regurgitation). A thorough family history revealed his 40 year-old wife and his sisters (50 and 43 years old) were no taller than 5 foot 4 inches. His

parents did not suffer from Marfan's Syndrome but his maternal grandfather did, who was 6 foot tall and died from cardiovascular consequences of aortic valve regurgitation.

He was slightly reticent in giving up this information because he did not think that it mattered.

DISCUSSION

Marfan's Syndrome: A Differential Diagnosis

Differentials in a case of shortness-of-breath with clinical evidence of aortic regurgitation, with or without aortic root aneurysm, include:

1. Congenital Abnormality
2. Valvular Disease:
   a. Rheumatic Fever
   b. Infective Endocarditis
   c. Rheumatic Arthritis
   d. SLE
   e. Pseudoxanthoma Elasticum
   f. Appetite Suppressants
3. Aortic Root Disease
   a. Hypertension
   b. Trauma
   c. Aortic Dissection
   d. Seronegative Arthritides
   e. Marfan's Syndrome
   f. Osteogenesis Imperfecta
   g. Syphilitic Aortitis

Marfan's Syndrome is a significant differential diagnosis in this scenario, yet other connective disorders can either mask or exhibit comparable MFS characteristics; for example, Ehlers-Danlos syndrome and Lujan-Fryns Syndrome. Autosomal dominant Shprintzen-Goldberg Syndrome often exhibits Marfanoid features and may even be a variant of MFS. Homocystinuria and Beals Syndrome (FBN2 mutation) show Marfanoid signs but with ear pathologies. MASS Syndrome, a forme fruste of MFS, presents with myopia, mitral valve prolapse, aortic dilatation, skin and skeletal involvement and may be associated with FBN1 mutations. Notably, aortic dilatation is mild and the risk of aneurismal rupture is low (4). Investigations into cases of autosomal dominant ectopia lentis have shown that some patients exhibit Marfanoid features or FBN1 mutations but lack cardiac involvement.

At this point, the overwhelming array of conditions may prove diagnosing MFS difficult due to overlapping features. Similarly, in this scenario, the chest radiograph was reported to be normal, opening up the possibility of misdiagnosis. Correct clinical diagnosis is thus important in the first instance, given that results of molecular studies will only then be sought and prophylactic treatment organised as necessary.

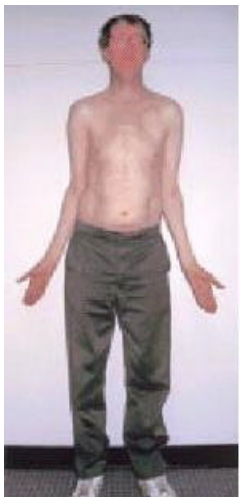

Figure 1. Patient with Marfan's Syndrome. Note pronounced marfanoid body habitus. Residual evidence of pectus carinatum can be seen. Adapted from John CS Dean. Management of Marfan's Syndrome. Heart 2002;88:97-103

Marfan's Syndrome

Marfan's Syndrome (MFS) is an inherited autosomal dominant connective tissue disorder, transmitted with full penetrance. It has a prevalence of 1/50003, with pleiotropic manifestations and marked inter-familial and intra-familial variability. It lacks a predilection for race or geographic location. Seventy five percent are diagnosed through molecular studies, locating a mutation at chromosome 15q21.1 whilst linkage studies are unremarkable in 25% of Marfanoid patients, suggesting sporadic mutation.

Two homologous genes encode the fibrillin proteins: FBN1 on chromosome 15 (15q15-32) and FBN2, chromosome 5 (5q23-31) (1). These genes encode large, cysteine-rich glycoproteins, mainly organized into calcium-binding epidermal growth factor (cbEGF)-like, EGF-like and cysteine-rich domains. Fibrillin, one of the main constituents of microfibrils, primarily represents the basal network for tropoelastin growth in elastic tissue and it also acts as an anchoring structure in nonelastic tissues (2).

The majority of FBN1 mutations detected so far are missense mutations and are probably as a result of slippage mispairing at the replication fork, primarily affecting EGF-like domains. Studies have also discovered a locus for an MFS-like disorder (3p24.2-p25) in patients with isolated features of MFS but who do not fulfill the diagnostic criteria of MFS.

Mutations in FBN2 primarily cause congenital contractural arachnodactyly. Affected patients are distinguished by specific crumpling of the helix of the ear and lack of ocular complications. Production of abnormal fibrillin-1 monomers prevent normal fibrillin being encoded on the normal fibrillin gene (1) by

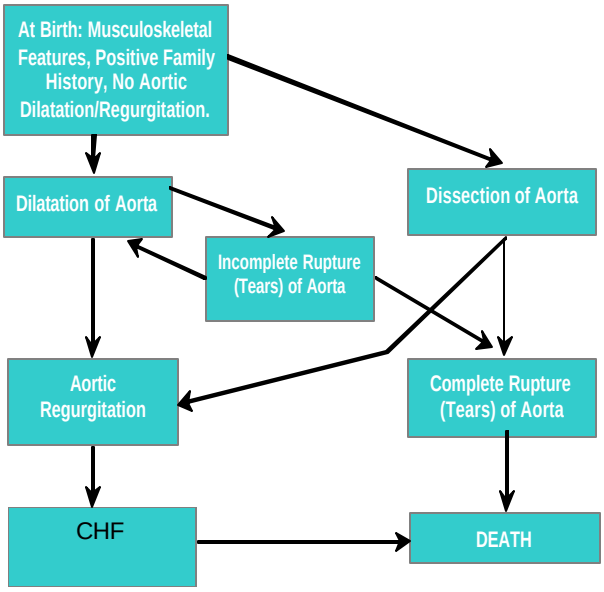

Figure 2 Scheme of development of cardiovascular complications in Marfan's Syndrome. Adapted from Fuster et al. The Heart. 10th Ed. Vol. 2. pp2160

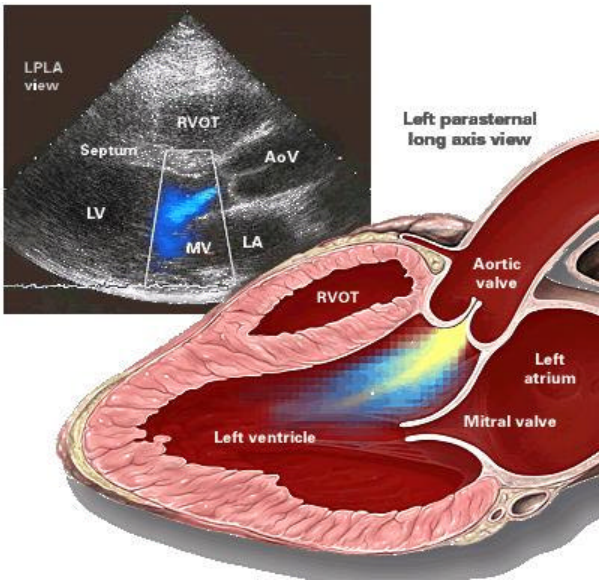

Figure 3 A typical Doppler echocardiograph in a MFS patient. The aortic valve regurgitation is apparent. The graphic shows its nature. Adapted.

disrupting its polymerisation: the dominant-negative effect.

The recognized systems affected in MFS are ocular, neurological, skeletal, cardiovascular, respiratory as well as the integument and dura (Fig.1). Some manifestations are age dependent.

Special attention must be directed to changes in the aortic root, the main cause of mortality. Abnormal fibrillin reduces the compliance and distensibility of the aortic wall to luminal ejection forces and associated increased pulse-wave velocity (seen by echocardiography or gated-MRI scanning). Consequently, progressive aortic dilatation, functional aortic regurgitation and eventual aortic dissection and rupture ensue; their risk increasing when the aortic root width exceeds 55mm (3). On histological analysis, 'cystic medial degeneration' is typically seen as deposition of collagen and mucopolysaccharides between medial cells with elastic fibre fragmentation and paucity of smooth muscle cells. Secondary consequences include mitral valve dysfunction, left ventricular dilatation, pulmonary artery dilatation and cardiac failure. Myocardial infarction is possible if coronary ostia become occluded (Fig.2).

Deficient fibrillin deposition also leads to reduced structural integrity of the lens zonules, ligaments, pulmonary airways and spinal dura.

Diagnosis

The 1986 Berlin Nosology of Heritable Disorders of Connective Tissue (4) (appendix 1) was the main mode of diagnosis of MFS. It stipulated the involvement of the skeletal system and two other systems, with the requirement of at least one major manifestation (ectopia lentis, aortic dilatation or dissection, or dural ectasia). In 1996, the Berlin nosology was revised to appreciate molecular data and family history. It became known as the Ghent nosology (appendix 2). Its intention was to serve as an international standard for clinical and molecular studies and for investigations of genetic heterogeneity and genotype-phenotype correlations (3). It identified the major and minor diagnostic findings.

However, the new criteria are, in some instances, found to be too stringent despite positive findings on computer tomography and magnetic resonance imaging. This highlights the ambiguity and the subjective nature in a clinical diagnosis of MFS.

Diagnostic gene sequencing (a tedious and expensive process) can identify an FBN1 mutation. Linkage analysis can track a mutated FBN1 gene within a family but a finding may represent normal variation, resulting in both false-positive and false-negative results.

At this point, no single gene probe or group of probes have been developed to detect most FBN1 mutations. Consequently, no molecular diagnosis is currently available commercially (3).

Non-invasive imaging supplements diagnosis and in some centres remains the method of quantification of the severity of cardiovascular disease, thereby aiding timely prophylactic surgical intervention.

Plain radiographs may depict medistanium widening or protrusio acetabula. Cross-sectional, transoesophageal and Doppler echocardiography will delineate heart chambers and grade valve function. It

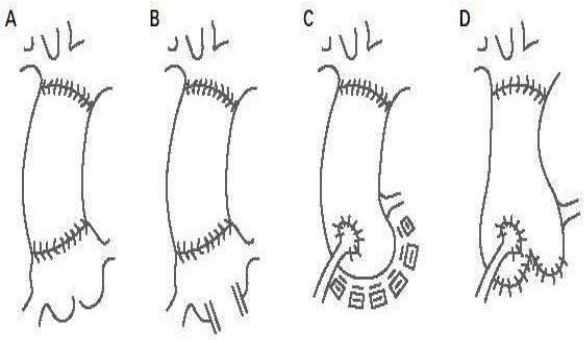

Figure 4. Operations for aortic dissection or ascending aortic replacement. (A) Simple tube replacement of the aorta for the sinotubular junction to the brachiocephalic origin. (B) Tube graft replacement and aortic valve replacement as separate components of the operation. (C) Composite graft replacement. (D) Leaflet-sparing aortic root replacement. Adapted from Tom Treasure. Cardiovascular Surgery for Marfan's Syndrome. Heart 2000;84:674-678

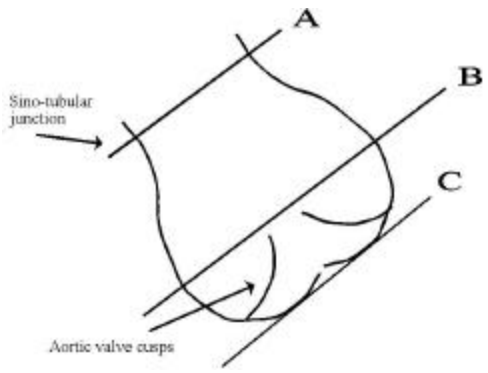

Figure 5. Echocardiographical measurements are made at A, B and C but the width at B determines the need for surgical intervention.

also aids visualisation of the aorta and measurement of the width of the sinuses of Valsalva. In MFS, the valve commissures are attached to an aorta of much greater circumference than at the nadir of the leaflet attachment; the leaflets no longer co-apt and aortic regurgitation ensues (Fig. 3) (5).

MRI favours imaging of aortic dissections. It should be performed on any patient who has actual-to-predicted aortic root dimension ratios greater than 1.5.

Considered to be the mainstay of diagnosis of aortic dissection, the sensitivity of aortography is not 100% and has its associated risks.

Immunohistologic evaluation of the skin for abnormal fibrillin is unpopular because of the high incidence of false-positive results in patients with other connective tissue disorders expressing Marfanoid characteristics (3).

Management

Management of MFS is essentially a multidisciplinary one (specific management is detailed in appendix 3).

Beta-Blockade, ACE inhibitors, Angiotensin II blockers

The risk of aortic dissection is intimately linked to mortality in MFS patients, and in the early 1970s, it was suggested that the reduction of the systolic impulse using -blockers may reduce this risk. Initial studies on turkeys and subsequent studies on MFS patients showed a reduced risk of dissection and fewer aortic complications with propanolol therapy, but noted a varied response to the treatment (6). Further studies have revealed that beta-blockade increases aortic distensibility and reduces aortic stiffness and pulse wave velocity (7,8,9). It also showed that the group who responded to -blockade tended to have smaller aortic diameters, suggesting increased efficacy in younger patients with smaller aortas (<40mm in one study (10)). Such studies provide strong evidence that -blockade should be considered in all Marfan patients, particularly in the younger age-group (4).

However, beta-blockade is not for everyone. Obvious contraindications are in patients with asthma, cardiac failure or bradyarrythmias. Instead, calcium antagonists, ACE-inhibitors or angiotensin II blockers may prove beneficial, particularly when the latter have been implicated in inhibiting vascular smooth muscle cell apoptosis, a process involved in cystic medial degeneration (11).

Emergency Surgery

Dissection of the aortic aneurysm is an absolute indication for surgical replacement. The standard operation involves replacement of the sinuses of Valsalva and as much of the ascending aorta as possible.

Elective Root Replacement

This option requires careful consideration of necessity, surgical risk, post-operative mortality rate and extent of aortic regurgitation.

The aortic root is replaced by the modified Bentall (composite graft-valve replacement) procedure (Fig. 4). This involves replacement of the sinuses, the aorta up to the innominate artery and button anastomoses of the coronary arteries. The excess (pathological) aorta, once used to contain the bleeding around suture lines, is resected and haemostasis gained under direct supervision.

An increasingly popular conservative operation, though not without criticism, involves resection of the aorta to the nadir of the aortic leaflets and attachment of the tube-graft proximally, so the valve operates within it. This method conserves the aortic valve and reverses the functional aortic regurgitation, on the premise that the aortic leaflets are without pathology.

A pertinent question is one of the timing of the replacement. Currently, there is no confident method to

predict the timing of a dissection. Elective aortic root replacement is a pre-emptive measure and its necessity is assessed by aortic root widths6. Measurement at the level of the tips of the valve leaflets is the most accurate (Fig. 5). As a rule, a width of 60mm will present a 10% risk of rupture within the next year, irrespective of site or aetiology 6. Current guidelines advocate prophylactic replacement when the width is 55mm in adults; 50mm in children. It is important to be weary that though the surgical risk may be lower than the risk of aortic dissection or rupture, post-operative mortality secondary to infection, false aneurysm formation, coronary anastomotic problems, anticoagulant bleeding and valve thrombosis is significant. Similarly, the rate of aortic root dilatation is important. A significant increase in diameter per six-month echocardiography (e.g. 3mm) should be promptly treated without waiting for the diameter to reach 55mm (12).

The surgical indications for aortic regurgitation do not alter in an MFS patient. Valve replacement is indicated if there are symptoms attributable to regurgitation and/or evidence of an increase in left ventricular end systolic dimensions with possible adverse effects to the left ventricle or patient's prognosis. It is also advisable to replace a 'Marfan' aorta at the same time as the valve replacement, particularly if there is no reason to avoid it (6).

Possible Advances

Possible advances in treatment of vascular disease in MFS include drugs that inhibit matrix-degrading enzymes formed in inflammation. Similarly, drugs that inhibit TGF have proved successful in reversing the abnormal lung structure in mice.

Currently, studies into using an FDA-approved drug, Losartan, may also adequately suppress TGF- signalling and thus, reverse lung problems, skeletal overgrowth, valve malformation and aortic aneurysm. It has also been found that drugs stimulating fibrillin production may benefit MFS patients, despite the mutated FBN protein too being formed (13).

CONCLUSION

MFS is a differential diagnosis for shortness-of-breath and more specifically, aortic regurgitation. It carries a high risk of mortality if left undiagnosed. The benefits of acquiring a thorough history and investigations are threefold. A full family history may well reveal a genetic condition affecting the patient, e.g. MFS. Early diagnosis of aortic dilatation will alert doctors not to initiate thrombolysis in a MFS patient who had an MI, thus preventing aortic rupture. Thirdly, medicolegal issues regarding failure to recognise signs of aortic dissection, failure to inform affected patients to limit strenuous exercise and failure to advise patients and their family of reproductive risks can be avoided. Timely diagnosis of MFS can save lives.

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Appendix 1. Berlin Nosology

An diagnosis of Marfan's Syndrome requires :
If there is No family History:
Involvement of Skeleton and 2 other systems
At least 1 major manifestation
If there is an unequivocally affected 1° relative:
Involvement of at least 2 systems
Requirement for a major manifestation depends on family phenotype

Table of Definitions

Systems	**Major Manifestations**
Skeletal	None
Ocular	Ectopia Lentis
Cardovascular	Dilatation Of Ascending Aorta
Aortic Dissection	None
Pulmonary	None
Skin And Integument	None
Central Nervous System	Dural Ectasia

Appendix 2. Ghent Nosology

An diagnosis of Marfan's Syndrome requires :	
Either:	A major criterion in at least 2 systems AND Involvement of a third system
Or:	Mutation known to cause Marfan's syndrome in others AND One major criterion in 1 system AND Involvement of a second system

Table of Definitions

Systems	**Features required to be considered a Major Criterion**	**System Involved**
Skeletal	>=4/8 major features	2 major OR 1 major and 2 minor features
Ocular	Ectopia lentis, myopia, global axial lengthening	2 minor features
Cardiovascular	Dilatation of ascending aorta involving Sinus of Valsalva Dissection of ascending aorta	1 minor feature
Pulmonary	None	1 minor
Skin/integument	None	1 minor
Dura	Lumbosacral dural ectasia	No additional features
Family/genetic history	- 1st degree relative who can be diagnosed affected without family history - Presence in the patient of Fibrillin mutation known to cause Marfan's syndrome - Presence in the patient of a haplotype around fibrillin, inherited by descent, known to be associated with unequivocal Marfan's syndrome in the family.	No additional features

Appendix 3. The Marfan's Syndrome Clinical Guideline

INITIAL ASSESSMENT AND DIAGNOSIS

" The diagnosis of Marfan's syndrome should be made on the basis of the Ghent criteria.
" The initial assessment should include the following: personal history, detailed family history, clinical examination including ophthalmology examination, transthoracic echocardiogram.
" The echocardiogram should include measurement of the aortic diameter at the Sinus of Valsalva, and this dimension should be related to normal values based on age and body surface area.
" The development of scoliosis and protrusio acetabulae and dural ectasia is age dependent. X-ray or MRI examination for these features should be considered in those of the appropriate age, if a positive finding would make the diagnosis of Marfan's or if other clinically important decisions depend on the findings.
" Younger patients with a positive family history who do not manifest sufficient clinical features to fulfill the diagnostic criteria for affected status, and in whom DNA testing is not successful, should have further clinical evaluations pre-school, before puberty and at age 18 or more frequently, particularly around puberty, as the clinical situation dictates.
" Younger patients with no family history, who fall short of fulfilling the diagnostic criteria by one system only should have further evaluations pre-school, at puberty and at age 18 or more frequently, particularly around puberty, as the clinical situation dictates.

MANAGEMENT: CARDIOVASCULAR SYSTEM

" Beta blocker therapy should be considered in any Marfan patient with aortic dilatation at any age.
" Marfan patients should be referred for consideration of prophylactic aortic root replacement when the aortic root at the Sinus of Valsalva exceeds 5 cm in an adult or child.
" Marfan patients of all ages should be offered at least annual evaluation with clinical history, examination and transthoracic echocardiography. In children, serial trans thoracic echocardiography at 6 -12 month intervals is recommended, the frequency depending on the actual aortic diameter (in relation to body surface area) and the rate of increase.

MANAGEMENT: SKELETAL SYSTEM

" Even if there is no clinical scoliosis children should have an erect A-P plain X-ray film of the spine i.e. between the ages of 9 - 11 years of age.
" A child with a clinical scoliosis requires formal orthopaedic assessment, and 6 monthly orthopaedic follow-up until the growth spurt is completed is recommended (Pyeritz 1979).
" Adults with angle of curvature is >40° should be referred to the orthopaedic department for indefinite follow-up (minimum yearly).
" Contact sports and diving should be avoided to reduce the risk of aortic rupture.

MANAGEMENT: OCULAR SYSTEM

" When there is a family history, initial examination by an ophthalmologist should take place at three to six months of age to look for evidence of lens dislocation, anterior chamber problems and incipient retinal detachment.
" When there is no family history, examination by an ophthalmologist should form part of the initial clinical assessment of the patient.
" To detect later changes in refraction in Marfan's patients, such as those caused by later childhood lens subluxation, and to prevent amblyopia, annual review by an orthoptist or optometrist until the age of 12 is recommended.
" Families should be informed about the risk of retinal detachment and glaucoma, to that they can seek appropriate advice promptly should symptoms develop.

MANAGEMENT: RESPIRATORY SYSTEM

" Pulmonary function tests should form part of the assessment of pectus deformity.
" Surgical repair of pectus excavatum should be delayed, if possible, until late adolescence, and should include internal stabilisation to reduce the risk of recurrence.
" If cardiac and pectus surgery are required as elective procedures, surgical repair of pectus excavatum should precede cardiac surgery by several months for optimal functional and cosmetic results.

Adapted from John C S Dean Et Al. Clinical Guidelines and an Integrated Care Pathway In Marfan Syndrome. Dr John C S Dean, Department Of Medical Genetics, Medical School, Foresterhill, Aberdeen AB25 9ZD, Scotland, UK

CASE REPORT

Sepsis Following Laparotomy for Trauma - Don't Watch and Wait

Piers R.J. Page*

INTRODUCTION

Exploratory laparotomy is one of the most frequently performed surgical procedures in the trauma setting, usually in the context of emergency surgery when abdominal injury has been demonstrated by appearance of free fluid on imaging. It has, for reasons yet to be fully understood, a comparatively high rate of infection, and this case demonstrates the potentially fatal course of such a complication left untreated.

CASE REPORT

EA, a 17 year old Hispanic male, was found face-down in a Washington DC park with multiple gunshot wounds. On arrival at the trauma facility, it was established that he had been shot in the left cheek, right shoulder and left flank, with extensive overt facial and thoracic injuries. As is dictated by protocol in these situations, a Focused Abdominal Sonogram for Trauma (FAST) was performed, revealing free fluid in the abdomen. This, in combination with haemodynamic instability, indicated a requirement for surgery, and so he was taken to the OR for exploratory laparotomy.

Damage was found to the spleen, liver, stomach and diaphragm, and the spleen was removed at this point. The abdomen was then packed and covered with a vacuum dressing, and the patient sent to SICU. On day 2 post-injury, he was taken back to the OR for closure of his abdominal wound. Once this was complete, the oromaxillofacial surgery team took him straight over on the table for reduction and fixation of his facial fractures, achieved with Lorenz plates and monocortical screws. He was then returned, still intubated, to the SICU.

On day 6, he developed an infection and fever, with marked leucocytosis, and on day 7 an area of periumbilical purulence was noted, from which several sutures were removed. On day 8, break evisceration occurred, and total fascial dehiscence with the appearance of necrotizing fasciitis was noted in the OR. Emergency debridement was performed over the next three days, with the decision taken to leave a ventral hernia for definitive closure at a much later date. A split-thickness skin graft was placed into the abdominal wound, and the patient was eventually discharged from hospital some 4 weeks later, to be reviewed later in the year for abdominal closure.

DISCUSSION

So what should we have done differently? EA's situation probably arose from a number of decisions, no single one of which can be deemed solely responsible. The first major decision with potential involvement was early closure of the abdominal wall. The natures of the injuries sustained by the patient were suggestive of potential abdominal contamination; gastric lacerations spilling stomach contents from the time of injury, followed by laparotomy on a full bowel. With hindsight, EA was definitely a candidate for delayed primary closure, which would have simply involved continuation with the vacuum dressing already in use between initial operation and closure. These devices have been proven [1] to provide sufficient medial traction of the abdominal layers to reduce elective ventral herniation rates, even in patients requiring multiple laparotomies. Another technique, described by Jernigan et al [2], is the use of absorbable polyglactin mesh, which can have pleats drawn in it at the bedside to gradually draw the wound edges together.

The main pointer against definitive early closure was his white cell count, which had climbed to 11,000 by early morning on day 2, from 4,300 after his initial

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Table 1. EA's White Cell Counts during early stages of treatment

Day	Time	Count (K/ul)	Remarks
0	0545	7.9	Initial surgery
0	1045	4.3	
1	0500	11.0	
2	0439	13.4	
2	1915	10.7	Abdomen closed & facial fxs repaired
3	0500	11.4	
4	0500	13.4	
5	0500	15.5	
7	0530	21.8	Purulence noted, local sutures removed
8	0530	25.6	Evisceration & re-operation

surgery. Even allowing for the body's inflammatory response to trauma surgery [3], it may well have been wise to have taken heed of this result and forestalled on closure to monitor the situation.

Having committed to closing the abdomen, close surveillance should have been in place for any signs of infection, with a very low index of suspicion for acting on them. Serial blood counts were taken daily (see Table 1 and Figure 1) except, crucially, on day 6. Between the mornings of days 5 and 7, the white cell count rose from 15,500 to 21,800, and a further rise to 25,600 preceded dehiscence on day 8. These counts were all recorded in the notes, and seem to have been dismissed as they were rising only small amounts relative to the previous counts. Shown in context of the counts over the entire admission, of course, they should have set alarm bells ringing, especially given that the steady climb began after definitive closure.

The patient's persistent pyrexia should also have been considered in the wider context. He was treated for his sepsis with appropriate antibiotic and fluid therapy, but this does not, of course, address the initial source of the infection; in a patient with a newly closed abdomen, the first suspicion should always be intra-abdominal. In combination with the medical notes documenting localized tenderness and erythema around the wound (which are, of course, criteria for sepsis), there should have been little doubt that EA

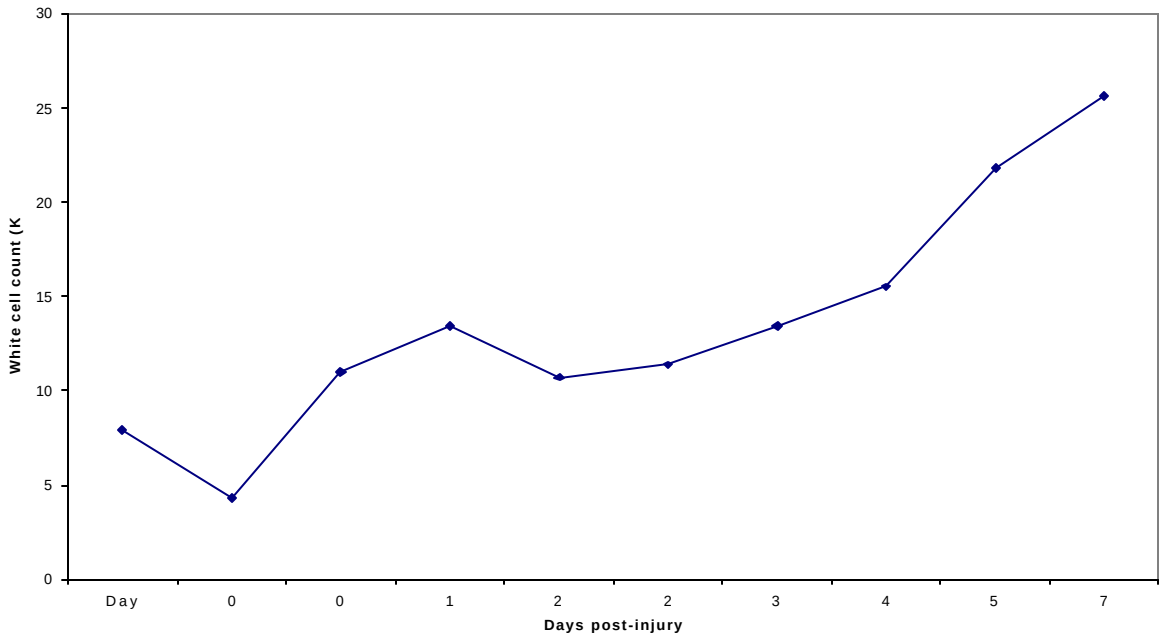

Figure 1. EA's White Cell Counts during early stages of treatment

needed urgent re-operation.

Are clinical signs alone enough justification for re-operation? In this age of readily available imaging studies, many would argue for obtaining at least a CT before taking the patient to the OR again. Studies have shown consistently, however, that there is an overall benefit from re-operation justified solely by clinical impression. In Hinsdale and Jaffe's work [4] in the mid 1980s, for example, it was found that clinical signs were at least as reliable as high-tech (for the time) imaging; of special note should be the benefits of early surgery when a patient appears to be entering multiple organ failure. Interestingly, in a later bout of infection not related to this incident, the patient had a negative CT scan but exhibited very definite clinical signs, caused by an abscess only discernible on repeat CT 48 hours later; anecdotal reinforcement of the evidence discussed here.

Tillou et al [5] found that 71% of patients, albeit in a small study (n=55), with fascial dehiscence had underlying intra-abdominal infection, and hence essentially that localized wound infection was likely to be the tip of the iceberg. Velmahos' review [6] of the evidence suggested re-laparotomy every 24-48 hours until sepsis is eradicated is still a lower risk method of management than either waiting for evolution of the situation or radiological confirmation. Recent work in America [7] found that laparotomy was becoming a more frequent intervention, as was delayed primary closure, which had a higher morbidity but overall improved survival rates.

In summary, a bad situation worsened through lack of decision making. The following points are salient in all cases:

- Never consider signs, symptoms or lab results in isolation. Look for the trend - there is very often an obvious pattern to be found
- A clinical picture of postoperative deterioration should not be left to evolve in the hope it will resolve or the cause will become more obvious
- In patients with a wound which is an obvious first choice for focus of infection, there should be a low threshold for decision to re-explore
- Only delay for imaging if the resulting information may substantially change management.

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REVIEW ARTICLE

The Fall of Titans: The Need to Reassess COX-2 Inhibitors

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INTRODUCTION

Two of the most popular arthritis medications came under great skepticism from the medical and scientific community in 2004. Long term clinical trials for both rofecoxib and celecoxib, also known as Vioxx and Celebrex, respectively, were stopped short by the Food and Drug Administration (FDA) due to increased cardiovascular risks to its subjects. The news came after five years of their use by the general public.

In 1999, an estimated 4 million Canadians and their doctors eagerly awaited the public launch of a revolutionary class of drugs: cyclooxygenase-2 (COX-2) inhibitors (1). These drugs were part of a new class of non-steroidal anti-inflammatory drugs (NSAIDs) that offered a welcomed alternative to the traditional non-selective NSAIDs that were already on the market. The main effects of COX-2 inhibitors were to reduce inflammation and to provide pain relief for osteoarthritis and rheumatoid arthritis patients without the unpopular gastrointestinal (GI) complications of acetylsalicylic acid (ASA) and other traditional NSAIDs. Pharmaceutical companies aggressively marketed these "miracle" drugs to doctors and patients --and it worked.

In the first three months of Pfizer Inc.'s public release of celecoxib, Canadian pharmacies filled more than 428,400 prescriptions worth $20,736,000 in sales (2). Celecoxib became the fastest selling consumer product, breaking the record of the widely-used sildenafil, better known as Viagra, which also happened to be a Pfizer product, of $13,306,000 in 1998 (2). Only six months later, Merck & Co. Inc. grabbed their part of the pie with their launch of their COX-2 selective inhibitor, rofecoxib. Rofecoxib was no ordinary copycat. It quickly became more popular than celecoxib and in 2003, rofecoxib was the 10th most prescribed medication in Canada (3). It became exceedingly common for an arthritis patient to walk out of a clinic with a COX-2 inhibitor prescription.

The popularity of these drugs was not at all surprising. Arthritic pain was and continues to be an important issue to many Canadians. Health Canada reported that nearly 4 million Canadians suffered from a form of arthritis, representing 16% of the population in 2000 (1). Arthritis was the second and third most common chronic condition reported by women and men, respectively. Although arthritis is commonly thought of as a disease of the elderly, nearly 60% of people that reported having arthritis were under the age of 65 (1). By 2026, Health Canada estimates the prevalence of arthritis to be 20.6%, or 6,360,000 million Canadians.

COX AND COX INHIBITORS

ASA and other NSAIDs are used primarily for their anti-inflammatory and analgesic effects through the inhibition of arachidonic acid hydrolysis by cyclooxygenase (COX). This leads to decreased production of prostaglandins and thromboxanes, collectively known as prostanoids, which are the end-products of the COX pathway. These various end-products perform a myriad of physiological functions ranging from constricting or dilating blood vessels, stimulating or inhibiting platelet aggregation, to causing pain sensation.

There are currently two defined COX genes: COX-1 and -2. COX-1 and COX-2 are believed to subserve different physiological functions due to their different expression patterns. COX-1 is considered a "house-keeping" gene that is constitutively expressed in most tissues. However, this may be an oversimplification because COX-1 expression can be regulated in T-cell

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development and altered in disease states such as atherosclerosis. COX-1 has important homeostatic functions, which include maintaining gastric mucosal integrity and mediating normal platelet function. In contrast, COX-2 expression is low and highly restricted under basal conditions. However, during inflammatory responses, COX-2 expression is dramatically upregulated. Its parallel expression with inflammation increases with inflammatory mediators such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), and decreases with glucocorticoids.

Although structurally similar to COX-1, COX-2 has small yet important differences. COX-2 has a valine substitution for isoleucine at position 523 (4). The smaller valine amino acid leaves a gap in the wall of the enzyme, giving rise to a "side pocket", which is the binding site of many selective inhibitors, including rofecoxib and celecoxib (4,5). When isoleucine was substituted with valine in the COX-1 enzyme, it was also inhibited by COX-2 selective inhibitors (6).

ASA and other traditional NSAIDs effectively decrease inflammation and reduce pain by non-selectively inactivating both COX enzymes. ASA irreversibly acetylates a specific serine residue on COX, thereby inhibiting its function. On the other hand, the traditional NSAIDs include both reversible and irreversible competitive inhibitors for the binding site of arachidonic acid. Interestingly, splice variants of both these enzymes exist. A splice variant of COX-1, sometimes referred to as COX-3, is thought to be the active target of another analgesic, acetaminophen (7). Although patients receive the anti-inflammatory and analgesic effects with the inhibition of COX-2 using traditional therapies, some patients endure the undesirable side effects from the inhibition of COX-1, namely GI irritation, erosion, ulcer and even haemorrhaging (8). Intuitively, COX-2 inhibitors would achieve the desired effects of traditional medications without their side effects. This indeed was the outcome of many of the first trials published.

ROFECOXIB

In the Merck-sponsored randomized, double-blinded, stratified Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, 8076 patients suffering from rheumatoid arthritis participated in determining the incidence of GI complications between rofecoxib and naproxen, a non-selective NSAID (9). The incidence of upper GI events such as perforations, obstructions, bleeding and/or ulcers, were significantly decreased in patients receiving rofecoxib treatment as compared to those using naproxen. This brought about wide acceptance of rofecoxib by many physicians and the general public. Luckily, some skeptics remained.

As clinicians and scientists sifted through the data from the VIGOR trial, questions were raised and skepticism grew. It was realized that only particular data were published for public reading, while other data were left out. Cardiovascular event data were later submitted to and reviewed by the FDA. The FDA Data and Safety Monitoring Board (DSMB) recommended a blinded adjudication of cardiovascular events of rofecoxib versus naproxen. A total of 98 cases (65/4047 from the rofecoxib group, 33/4029 from the naproxen group) were adjudicated for adverse events. There were 46 cases (in 45 people) in the rofecoxib group compared to 20 in the naproxen group to have confirmed serious adverse thrombotic cardiovascular events, such as myocardial infarctions (MI), unstable angina, cardiac thrombi, resuscitated cardiac arrests, sudden or unexplained deaths, ischemic strokes, and transient ischemic attacks. The cumulative incidence of developing thrombotic events was significantly higher with a relative risk (RR) of 2.38 (95% CI, (1.39-4.00), P<.001) in the rofecoxib group (10,11).

In addition, a subgroup analysis was performed on patients with a past medical history of stroke, transient ischemic attack, MI, unstable angina, angina pectoris, coronary artery bypass grafting, or percutaneous coronary interventions, who were classified as aspirin-indicated, versus those whom aspirin was not indicated. The RR of developing thrombotic events between the rofecoxib group and the naproxen group was 4.89 (95% CI, 1.41-16.88, P=.01) and 1.89 (95% CI, 1.03-3.45, P=.04) in aspirin-indicated patients and aspirin not indicated patients, respectively. Rofecoxib clearly increased the risk of suffering cardiovascular events, especially in patients with a previous history of significant cardiovascular disease (10,11).

Although the sponsors of the VIGOR trial attempted to explain the increased cardiovascular risk of rofecoxib compared to naproxen was primarily due to naproxen's anti-platelet cardioprotective effect (11), the DSMB nevertheless suggested the Vioxx label include a warning to consumers of the increased cardiovascular risks. Unfortunately for Merck, this would not be the end of its problems.

On September 30th, 2004, Merck voluntarily announced a worldwide withdrawal of rofecoxib after preliminary results from a clinical trial showed a significant overall increase in incidence by a factor of 3.9 of serious thromboembolic events such as MIs and strokes in patients receiving 25mg/day of rofecoxib compared to placebo (12). The planned 3-year clinical trial called APPROVe (Adenomatous Polyp Prevention of Vioxx) was forced to stop short by two months by the DSMB. The randomized, double-blinded study, which enrolled about 2600 patients at 100 sites, was evaluating

the efficacy of rofecoxib in preventing the recurrence of colorectal polyps in patients with a past medical history of colorectal adenomas. After 18 months of treatment, patients receiving rofecoxib were 1.8 times more likely (attributable risk=1.5%) to suffer from MIs or strokes compared to those receiving placebo (13).

CELECOXIB

Since rofecoxib's withdrawal from the market, Pfizer's celecoxib, the next most commonly prescribed COX-2 inhibitor, received major attention as to its safety. Canada's Adverse Drug Reaction Information System (CADRIS) database maintained by Health Canada showed nearly the same number of suspected adverse reaction reports for both celecoxib and rofecoxib (14). Although these are unproven reports from patients, consumers, doctors, pharmacists, and/or other health professionals, Health Canada uses this database as an early detection system for possible safety concerns with medications.

Similar to Merck, Pfizer sponsored a large scale clinical trial to determine the efficacy of celecoxib. The Celecoxib Long Term Arthritis Safety Study (CLASS) trial consisted of two separate studies comparing the effects of celecoxib to ibuprofen (400mg bid) and diclofenac (75mg bid). In the original report, celecoxib appeared to have a decreased risk in developing GI side effects such as bleeding, perforation, and obstruction, and no increased cardiovascular risk (15). But it was soon realized that data were again withheld from the public. The study lasted 13 months but only 6 months of follow-up data were published. Analysis of the subsequent data revealed that celecoxib had no statistically significant difference in the overall incidence of the predefined GI end points (0.8% in the celecoxib group versus 1.5% in either NSAID group, P=0.09) (16,17). Celecoxib's lack of long-term gastroprotective effects may be explained by its low selectivity ratio (COX-2/COX-1) as compared to rofecoxib (8).

On December 17th, 2004, the National Cancer Institute announced its premature cessation of a celecoxib trial known as Adenoma Prevention with Celecoxib (APC) due to a significant increase in cardiovascular risk. The APC trial enrolled 2026 patients, who were randomized into 1 of 3 groups: placebo, celecoxib 200mg bid, or celecoxib 400mg bid. The groups were followed for an average of 33 months of a planned 60 months. There was a significant increase in the number of cardiovascular events, which included cardiovascular deaths, MIs, and strokes, in both celecoxib groups. A dose-response effect was observed between the celecoxib and placebo groups. There were 2.5-fold and 3.4-fold increases in cardiovascular risk in those taking daily doses of celecoxib 400mg and 800mg, respectively (19,20).

PROSTANOID BALANCE

Rofecoxib, celecoxib and arguably other COX-2 inhibitors, are thought to increase the risk of adverse cardiovascular events due to the suppression of prostaglandin I_2 (PGI_2), also known as prostacyclin. PGI_2 has been shown to be the predominate COX end-product in the vascular endothelium where its functions include inhibition of platelet aggregation, inhibition of platelet and neutrophil adhesion, and dilation of bronchial and vascular smooth muscle. It was previously thought that PGI_2 was mainly derived from COX-1, but it was later shown that PGI_2 is a COX-2 product (21). The cardiovascular effects of PGI_2 contrast those of thromboxane A_2 (TXA_2), a major product of platelet COX-1. Whereas ASA and other traditional NSAIDs inhibit both COX enzymes and thus both PGI_2 and TXA_2 production, the selective COX-2 inhibitors do not appreciably inhibit TXA_2 production.

It is believed by some groups that COX-2 may be induced by haemodynamic stress on endothelial cells *in vivo* as *in vitro* studies have shown (22). If so, the suppression of PGI_2 formation by selective COX-2 inhibitors may predispose patients to thromboembolic events (12). This is especially important in patients with a history of cardiovascular disease. Depression of PGI_2 formation by COX-2 inhibitors would increase their intrinsic risks of suffering clinical cardiovascular events (23).

CONCLUSION

Individual patient accounts claim improved analgesia with COX-2 selective inhibitors over traditional NSAIDs. However, the superiority of COX-2 inhibitors over traditional NSAIDs has not been clinically tested. In considering the anecdotal efficacy, higher cost, and proven cardiovascular risks, the public use of COX-2 inhibitors is controversial, to say the least. So where does this leave arthritis patients? As the hype of these miracle drugs turn to concern, should the public turn its back to all COX-2 inhibitors? The burden of proof rests with the pharmaceutical companies to prove the safety of their drugs. Although there are other pharmacological uses and risks of these drugs that are beyond the breadth of this review, there is a clear need to exercise prudence and caution to the use of COX-2 inhibitors. More research is required to determine the safety of all COX-2 inhibitors, including Pfizer's valdecoxib (Bextra) and its prodrug, parecoxib (Dynastat). Concerns over the safety of both valdecoxib and parecoxib have already risen. Two randomized, double-blinded, placebo-controlled

clinical trials showed that both valdecoxib and parecoxib increased the risk of cardiovascular events by approximately 3-fold in patients after coronary artery bypass grafting (24,25). On April 7th, Pfizer withdrew valdecoxib from the market due to concerns over valdecoxib's associated increased risk of cardiovascular events and of serious skin reactions (26,27).

The Merck and Pfizer cases have attracted much public attention and concern. Physicians and the general public are demanding answers and some are even seeking monetary compensation through class-action lawsuits. The onus is on pharmaceutical companies to produce the required research data on their drugs. Long term, randomized, double-blinded clinical trials provide the best evidence of a drug's potential use and more importantly, of its safety. Moreover, the FDA and Health Canada have the duty and responsibility to be more stringent on their approval of drugs for public use. This is a failing on both sides. Let us hope that these important lessons are well-learned.

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REVIEW ARTICLE

Pregnancy and Its Effect on the Progression of Diabetic Retinopathy

Jeff Van Impe, MD*

INTRODUCTION

Visual changes may occur during pregnancy (1). Women with type I diabetes are particularly vulnerable to ocular changes during pregnancy. Multiple studies have demonstrated that a worsening of retinopathy in diabetic patients can occur during pregnancy (2-9). The significance of this problem should not be overlooked considering the prevalence of diabetes and diabetic eye problems in North America. Diabetes is the leading cause of new cases of blindness in American adults between the ages of 20 and 74 (10). The incidence of diabetes has been found to be slightly higher in women than men (11), and the age-adjusted female-to-male ratio of blindness due to diabetes is 1.4:1 (10). In light of these statistics it is imperative that young diabetic women of childbearing age be examined by an ophthalmologist prior to pregnancy or at least in the first trimester (12).

In this article, the classification of diabetic retinopathy is reviewed together with the current understanding of the pathophysiology of its progression during pregnancy and the factors associated with this progression. A discussion of the optimal management of patients with diabetic retinopathy both before and after conception is provided.

STAGES OF DIABETIC RETINOPATHY

Before elucidating the factors associated with progression of retinopathy during pregnancy, it is beneficial to outline the stages of diabetic retinopathy. The most commonly used classification system, the Modified Klein Classification of Diabetic Retinopathy (13), contains eight levels and is outlined in Table 1.

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PROGRESSION OF DIABETIC RETINOPATHY DURING PREGNANCY

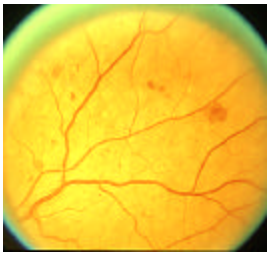
Although some studies have suggested pregnancy does not alter the course of diabetic retinopathy (14, 15), the majority have demonstrated the opposite to be true. Reported rates of progression of retinopathy range from 5%-70% (2-9).

A cohort study, the Diabetes Control and Complications Trial (DCCT), performed a longitudinal analysis on 180 women who had 270 pregnancies and 500 women who did not become pregnant during an average of 6.5 years of follow-up (8). Fundus photography was performed every 6 months throughout the study period (8). All subjects recruited into the DCCT were 13-39 years of age and had had type I diabetes for 1-15 years (8). This study divided the patients into conventional and intensive treatment groups with respect to insulin therapy and made use of odds ratios. In the conventionally treated group the pregnant women were found to have a 2.48-fold greater risk of worsening retinopathy during pregnancy (8). The DCCT found that the greatest risk of worsening retinopathy occurred during the 2nd trimester and persisted for as long as 12-months postpartum (8). In the intensive treatment group, the pregnant women had a 1.63-fold greater risk of worsening of retinopathy in the course of pregnancy (8). Axer-Siegel et al. (9) reported in a study of 22 women with diabetic retinopathy, those with nonproliferative diabetic retinopathy (NPDR) at the start of pregnancy 55% experienced progression of their existing NPDR while 22.5% progressed to proliferative disease.

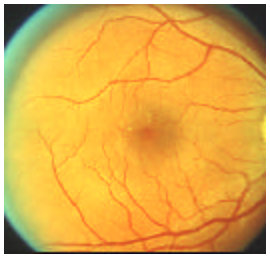
Fortunately, many studies have concluded that diabetic retinopathy which progresses during pregnancy has a high-rate of spontaneous resolution after delivery (8, 9), although the length of time required for resolution is variable. Axer-Siegel et al. (9) found that in

Table 1. Modified Klein Classification of Diabetic Retinopathy

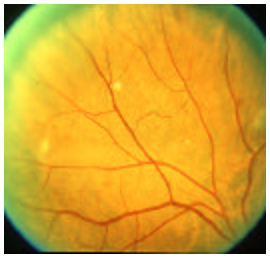
LEVEL	DEFINITION
1.0	No retinopathy
2.0	Microaneurysms (1 or more) only
3.0	Microaneurysms and 1 or more of the following: ·Retinal hemorrhage < standard photo #2A ·Hard Exudates (HE) < standard photo #3 ·Retinal infarcts questionably present ·Intraretinal microvascular abnormalities (IRMA) questionably present ·Venous beading (VB) questionably present ·Small venous loops definitely present
4.0	Microaneurysms and 1 or more of the following: ·Retinal hemorrhage > standard photo #2A ·HE > standard photo #3 ·Retinal infarcts definitely present ·IRMA definitely present ·VB definitely present
5.0	In fields 4 through 7 only: At least 3 of the following: ·Microaneurysms/retinal hemorrhage >= standard photo #2A in 1 field or more ·Retinal infarcts in at least 2 fields ·IRMA definitely present in at least 2 fields ·VB definitely present in at least 2 fields Or ·IRMA present in 4 fields and >= standard photo #8A in at least 2 fields
6.0	·New vessels on or within 1 disc diameter (DD) < standard photo #10A Or ·New vessels elsewhere or preretinal or vitreous hemorrhage, but level 7 definition not met
7.0	Diabetic Retinopathy Study (DRS) high-risk characteristics include one or more of the following: · New vessels elsewhere > 1/2 disc area in any single photographic field when associated with fresh vitreous or preretinal hemorrhage in any field · New vessels on or within 1 DD of the disc graded < standard photo #10A with preretinal or vitreous hemorrhage · New vessels on or within 1 DD of disc graded >= standard photo #10A with or without preretinal or vitreous hemorrhage
8.0	Unclassifiable due to large vitreous hemorrhage, Phthisis or enucleation secondary to Diabetic Retinopathy



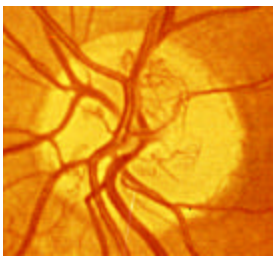
Standard Photo #2A



Standard Photo #3



Standard Photo #8A



Standard Photo #10A

Table 2. Summary of the risk factors associated with the progression of diabetic retinopathy during pregnancy

RISK FACTORS	SUMMARY
The pregnant state itself	·Even when controlling for glycemic control, blood pressure and duration of diabetes, the current pregnancy itself was a major risk factor for progression of diabetic retinopathy
Duration of diabetes	·Women who have had diabetes longer are more susceptible to worsening of their diabetic retinopathy during pregnancy ·Younger age at onset of diabetes is associated with increased incidence of progression of retinopathy
Degree of retinopathy at conception	·Risk of worsening of retinopathy increased with increasing severity of retinopathy at conception
Glycemic Control	·Rapid tightening of glycemic control during pregnancy is associated with a higher risk of progression of retinopathy ·Higher glycosylated hemoglobin levels at conception are associated with higher rates of progression of retinopathy
Coexisting Hypertension	·Progression of diabetic retinopathy is more likely to occur in patients with either chronic hypertension or pregnancy induced hypertension ·Both elevated diastolic and systolic pressures have been independently associated with DR progression

a subset of patients with no retinopathy at onset who went on to develop mild NPDR during pregnancy, 50% had complete regression and 30% had partial regression of their disease after delivery. However, the rates of regression were reduced in patients with mild NPDR at onset. In this group only 17% had total regression to their baseline and 58% had partial regression (9). Although the DCCT Trial (8) demonstrated that the progression of retinopathy often continued into the first year postpartum, it was found that worsening of existing retinopathy during pregnancy had no long-term consequences as women who did and did not become pregnant during the study had similar retinopathy levels 6.5 years later.

PATHOPHYSIOLOGY OF PROGRESSION

Despite the preponderance of evidence suggesting worsening of diabetic retinopathy during pregnancy, the pathogenesis is still unclear. Several studies have examined retinal blood flow and vessel diameter in diabetic subjects during pregnancy (16-18). Chen et al. (16) studied retinal blood flow in pregnant females with and without diabetes and found a 14-19% increase in volume of retinal blood flow in diabetic patients who had progression of their diabetic retinopathy. Loukovaara et al. (17) also found, that when compared to nondiabetic pregnant women, retinal capillary blood flow was higher in diabetic women during pregnancy. In women with diabetes, retinal capillary blood flow tended to increase during pregnancy until the 3rd trimester and to be lower 3 and 6 months postpartum, compared to capillary flow during the 3rd trimester (17). Chen et al. (16) proposed that the progression of diabetic retinopathy in pregnant diabetics may partly result from increased retinal blood flow caused by hyperperfusion. The ability of the retina to autoregulate its blood flow is impaired in diabetic retinopathy (16), and thus in a diabetic patient, the physiologic changes of pregnancy impose an added stress on an already compromised retinal circulation (16).

Conversely, Schocket et al. (18) found a decrease in retinal venous diameter and volumetric blood flow during the third trimester in both diabetic and non-diabetic mothers, with the decrease significantly larger in diabetics. This group theorized that the decrease in retinal blood flow may exacerbate retinal ischemia and hypoxia (18), leading to the progression of diabetic retinopathy.

FACTORS ASSOCIATED WITH THE PROGRESSION OF DIABETIC RETINOPATHY DURING PREGNANCY

Various factors have been shown to influence the progression of diabetic retinopathy during pregnancy. These include, but may not be limited to, the following: the pregnant state itself, duration of diabetes prior to the

pregnancy, degree of retinopathy at time of conception, metabolic control before and during pregnancy, as well as the presence of coexisting hypertension. The factors involved are reviewed in detail below and summarized in Table 2.

PREGNANCY

Klein et al. (19) demonstrated in a 1990 study that after accounting for glycemic control, blood pressure and the duration of diabetes, the current pregnancy state itself was a major risk factor for progression of retinopathy. Furthermore, the DCCT found that pregnancy itself was related to changes seen in retinopathy (8).

DURATION OF DIABETES

Several studies have shown that women who have had diabetes longer are more susceptible to worsening of their diabetic retinopathy during pregnancy (2, 9, 20). Axer-Siegel et al. (9) found that patients with progression of their retinopathy during pregnancy had diabetes for an average of 15.4 years (±5.3 years) compared to 10.86 years (±6.7 years) in those who did not have any progression. The findings of Temple et al. (2) supported this observation. Progression of retinopathy was significantly increased in women with duration of diabetes 10-19 years compared to those with duration less than 10 years. Ten percent of those with diabetes of duration 10-19 years demonstrated progression of their retinopathy, compared to 0% in the group with diabetes for less than 10 years (2). Similarly, an association has been demonstrated between younger age at onset of diabetes and increased incidence of progression of retinopathy. Lauszus et al. (20) found that in women who had progression of their retinopathy, the average age at onset of diabetes was significantly younger (14±8 years), compared to the group with no progression of their disease (19±8 years). It has been suggested that women with type I diabetes be encouraged to plan pregnancies early in life if possible (20).

DEGREE OF RETINOPATHY AT TIME OF CONCEPTION

Another important risk factor in the progression of retinopathy during pregnancy is the degree of retinopathy prior to conception. The Diabetes in Early Pregnancy study (21) demonstrated that the risk of worsening retinopathy during pregnancy was increased with the severity of retinopathy at the time of conception. Of women with no retinopathy at baseline, 10.3% progressed to demonstrate some nonproliferative retinopathy. In women with nonproliferative retinopathy with microaneurysms only, 21.1% demonstrated some progression of their disease. And, in women with moderate-to-severe nonproliferative retinopathy, 54.8% demonstrated progression of their disease. Progression to proliferative retinopathy in the absence of initial nonproliferative retinopathy in early pregnancy is extremely rare. Temple et al. (2) have provided further support by demonstrating that progression of retinopathy was significantly more common in women with moderate or severe background diabetic retinopathy at conception compared with women with minimal or no retinopathy at conception (30% vs. 3.7%).

GLYCEMIC CONTROL

Glycemic control is generally better during pregnancy because more intensive therapy is undertaken in an attempt to minimize fetal and maternal complications (24). Interestingly, Chew et al. (21) found that a greater magnitude of improvement in glucose control during pregnancy is associated with a higher risk of progression of retinopathy, compared to those with a more moderate improvement. In the Diabetes in Early pregnancy study (21), worsening of retinopathy was associated with the largest improvement in glycosylated hemoglobin during pregnancy. Other studies have also found that intensive insulin therapy is often associated with worsening of retinopathy during the first year of treatment (22, 23), although these studies did not specifically deal with pregnant patients. Wang et al. (23) found that the deterioration is associated with an increased number of nerve fibre layer infarcts in the superficial layer of the retina. It has been suggested that intensive therapy may be associated with closure of small retinal vessels that were narrowed but previously patent. Correction of hyperglycemia results in decreased plasma volume which can put marginal vessels at risk (24). Whether the transient worsening of retinopathy during pregnancy is similar to that seen with the institution of intensive therapy (22, 23) is not clear. The above findings may provide a dilemma for the management of glucose levels, via insulin therapy, in pregnant diabetic women. The argument for excellent metabolic control prior to conception is also strengthened by the above findings (21).

Also, several studies have demonstrated that higher glycosylated hemoglobin levels at conception are associated with higher rates of progression of retinopathy. Temple et al. (2) found that in pregnant women who had progression of their retinopathy, the HbA1C was 7.5%. Conversely, in pregnant women with no progression of their retinopathy the HbAIC was 6.6% at conception. Chew et al. (21) found that the rates of progression almost doubled in women with

Table 3. Recommendations for the management of pregnant patients with Type I diabetes mellitus with the goal of decreasing the risk of progression of diabetic retinopathy

Time Period	Recommendations
Preconception	·Counsel diabetic women in childbearing years (especially those with preexisting retinopathy) about the risk of progression ·Discuss postponement of conception until ocular disease is treated and stabilized ·Diabetic patients should be brought under optimal glycemic control prior to conception ·Counsel patients about the benefits of planning pregnancies early ·Comprehensive ophthalmologic examination to detect preexisting retinopathy and define a baseline level
First trimester (0-12 weeks)	·Comprehensive ophthalmologic assessment ·Frequent monitoring of blood pressure ·Tight glycemic control: diet is first line and if blood glucose is not well controlled, initiate insulin therapy
Second Trimester (12-28 weeks) Third Trimester (28-40 weeks)	·Comprehensive ophthalmologic examination at the discretion of the examiner, but preferably every 3 months until delivery ·Continue to monitor blood pressure ·Tight glycemic control
Postpartum	·Conflicting recommendations ·Some sources suggest frequent ophthalmologic surveillance for the first year postpartum

glycosylated hemoglobin levels greater than six standard deviations above the control mean. The results of these studies (2, 21) seem to also suggest the importance of controlling glycosylated hemoglobin levels prior to conception in diabetic women planning to have children.

It has been suggested that intensive therapy may be associated with closure of small retinal vessels that were narrowed but previously patent. Correction of hyperglycemia results in decreased plasma volume which can put marginal vessels at risk (24). The possible role of IGF-1 is supported by the clinical observation that retinopathy often worsens in the first year after the onset of intensive insulin therapy (22, 23), which increases serum IGF-1 concentrations (22, 23). The progression of retinopathy can be reversed by pituitary injury or hypophysectomy, which lowers serum IGF-1 concentrations (25).

THE PRESENCE OF HYPERTENSION

The progression of diabetic retinopathy is more likely to occur in patients with either chronic hypertension or pregnancy induced hypertension (9, 15, 19, 26). Lovestam et al. (9) found that pre-eclampsia was a potent risk factor for deterioration of retinopathy during pregnancy in type I diabetic patients. Both elevated diastolic and systolic blood pressure have been associated independently with diabetic retinopathy progression (9, 19).

MANAGEMENT OF THE PREGNANT PATIENT WITH DIABETIC RETINOPATHY

A consensus regarding the management of women with diabetic retinopathy who become pregnant is difficult to identify as many sources recommend slightly different strategies. A brief summary of recommendations for the management of diabetic patients with retinopathy who are planning a pregnancy or are already pregnant is presented in Table 3. It is very important to counsel diabetic women in childbearing years, especially those with pre-existing diabetic retinopathy, about the risk of progression of their disease while pregnant. Due to the fact that patients with severe nonproliferative diabetic retinopathy or proliferative retinopathy are at greatest risk for progression of their disease (2, 21) during pregnancy, postponement of conception should be considered until ocular disease is treated and stabilized (27). Furthermore, as the risk of progression of retinopathy during pregnancy is higher in patients with inadequate glycemic control (8, 21) and also in those who have rapid tightening of their glycemic control (21), it is recommended that diabetic patients be brought under tight glycemic control prior to conception (21). Also,

since the risk of progression of retinopathy during pregnancy is greater in women who have had diabetes for longer periods of time (2, 9, 20), it is beneficial to counsel women in their childbearing years about planning their pregnancies early (27), if possible.

The American Academy of Ophthalmology suggests guidelines for the monitoring of pregnant diabetic patients (28). They suggest that pregnant women should receive an ophthalmologic examination before conception (to determine baseline) and then again in the first trimester. Subsequent examinations should be at the examiners discretion, but preferably every 3 months until delivery.

This is in accord with the recommendations of The American Diabetes Association which recommends that women with preexisting diabetes who are planning a pregnancy should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy (29). These women should have a comprehensive eye examination in the 1st trimester and close follow-up throughout pregnancy. It is important to note that these guidelines do not apply to pregnant women who develop gestational diabetes because such individuals are not at increased risk of developing retinopathy (29).

There is some discrepancy as to the frequency of eye examinations in pregnant women with diabetes. Several studies have shown that progression of retinopathy was seen most frequently in the second trimester (3, 8) and in most cases progression of retinopathy is present by the end of the second trimester (4). It is not clear how often patients will have no progression during the 1st trimester but then experience progression during the 2nd trimester. This group of patients may be missed by the above recommendations which state a comprehensive eye examination should be done in the 1st trimester, with subsequent exams at the discretion of the examiner. Another source notes that the persistent effect of pregnancy on retinopathy progression requires continued frequent ophthalmologic surveillance for the first year postpartum (30).

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Future Legal Issues in Medical Research and Technology: The Obligations of Researchers in the Light of Recent Developments in Genetic Testing

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INTRODUCTION

In an earlier paper in this Journal, we examined the fundamental principles of negligence and the approach taken in recent Australian decisions in setting out boundaries to any categorisation of a fiduciary relationship between doctor and patient. In this paper we focus on the scope of the doctor-patient relationship and the extent of the medical practitioner's duties in this relationship. The boundaries of the medical relationship have raised a number of important ethical and legal concerns. For example, does a patient have a right of access to his or her medical records on the basis of a fiduciary relationship that exists between the doctor and the patient?

Our contention in this paper is that the scope or boundaries of the fiduciary relationship duties owed by medical practitioners will become even more significant in view of recent developments in genetic testing. Genetic testing allows the medical profession to determine if a pre-disposition to develop disease exists prior to the onset of such symptoms as breast and ovarian cancer. However, this raises the central issue as to who should have control of these records of diseased people. Will a plaintiff be able to rely on a doctor's fiduciary duty to his or her patients in order to gain access to genetic records?

It will be further suggested that genetic technology also raises important ethical and legal issues of confidentiality and discrimination. A situation may increasingly become common where commercial organisations screen clients or customers on the basis of their genetic susceptibility to diseases or a particular medical condition. In this context, we focus attention on the insurance industry and address the question as to whether insurers can refuse insurance on the basis of a genetic predisposition to a particular condition or disease.

These issues will undoubtedly become major aspects of litigation in the future. In this paper, we attempt to develop the doctrine of fiduciary duties to deal with these unresolved issues and potential future causes of action.

ACCESS TO MEDICAL RECORDS AND GENETIC DATA

An important issue in recent medico-legal debates concerns the scope of the doctor-patient relationship and the extent of the medical practitioner's duties in this relationship. For example, does the medical practitioner's duty of care extend beyond the treatment of a patient to providing access to his or her medical records? That is, do patients have a right to their medical records on the basis of the fiduciary relationship that exists between the doctor and patient?

The boundaries of the doctor-patient relationship and the patient's right of access to medical records were explored in the relatively recent Australian High Court in Breen -v- Williams. This decision approached the doctor-patient relationship narrowly. It was held that the patient's medical records were the medical practitioner's intellectual property and therefore the patient had no legal right to her records. The patient, Ms Breen, contended that the previous Australian High Court decision, Rogers -v- Whitaker, endowed her "with a right to know" which extended to a right of access to the entire record of her attending doctor. In

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other words, the fiduciary relationship that existed between herself and Dr Williams went beyond her medical treatment to any written records that were associated with her case.

This argument was dismissed by Dawson J and Toohey J who held that the decision in Rogers -v- Whitaker did not seek to extend the fiduciary duty to one which allows the patient a right to his or her medical records. Meagher JA, who is co-author of an authoritative text on the subject , commented that no basis could be found in the equitable doctrine of fiduciary duties for Ms Breen's claim to access to her records.

The scope or boundaries of the fiduciary duties owed by medical practitioners will become even more significant in view of recent developments in genetic testing. In brief, genetic testing enables the medical profession to determine if patients have a pre-disposition to develop particular conditions or diseases. However, the process of genetic testing would appear to raise the central issue as to who should have control of these records of deceased people. Will a plaintiff be able to rely on a doctor's fiduciary duty to his or her patients in order to gain access to genetic records? On the basis of Breen v. Williams, it would appear that a patient would have no such right of access to his or her records.

NEW GENETIC TECHNOLOGIES AND ETHICAL CONSIDERATIONS

In Breen -v- Williams the Australian High Court also considered the extent of the medical practitioner's fiduciary duty to his or her patient. The court refused to accept that the entire doctor/patient relationship should be fiduciary in nature. However, aspects of the judgement of Dawson and Toohey JJ would tend to emphasise a broader conception of the medical practitioner's fiduciary obligations to his or her patients. In particular, their Honours identified a duty of confidentiality owed to the patient, a duty to avoid a conflict of interests, as well as a presumption that where a medical practitioner receives substantial benefit in excess of proper remuneration it is as a result of undue influence.

It is suggested that these fiduciary duties may, in future, affect a medical practitioner's use of a removed tissue or genetic information. If, for example, a medical practitioner was to receive remuneration from the patenting of an invention derived from donated biological material, then the medical practitioner will have a conflict of interest which, as a result, would lead to a breach of fiduciary duty.

This raises the further issue as to the ethical duties and obligations of medical researchers and commercial organisations, as opposed to medical practitioners, that have obtained human genetic material. It has been argued that the ethical and legal obligations of a medical researcher should be higher than a treating medical practitioner because participation of the patient in research is voluntary and without immediate benefit to the patient. It is suggested that the relationship between a commercial organisation (which comes into possession of biological material) and the individual who provided it, is not fiduciary in nature unless the commercial organisation obtains that material directly from the source. Accordingly, the commercial user who receives the material indirectly will not be under a duty of confidentiality to the source but will be bound by privacy legislation. Nor will there be a conflict of interest with the source (ie the patient) if it receives profits from a patenting invention that uses the biological material.

While this situation is alarming, a recent UK authority (which provides some guidance in Australia) considers the proposition that the duty of confidentiality of a medical practitioner or researcher will not be breached where commercial use is made of de-identified (anonomised) data without the consent of the source of that information. The UK Court of Appeal held that anonomised information can be sold to commercial third parties without liability provided that the personal privacy of the information is protected.

Ethical standards

The Australian National statement on ethical conduct in research involving humans (1999) deals in detail with the use of human tissue samples and human genetic research. However, there is little treatment of the issue of consent to commercialisation of biological material. Principle 19 of the National statement acknowledges that some research involving humans "may be intended for, or later directed towards, purposes of commercial exploitation". It also stipulates the general principle that disclosure of interests by researchers should be made to the Human Research Ethics Committee, and that the consent of participants should be obtained. Whilst there are no specific provisions in the National statement dealing explicitly with issues of disclosure and consent in respect of commercial use of biological samples, it has been stated that the National statement can be interpreted as supporting the need for full disclosure and specific consent from the subject to potential commercial users of their tissue samples.

INSURANCE

Genetic technology and the insurance position

The human genome project and other genetic research are creating scientific, legal and ethical issues

of major international importance. Issues associated with genetic screening are arguably the greatest challenges to our legal system. The potential for screening raises legal and ethical concerns. One of those concerns is the issue of confidentiality and discrimination. These problems are particularly acute in the insurance industry and in the workplace. For example, can insurers refuse insurance on the basis of genetic susceptibility to a particular disease? Such areas have the potential to become major aspects of litigation in the future. It is arguable that because there are so many factors responsible for people's health, insurance companies will soon realise that genetics is not a very useful tool for assessing risk. If too many factors are taken into account, insurance may be unaffordable, which in turn would considerably reduce insurance companies' income.

Financial interests and dishonesty

There are strong ethical overtones which arise in the legal profession, which have commonly been dealt with in the context of insurance. For the legal profession (in comparison to the medical profession) who obtain their insurance on the open market, the terms and conditions of those policies are more stringent where the insured is seen to have been dishonest, fraudulent or involved in some criminal or malicious act. It is not uncommon to find that most policies will only cover an insured for breach of professional duty "in the conduct of the business … of the insured in a professional capacity". Unless the insured has opted for an extension to cover claims arising out of dishonesty, any such claim amounting to dishonesty will be excluded under the policy.

A common type of dishonesty exclusion clause relates to claims "brought about or contributed to by any dishonest, fraudulent, criminal or malicious act or omission of the insured (or their predecessors in business) or of any person at any time employed by the insured (or their predecessors in business)". The authors are aware that some policies will even exclude circumstances where the insured has been "in reckless disregard for the consequences".

So how does the exclusion clause work in practice? This was tested in the New South Wales Supreme Court decision of Murphy & Allen -v- Swinbank. This case involved allegations that a firm of solicitors (engaged by managers of a mortgage trust) acted for the trustees in the trust in respect of a number of loans made by the trust. The solicitors were involved in two loan transactions, one in November 1995 for approximately $20 million, and a second loan for $14 million, both relating to the purchase of 2 properties. The arrangements included an equity sharing agreement which entitled the company to 50% of the development. The solicitors provided certificates to the trustee company enabling the funds to be advanced, but no mention was made of the equity sharing arrangement. Indemnity was in issue and the insurers raised a number of defences. Relevant here, the insurers relied upon the dishonesty exclusion clause which read:

> "This insurance shall not indemnify the insured in respect of any liability brought about by the dishonest or fraudulent act or omission of the insured including any partner or former partner of the insured or any person employed in connection with the practice."

Einstein J considered the definition of "dishonesty" as "discreditable, as being at variance with straightforward or honourable dealing; underhand, fraudulent, thievish, connivish." He concluded that it was not necessary to show that the solicitors had any intent to be dishonest but that breach of duty, including fiduciary duties, owed by a solicitor to a client could be sufficient. The failure to adhere to professional standards will amount to dishonesty if the standards involve an express obligation to attest to the truthfulness of a matter.

The judge also held that the solicitors' conduct fell within the description of "discreditable" as being at variance with straightforward or honourable dealing. His Honour held that a number of steps taken by the senior partner included deliberate false representation which was in breach of his fiduciary obligations. It also involved a degree of moral turpitude or delinquency which went well beyond and transcended breach of duty.

Professionals who take their insurance on the open market must adhere to a high standard of care. The insurers are not likely to entertain claims where there is the slightest degree of recklessness. Murphy and Allen -v- Swinbank affirms that there need not be an intent to be dishonest or fraudulent but that a failure to adhere to professional standards, particularly if there is a duty to pass on information to a client, may objectively amount to dishonesty.

In McCann -v- Switzerland Insurance Australia Limited the facts involved a solicitor taking a secret commission from money placed with the solicitor to invest in a "prime bank instrument" in the international money market. Whilst the solicitor took a secret commission, he did purport to place an investment on the international money market, where it was stolen by a third party. The issues were two-fold. Firstly, whether the solicitor's conduct was dishonest or fraudulent, and secondly, whether the liability was "brought about by" such act or omission. The court held that both issues should be determined against the claimant and hence indemnity did not lie under the policy. The court determined that the solicitor had acted dishonestly and

fraudulently as he had consciously preferred his interests to those of his clients.

The contentious issue was whether or not the loss was "brought about by" his actions, since it was not the solicitor's act but the theft by the third party which created the loss. In determining "brought about by" the court found that there was a sufficient casual nexus between the placement of the funds and the loss to satisfy the exclusion. The fiduciary duty of solicitors is far-reaching, considerably more so when compared to that of the medical profession. Traditionally, fiduciary duties have been concerned with the protection of monetary interests, the courts have been reluctant to extend the medical practitioner's fiduciary obligations to personal interests as this traditionally was not perceived as a problem by the courts.

The issue of dishonesty has also been considered by the courts in the United Kingdom. In the recent decision of Royal Brunei -v- Tan Lord Nicholls held that the test for dishonesty was an objective one: "If a person knowingly appropriates another's property, he will not escape a finding of dishonesty simply because he sees nothing wrong in such behaviour … nor does an honest person in such a case deliberately close his eyes and ears, or deliberately not ask questions, lest he learn something he would rather not know and then proceed regardless."

It has been argued that this test provides two conflicting definitions. Firstly, there is the negative definition: an honest person does not take another person's property without asking, and does not participate in a transaction if he knows that someone will unfairly lose out as a result. Secondly, there is an idealistic extension of that negative definition: the standard is what an honest person would have done in the circumstances.

In the United Kingdom, at common law a cause of action cannot be founded on the defendant's dishonourable behaviour per se, as there is no generalised tort of fraud. However, common law will stop a cause of action which is contrary to public policy. In equity, the approach to dishonesty pays less regard to the defendant's state of mind and more to the circumstances of the claimant's loss. The crucial distinction between the two in determining dishonesty is that the common law will ask "what did the defendant actually do?" whereas equity asks "what should he/she have done?"

CONCLUSION

In short, ethical standards continue to define the duties of the medical profession and appear to be more onerous than legal standards, in some respects. Both access to records and disclosure of information in the doctor-patient and third-party relationship continue to trouble the common law and the courts. It is timely that we set about developing the doctrine of fiduciary obligation to resolve the many and presently unanswered questions in relation to such issues as those involving access to medical records and the disclosure and use of a patient's genetic information.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Conscience and Compromise: Abortion and the Requirements of Justice in Medical Schools

Kevin Belgrave*, BA

CORE CURRICULUM COURSES: A WORKABLE COMPROMISE?

There is general agreement that no physician, medical student or resident should be forced to perform or even observe an abortion against her will (1). Furthermore, consonant with the Canadian Medical Association's clearly articulated policy on the subject, it is equally understood, at least in theory, that such a physician or student should be shown no discrimination as a result of her bona fide religious or conscience-based objection (2). Short of actually requiring students to perform or observe an abortion, however, should its methods and procedures form part of the core curriculum of Canada's medical schools? Should a medical student be required to know in detail these methods and procedures and be graded on her knowledge? The answer to these questions seems less certain. If a medical student has the well-established right, even obligation - on the grounds of conscience or religion - to object to performing or observing an abortion, does this same right allow her to object to mandatory theoretical training in the procedure? In such a "theoretical training only" situation, we seem to have the best of both worlds - a workable compromise. On the one hand, those students who have no objection to abortion are given the opportunity and, in a way, the encouragement, to learn its methods, while on the other hand, those students who object need not progress past the general education offered in a classroom setting.

CORE CURRICULUM COURSES AND DISCRIMINATION

Remaining within the useful but ultimately limited framework of "legal rights", let us examine this solution more closely. The right of a physician or medical student not to perform or observe an abortion is not arbitrary. It is grounded ultimately in beliefs about the nature of the human person and proximately in the concepts that flow from this: justice, autonomy etc. Positive expression of this right is given in the Canadian Charter of Rights and Freedoms which protects the fundamental freedom of religion and conscience (3). Why is this relevant to evaluating the question at hand? Because at no time is the allowable content of one's freedom of religion and conscience defined by the Charter. In other words, there is no list that details the instances where one is legitimately able to exercise their right to object. The test for a valid objection is ultimately in the subject herself and not the object of her belief. Furthermore, even when an argument can be made that a certain required action is "part of the job", this cannot, in and of itself, trump an appeal to conscientious objection. For what may, on the surface, appear as a fair compromise to one person, may still run contrary to another's deeply held beliefs and convictions. Even a cursory attempt to understand the reason behind a student's objection to abortion would reveal the grave difficulty of an obligation to learn and be examined on her knowledge of what she considers to be a morally tragic reality. To illustrate this point, consider for a moment the theoretical situation faced by medical students in a country where physicians are required to facilitate the death penalty through lethal injection or otherwise. Like abortion, there is a range of opinion about the morality of capital punishment. Like abortion, capital punishment is legal in some countries and illegal in others. In countries which allow capital punishment, physicians who conscientiously object would not be ethically obliged to co-operate in the execution of prisoners. One can understand why these same physicians could not accept the "compromise"

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solution of freedom from directly facilitating execution, on the one hand, but a requirement to learn and be examined on its techniques, on the other.

ADVERSE EFFECT DISCRIMINATION

The legal concept of Adverse Effect Discrimination can help us appreciate how both the Canadian Supreme Court and provincial human rights commissions have evaluated situations analogous to the one under consideration here. Adverse Effect Discrimination occurs when some uniform practice or standard in an organisation, however honestly implemented, has a negative or "adverse" effect on a member of that organisation (4). The adverse effect results from the failure to accommodate some defined characteristic of the person when such accommodation would not involve undue hardship or sacrificing the legitimate objectives of the organisation. This principle was applied in a British Columbia human rights case in 1985 (5). Social worker Cecilia Moore was fired for refusing to sign a cheque that would release funds for a client's abortion. Despite the Ministry of Social Services' argument that such a task was "part of the job" and "related to the health of women using social services", Cecilia Moore won her case. No attempt had been made by the Ministry to accommodate her bona fide conscientious objection. Moore's supervisor had even implied that signing the authorisation would not really involve her in abortion because Moore, herself, was neither making the decision nor performing the abortion (6). This argument also failed to convince the British Columbia Council of Human Rights.

Though not an employment setting for the students, the principles at work in the Cecilia Moore case can be applied to the provision of abortion training in medical schools. In a matter as grave and highly-charged as abortion, a heavy burden rests on advocates of core curriculum change to show why a student should be required to learn the methods and procedures of abortion when her legitimately held view can be accommodated without undue hardship. Arguing that the "legitimate objectives" of medicine would be compromised as abortion is a good and necessary part of comprehensive care to women is not enough. This is far from a universally held belief. An October 2003 Leger Marketing Poll showed that 63% of Canadians believed that some measure of legal protection should be extended to human life before birth (7). This is not an insignificant number.

To mandate abortion training in medical schools would deliberately create a situation that discriminates against a significant body of students. This is neither just, nor does it respect the autonomy of the objecting student. Both legal precedent and respect for the legitimate freedom of the students and faculty argue against offering abortion training in the core curriculum of medical school.

ELECTIVE OFFERINGS: A TRUE COMPROMISE?

A second "compromise" presents itself: what about elective course offerings in abortion? In the case of elective offerings, accommodation is made for students who refuse to learn the methods and procedures of abortion. Two issues immediately present themselves, however. First, given the competitive environment of medical school and the personal and emotional dimension of many people's beliefs on abortion, including medical school faculty and students, one would be creating a situation with a possibility of discrimination. Unless there can be a high degree of certainty that no discrimination will be shown to students once their unwillingness to take abortion electives is made known, how is a school to prevent creating an environment of anxiety, fear and potential hostility among faculty and students?

Second, and more importantly, what reason is there to add such courses? The very posing of this question may rouse a certain spontaneous indignation, but honest reflection shows that the answer is not clear. One could argue that failure to make such courses available to willing students compromises their ability to provide quality and comprehensive medical care to women (8). This statement in itself is fair, but it makes the definite and clear assumption that abortion is indeed a good and necessary part of women's reproductive health care. While courts have determined that considerations of autonomy justify elective abortion, it has not been demonstrated - aside from the rare situation in which the life of the mother is endangered by the continuation of the pregnancy (9) - that abortion is ever a medically necessary procedure. In fact, in an October 2001 submission to the Canadian House of Commons Finance Committee, Canadian Abortion Rights Action League Executive Director Marilyn Wilson admitted that women who seek abortion "do so for socio-economic reasons." (10) She continues:

> Sometimes it is a desire to complete their education and become financially independent. In many cases, couples with children wish to restrict their family size in order to provide adequate financial support. Often, choosing abortion is a conscious decision not to become a socio-economic burden on society (10).

In the United States, the research arm of Planned Parenthood offered a similar view in its 2003 fact sheet on abortion:

On average, women give at least 3 reasons for choosing abortion: 3/4 say that having a baby would interfere with work, school or other responsibilities; about 2/3 say they cannot afford a child; and 1/2 say they do not want to be a single parent or are having problems with their husband or partner (11).

At best, these facts seriously call into question the assumption that abortion is a necessary part of reproductive health. There are many truly valuable topics related to "quality and comprehensive" reproductive health that could be offered to medical students: examples include neo-natal hospice, fertility awareness methods (both single and multi-marker methods), ovulation kits based on urine and saliva, and targeted hormone replacement. What motivation is there to insist on one particular surgical or chemical procedure to the exclusion of other relevant interventions that might benefit the reproductive health and options of women? An honest evaluation of this question will again place a real burden of proof on those advocating curriculum change. Why is it necessary, over and above what is already taught in medical schools, to make available the methods and procedures of abortion? Medical students are already taught about reproductive options, their indications and sequelae.

CONCLUSION

The concerns of students opposed to abortion go well beyond simple personal preference, opinion, or even political leaning. Opposition to abortion rests firmly in the realm of one's most fundamental beliefs and convictions about human life, human dignity and human rights. Together with this fact is the freedom of an individual to hold and manifest such fundamental beliefs and convictions and not be discriminated against as a result. It is well known that neither physicians, medical students, nor residents could ever be compelled to perform or observe abortions against their will. In this article, however, we have considered the closely related question: is it possible to require medical students to learn in detail the methods and procedures of a medical act that conflicts with their most fundamental beliefs and convictions? The answer has to be no. So long as the bona fide beliefs of an individual - explicitly grounded in conscience or religion - can be reasonably accommodated, they must be. We must respect this basic requirement of freedom in our community. Given the nature of the belief that underlies objection to abortion, it is not difficult to see how thin would be the line between performing an abortion and learning the procedure in all the detail required of a physician.

On the surface, elective course offerings appear to solve the problematic human rights question of mandatory training; however, they raise further issues that call into question the motivation behind such offerings. With strong evidence coming from the abortion advocacy community arguing against the medical necessity of abortion, and with Canadians divided on the protection that should be offered to prenatal human beings, there is little to recommend these courses. In the end, no legal reason may prevent medical schools from offering elective courses on abortion in the future; however, great care should be taken to evaluate the motives of any decision that may affect the education of future physicians, lest we do a great disservice to medical students, faculty, and mothers seeking genuine options for the care of their reproductive health.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Abortion in Medical School Curricula

Atsuko Koyama*, MD, MPH, Robin Williams, MD

Studies show that in a group of five women- your mother, sister, aunt, daughter, girlfriend- two of them will have an abortion by age forty-four (1). Although this statistic varies by several factors including race and marital status, abortion is one of the most commonly performed surgical procedures in the United States and Canada (1, 2).

Abortion is a safe, legal and common procedure, yet it is not routinely taught in medical schools (3, 4). In fact, there are no requirements that abortion be included in medical school curricula (5). Because it is so common, it is important for medical students to learn about abortion- the technical aspects of the different types of procedures, as well as the social, global and public health issues involved in abortion provision. Regardless of an individual physician's personal beliefs about abortion, every physician has a responsibility to help patients achieve optimal mental and physical health, to inform patients of their reproductive health options, and to serve as patient advocates. Only through comprehensive education and training will future physicians be able to meet the reproductive health needs of women.

BACKGROUND: A GLOBAL PERSPECTIVE

To understand the importance of abortion from a public health perspective, one need only look at abortion incidence and maternal morbidity and mortality. Unintended pregnancies account for 40% of pregnancies in the developing world and 50 to 60% in the United States and Eastern Europe (6). Globally, more than a quarter of women who become pregnant either have an abortion or an unwanted birth (7). Recent statistics show that in the U.S. and Canada, 2 to 3 out of 10 pregnancies end in abortion, and up to 40% of women will have an abortion during their reproductive life (1, 2, 7-10). These figures demonstrate that many physicians and medical students who include women in their clinical practice will inevitably treat someone who has had an abortion.

Of the 46 million women who obtain abortions worldwide, 20 million of them obtain illegal abortions, resulting in 70,000 deaths per year (7, 10). Maternal mortality rates from abortion in developing countries are estimated to average 330 deaths per 100,000 abortions, with the rate in Africa approaching 700 deaths per 100,000 abortions, a rate hundreds of times higher than that of developed countries (7).

The high mortality rates from abortions seen in developing countries are unheard of in developed countries such as the U.S. and Canada where abortion is legal (7, 11). When abortion is provided by trained medical professionals, it is one of the safest surgical procedures (2, 10). In the United States, the death rate from abortions is less than 0.6 per 100,000 procedures (7, 12). Although deaths caused by abortions are rare in the U.S. and Canada, it is important for medical students to learn about the effects of illegal abortions in order to appreciate the importance of safe, legal abortions to maternal health. As Dr. Mildred S. Hanson, an abortion provider who began providing before Roe v. Wade, said,

> "We have to let young women and men know the tragedy and the horror of illegal abortion…And young doctors especially must realize what it was like when abortion was illegal" (13).

THE LEGALITY OF ABORTION

Not every pregnancy is planned, and as shown by the high maternal mortality rates in countries where abortion is illegal (7), access to safe, legal abortion is a key component to women's health. In the United States,

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in 1973, the Supreme Court recognized for the first time that the constitutional right to privacy "is broad enough to encompass a woman's decision whether or not to terminate her pregnancy," providing the possibility of safe, legal abortions for American women (14). In Canada, the right to safe, legal abortion was recognized by the Supreme Court of Canada in 1988 in the Morgentaler decision (15). In this landmark case, the abortion law requiring the approval of a therapeutic abortion committee before allowing women to have an abortion was struck down as it violated a woman's right to life, liberty and security of the person (15).

The rates of safe abortions substantially increase with the legalization of abortion, and the complication and death rates from abortion decrease, yet the overall rates of abortion do not substantially change simply because abortion is legal (7, 11). This suggests that the reasons women have abortions are not affected by the legality or safety of abortion, but rather, by the life circumstances of the woman.

While this situation is alarming, a recent UK authority (which provides some guidance in Australia) considers the proposition that the duty of confidentiality of a medical practitioner or researcher will not be breached where commercial use is made of de-identified (anonomised) data without the consent of the source of that information. The UK Court of Appeal held that anonomised information can be sold to commercial third parties without liability provided that the personal privacy of the information is protected.

WHO HAS ABORTIONS

In 2000, U.S. women of all ages, races, socioeconomic status and marital status had abortions (16). The highest rates were among women who were unmarried, poor, black or Hispanic, or aged 18-29 (16). Forty-three percent of women who have had an abortion identified themselves as Protestant, and 27% as Catholic (16). Sixty-one percent of women had previously had one or more births (16). Abortion rates were inversely proportional to income level (16).

The reasons women have abortions are many and complex, and they are similar worldwide (6, 7). The timing of births, the desire to control family size, socioeconomic reasons, relationship problems, age, marital status, maternal health, and fetal defects are all reasons women give for having an abortion (6, 7).

ACCESS TO ABORTION SERVICES IN CANADA AND THE U.S.

In spite of the legality of abortion in the U.S. and Canada, many women continue to lack access to abortion services. Two factors in particular- the declining number of abortion providers and a change in the distribution of abortion facilities- have significant adverse consequences for women's health, particularly for poor and rural women (17, 18). In Canada, only 17.8% of hospitals provide the service, and some provinces have no provider (17). Similarly, in the United States, in 2000, 87% of counties had no provider (18).

A variety of factors have contributed to the decline in the number of providers. They range from physicians' personal moral objections to fears of becoming targets of violence or harassment (19-26). In addition, certain laws in the U.S. targeting abortion providers create barriers, while physician-only laws restrict other medical personnel such as nurse practitioners from providing abortions (27, 28). Abortion education in medical schools and residency programs is limited, which has been shown in several studies to decrease the likelihood of physicians choosing to provide abortions (25, 26, 29, 30). Lastly, Catholic hospital mergers have contributed to the lack of training opportunities while also decreasing the number of facilities offering abortion services (31-33).

The effect of the decrease in the total number of abortion providers is compounded by a related trend: a decrease in the number of hospital- based abortion services. Data from 1998 and 2000 in the U.S. show an 18% and 14% loss, respectively, in the number of hospitals providing abortions (18, 34). Although hospital abortions constitute only 5% of total abortions performed (18), this decrease disproportionately affects poor and rural women, who rely most heavily on hospital emergency rooms for medical care and who must travel great distances to obtain abortion services (8, 17, 18). In addition, abortions performed in clinics are not always covered by Medicaid in the US or Medicare in Canada (17, 18). The decrease in hospital abortions also negatively affects the education of medical students and residents, who receive the majority of their training in hospital settings (17, 18, 35).

ABORTION IN MEDICAL SCHOOL CURRICULA: THE REALITY

As 48% of women aged 30-34 in the U.S. have experienced an unintended pregnancy, and 4 out of 10 women seek abortion services sometime during their reproductive life, the lack of abortion education in medical curricula significantly affects medical students' ability to address women's reproductive needs (1).

Espey et al. (2005) (3) surveyed Obstetrics and Gynecology clerkship directors to determine the extent of abortion education in U.S. medical schools. They found that 17% of schools had no abortion education at

all and that in many other schools, coverage was minimal (3). One organization, Medical Students for Choice (MSFC), is currently surveying medical schools in the U.S. and Canada about their individual curricula. The preliminary results of MSFC's study of the reproductive health content of preclinical medical education found that nearly 40% of the more than 50 schools surveyed do not teach any aspect of abortion in the preclinical years (4). Indeed, the study found that, on average, more class time is dedicated to Viagra than to abortion procedures, pregnancy options counseling, or abortion law and policy (4). This glimpse into U.S. and Canadian medical curricula reveals that abortion is not a standard component of preclinical education.

ABORTION IN MEDICAL SCHOOL CURRICULA: THE GOAL

The teaching of abortion in medical schools and residencies is supported by numerous professional organizations, such as the American Medical Women's Association (AMWA) and other international health and human rights organizations (10, 36-39). Abortion education in medical school curricula should include descriptions of the different methods and procedures of medical and surgical abortions, as well as pregnancy options counseling, contraception, and a more global view of abortion, such as abortion from a human rights prospective and the effects of unsafe abortions on maternal health. If abortion were taught in this way, graduating medical students would understand not just the how of abortion, but the why, resulting in more compassionate care (2). This will also help to de-stigmatize the procedure, possibly encouraging medical students to become future providers.

There are many resources available for teaching pregnancy options counseling and contraception. Anne Baker's "Abortion and Options Counseling: A Comprehensive Reference" and the American College of Obstetricians and Gynecologists' "Pregnancy Choices: Raising the Baby, Adoption and Abortion" are excellent resources for discussing pregnancy options in the classroom (40, 41). For discussing contraception, Family Health International provides a slide set called, "Contraceptive Technology Expert." (42) The slide set covers topics such as injectables, lactational amenorrhea, postpartum contraception, and intrauterine devices and includes teaching modules with narrative, slides, audience handouts, references and reprints of scientific articles (42). Lastly, for students and professors interested in improving reproductive health education or developing a comprehensive reproductive health elective, the AMWA Reproductive Health Model Curriculum is an excellent resource (43).

In discussing abortion beyond the technical and individual aspects and expanding the discussion into abortion and comprehensive reproductive health as a human right, The Society of Obstetricians and Gynecologists of Canada sets out recommendations on how physicians can put reproductive health in a human rights perspective (36). A recommendation pertinent to medical education is that ethical and human rights principles be addressed early in medical training (36). Topics of discussion could include how stereotypical gender roles, power imbalances between men and women, cultural standards and the level of women's empowerment in society are linked to women's reproductive health (36).

CONCLUSION

Abortion, as one component of comprehensive reproductive health care education, should be a standard part of medical school curricula. The public health reasons for providing safe abortions, the number of women seeking the procedure, and the human rights implications involved, all contribute to making abortion an essential part of medical school curricula. If your school is not teaching you what you need to know to provide women with comprehensive medical care, here are some suggestions for how you can make a difference.

Actions to take: ask questions about medical abortion in pharmacology, pregnancy options counseling in behavioral science, and abortion procedures during your obstetrics and gynecology clinical rotation. Get involved in curriculum committees, support your local providers and professors who are including abortion in their curricula, and encourage your peers and faculty to talk about the myriad of issues around reproductive health. Most importantly, find your like-minded peers and work together to create change and make a difference in your schools.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

The Psychopharmacological Fix: The Suppression of Sadness and the Search for Meaning

Laura Gallo*, BA

INTRODUCTION

As humans, emotions are the most basic resources we have to express ourselves. Feelings are markers of the human condition; they can be our most reliable indicators of pleasure or distress. Over the past few years, we have neglected the fact that feelings, like sadness, are a natural part of life. At some point we have learned that sadness is a forbidden emotion and that melancholia experienced for more than two weeks is cause for serious concern. Certainly, depression can be a grave condition with debilitating effects. While medication is often a requirement for some, it is currently being used as a convenient coping mechanism for others. Why we have turned to the psychopharmacological fix is a question worth examining.

As part of the 2005 Biomedical Seminar Series at McGill University, Joseph Davis Ph.D., a Sociologist from the University of Virginia, gave a talk entitled: "Direct-to-consumer advertising and the anxious self." Twenty-five years ago Social Anxiety Disorder (SAD) was considered to be a very rare condition (1), but today it is the third most commonly diagnosed mental disorder in North America (1). Davis proposed that such a significant increase in the diagnosis of this disorder is linked to the upsurge in the advertisement of prescription drugs like Paxil and Zoloft. Since 1997, when the FDA loosened its restrictions on advertisements of such medication, we have been bombarded with ads promising personal transformation and brighter days to come (1). In 2001, GlaxoSmith-Klein spent $91 million dollars in direct advertisement to its consumers for Paxil, whose campaign insists shyness, anxiety and sadness are debilitating problems that threaten to hold us back from living full lives (2). After all, time is precious in our fast-paced society and we don't have a moment to spare on introspection. But who doesn't feel sad or anxious sometimes? Will popping a pill for every dilemma really make us more capable of living more meaningful lives? The progress of science and the growth of research have allowed the pharmaceutical business to flourish. From the common cold to heartburn to the wintertime blues, there is something available for every discomfort that plagues the North American consumer. The aches and pains that were once simply a part of life are now seen as symptoms to be treated. There is no denying that modern medicine has accomplished many wonderful things, but let there be no doubt that it has also brought with it some potentially harmful side effects. There is no perfect fix and the advent of the anti-depressant era has already raised some important ethical concerns.

One particularly disturbing issue is the fact that pharmaceutical companies profit by marketing to a generally healthy population (1). Ads market anti-depressants to a very widespread audience by stigmatizing feelings like sadness and anxiety- feelings almost all of us can relate to. We are made to believe that the images of shiny happy people in these commercials are the way we are supposed to be. Advertisements also encourage self-diagnosis while creating a responsibility to act so that happiness is not only a right, but also a duty (3). Canadians have certainly taken this to heart, as Effexor, Paxil and Celexa were prominent on the top twenty most prescribed medications list for the year 2003 (1). The ease at which these drugs are dispensed is due in part to the de-stigmatization of mental illness (1). Disorders like depression are no longer connected to moral failure because advertisements have shown us that depression

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is purely biological, summing it up to a slight chemical imbalance in the brain (1). But can such a serious problem really be that simple? Probably not. Some argue that the supposed biological causes of depression have never even been proven scientifically. Allen J. Frances, professor of psychiatry at Duke University Medical Center, refutes the claim that depression is even a brain disease at all (4). Unlike most bodily diseases, which can often be detected through concrete means, such as, blood tests and biopsies, there is no such test for mental illness. This fact alone provides insight into another reason why anti-depressants might be doled out so easily: a personal testimony to feelings of sadness could suffice (1). Of course, not all doctors will dispense anti-depressants without evidence of significant distress AND dysfunction. in 1 or more areas of life. Nonetheless, millions of dollars are spent in advertising and gifts to convince doctors to prescribe these medications (5). Even if there is an association between low levels of serotonin and depression it does not necessarily imply that this is the cause of depression. It may also be an effect of mental illness. If this is the case, would it not make more sense to treat the underlying cause, rather than placating the symptoms?

Carl Elliott, a prominent bioethicist at the University of Minnesota Medical School and former professor at McGill University, attempts to address the cause itself. He believes the problem lies in cultural alienation (6). He writes in his article Pursued by Happiness and Beaten Senseless, "Part of the nagging worry about Prozac and its ilk is that the ills they treat are part and parcel of the lonely, forgetful, unbearably sad place where we live" (6). Rather than placing the blame solely on seretonin, Elliott believes that prevalent sadness is a symptom of the unnatural, isolated, and unhealthy society in which we live. Indeed, these are sad times when the general public embraces a . Perhaps the predicament we are faced with is not something that can be fixed with a trip to the pharmacy, as anti-depressants are not the cure-all that their producers make them out to be. Some of our sadness is rooted in the way we live. With modernity and rapidly changing technology, we are drowning in excess: too many choices and too many changes too quickly, overwork and overstimulation (5). We are constantly overwhelmed. Prevalent anxiety and insecurities are more indicative of cultural alienation than of our individual psyches. Unfortunately, medications are geared towards changing our minds not our lifestyles-which brings us to another ethical concern.

The suppression of sadness, insecurities and anxieties will undoubtedly affect our sense of self, if the way we think and the way we feel are basic constituents of our character. Peter Kramer M.D., the author of one of the last decade's best sellers, Listening to Prozac, cites cases of mildly depressed patients who after taking Prozac underwent remarkable personality transformations (7). People were not just feeling better while on the drug, but better than well. This is somewhat disconcerting. Is Prozac masking the person's true self with a blanket of serotonin, or is it uncovering the self that was hidden in anxiety? SSRI's (selective serotonin reuptake inhibitors) change the functioning of the brain so that the authentic self is altered, perhaps unrecognizably (5). According to Kirmayer, antidepressants alter the self in three ways: "(i) it changes the bodily feeling and stance that subserve our metaphorical constructions of the self, for example, by making us feel more uptight and energized; (ii) it provides a new inner agent to which to attribute our feelings…and (iii) it may reshape our empathic response to others" (5).

The question of the authentic self spawns several dilemmas. First, in a society that values individuality, what will become of our uniqueness if we all conform to car-salesmen personalities? One of the reasons that people become depressed in the first place is because they feel their lives are not unique (3). Have we come full circle? Secondly, a drug that alters mood changes the emotional reactivity to persons and events, therefore reshaping one's sense of self (5). Again, this is contradictory to popular belief that says that an inauthentic life is a failed life (3). How can a life be made meaningful through inauthentic means? It is a Catch-22.

Perhaps part of the problem is that leading a fulfilling life is so completely dependent upon a person's internal state (3). With the decline of religious adherence (especially here in Quebec) (8), the weakening of social support networks (3) and the burden of the workweek, people are lacking anything of value beyond the self (3) . If all that matters is self-fulfillment then occasionally-normal feelings such as unfulfillment or unhappiness can become socially unacceptable. Dissatisfaction with life implies failure and because failure is not an ideal to which anyone aspires, it should be changed. As the slogan for Paxil goes, "your life is waiting." (1).

But in "getting our lives back", what exactly are we reclaiming? A life free of pain and suffering? A life sheltered from the dissatisfaction and distress with the social world? Rather than teaching ourselves how to avoid suffering, perhaps we need to learn how to suffer, even if it is socially unacceptable. Rather than dulling our senses when they tell us something we don't want to hear, it is time to listen to them, for they are our most reliable assets.

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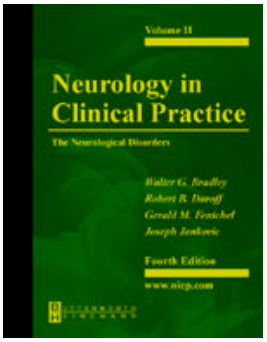
Laura Gallo recently completed her Bachelor of Arts in World Religions at McGill and will begin her Masters in the History and Philosophy of Religion this fall. Her current areas of interest lies in religion and medicine. She has been writing for Radix, McGill's multifaith publication, and plans to pursue academic writing and professorship in future endeavours.

BOOK REVIEW



Neurology in Clinical Practice, 4th edition
Edited by Walter G. Bradley, Robert B. Daroff, Gerald M. Fenichel, Joseph Jankovic

Butterworth Heinemann, 2004, 2545 pages
ISBN: 0750674695
$650.00

In this era of sweeping advances in clinical neurology and the associated neurosciences alike, an update to the acclaimed third edition of Neurology in Clinical Practice, published in 2000, was somewhat overdue. In its fourth incarnation, the authors have substantially revised and updated their textbook to incorporate the latest advances from the clinical and scientific fronts. The result is an extensive, yet elegantly written and comprehensive compendium of the principles and fundamentals of clinical neurology.

The book itself is divided into two sturdily bound volumes. The first covers the principles of diagnosis and management; the second examines the neurological disorders. Each chapter is covered in excellent breadth and depth and is penned by an internationally known expert in each particular field.

The first half of Volume One offers a brief yet complete synopsis of common neurological phenomena. The topics covered include loss of consciousness, intellectual and memory impairment, ataxias amongst others. The appeal of these sections is that they provide a structured approach to each of these common neurological conditions. Furthermore, they provide a detailed discussion describing the features that enable one to arrive at the appropriate diagnosis. Many chapters even include colourful historical anecdotes about the history of the disease or the individuals who first described it. The second half of Volume One examines neurological investigations and related clinical neurosciences. These chapters are comprehensive, but not excessively detailed. They cover topics such as neurophysiology, neuroimaging and neuropharmacology and therapeutics. Most of these chapters are further subdivided into key topics and include concise diagrams and tables to compliment the text. This feature is of particular benefit in the chapters describing the neurology of the special senses where the illustrations of the neural pathways help considerably in clarifying the concepts.

Volume Two focuses on disorders of the nervous system. The first five chapters address a large scope of problems including neurologic complications of systemic disease, trauma, vascular disease, tumours and infections. Despite the large spectrum of disease encompassed under these headings, each chapter succeeds in its goal of delivering a concise and complete summary of all the pertinent disorders. The remaining chapters in Volume Two focus on specific disorders such as encephalopathies, dementias, demyelinating diseases, movement disorders and disorders of peripheral nerves. These chapters are well organized and provide the reader with a thorough description of the pathophysiology and treatment of each specific disease or class of disorders. Volume Two concludes with thee chapters addressing neurology in the newborn, pregnancy and the geriatric patient.

Despite its enormous number of contributors, Neurology in Clinical Practice manages to maintain a fairly consistent style of writing that makes the chapters enjoyable to read. Moreover, the book manages to avoid a common pitfall that entraps many 'bibles' of medicine; the authors cover a vast amount of material without appearing overly laconic and they succeed in addressing their subjects in appropriate detail. Furthermore, all chapters are copiously referenced from recent articles culled from the premiere neuroscience journals. The helpful illustrations and ample photographs also lend to the appeal of this text. Although the vast majority of these photographs are in black and white, many PET images to pathology slides, appear as colour plates. Although few in number, the colour plates are beautifully rendered on high quality glossy paper yielding excellent image quality that sacrifices neither detail nor resolution.

Overall, Neurology in Clinical Practice fourth edition is an excellent textbook that is a must-have for all neurologists and neurology residents. Although the text is geared at the senior resident or practicing physician, the majority of the chapters can still be of benefit to the medical student with an interest in neurology. The one major drawback is the exorbitant cost. At close to 700$ it is beyond the means of most medical students or junior residents. However, given that you are getting over 2500 pages of updated information as well as online access, the cost seems very reasonable.

Paul S. Giacomini B.Sc., MD
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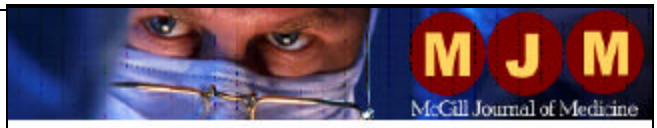

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