Français à la page suivante

The sacred and the secular: the life and death of Terri Schiavo

I urge all those who honor Terri Schiavo to continue to work to build a culture of life, where all Americans are welcomed and valued and protected, especially those who live at the mercy of others. The essence of civilization is that the strong have a duty to protect the weak. — US President George W. Bush, Mar. 31, 2005

[I]deological thinking is a direct and explicit challenge to political thinking. — Bernard Crick, *In Defense of Politics*, 5th rev, 2000

In the last weeks of Terri Schiavo's life, strangers around the world became familiar with photographs and video clips of this profoundly incapacitated woman smiling in what her parents interpreted as recognition and her physicians as a subcortical reflex. In medical and legal opinion, Terri Schiavo's cognizance of her self and her life ended in 1990, when she suffered a cardiac arrhythmia and massive cerebral cortical encephalopathy that left her in a persistent vegetative state. Her facial expressions, along with a seemingly "normal" sleep–wake cycle, constituted but one dimension of the cruelty of this condition.

The personal tragedies of end-of-life decisions normally pass unnoticed beyond the afflicted circle of family and friends. In 1976 the case of Karen Ann Quinlan established in the United States the principle that families may take precedence over the state in end-of-life decisions; after a long and public battle, Quinlan's parents were allowed to unplug the respirator that maintained this comatose young woman in a merciless semblance of life. Despite multiple appeals to the courts, the Schiavo case has created no major legal precedents in the US, but Schiavo's very public death may well set in motion legislative changes to satisfy those social conservatives who would like to translate all knotty questions into the rhetoric of a "culture of life."

The trouble with slogans of any stripe is that they obfuscate complex questions that need to be examined clearly. Thus the "culture of life" catchphrase serves to cloud important distinctions between a range of ethical questions, from end-of-life decisions, including assisted suicide, to stem-cell research, cloning and access to abortion. More than one commentator has viewed the "right-to-life" fight to prolong Schiavo's pitiable existence as an anti-abortion campaign "by other means." Even the President of the United States has used her case as a stalking-horse for his government's agenda, couching his condolences to the Schiavo "families" in the same sort of language he has used to describe the "War on Terror." This same government is eager to tackle other metaphysical matters through legislation on stem-cell research and abortion, and has also been accused of stacking national scientific advisory committees on the basis of the religious and moral views of scientists.[1]

Few of us could honestly say that we would prefer governments and courts never to weigh in on questions concerning the sanctity and dignity of life, never to exert a protective influence in these matters. But there seems little doubt that, in North America, ideology and religion have begun to seriously distort the type of consensus-building that is the proper business of democratic politics.

Where do physicians find themselves in such debates? Medicine is a secular and scientific profession that, for all that, must still contend with the sacred matters of birth, life and death. In practice, physicians must set aside their own beliefs in deference to the moral autonomy of each patient — or else transfer that patient's care to someone who can meet this secular ethic. If the Schiavo case teaches nothing else, it is the pragmatic lesson that physicians do well to encourage patients to discuss end-of-life preferences with their families and loved ones long in advance of what they might imagine to be their appointed hour. And, in helping families face that end, whenever it comes, the CMA Code of Ethics states that physicians should "ascertain wherever possible [their] patient's wishes about the initiation, continuation or cessation of life-sustaining treatment." In this issue, Glenys Godlovitch and colleagues describe a little-known case in which an Alberta court helped a family to make, peaceably, such a determination (page 1172),[2] and a commentary by Charles Weijer reflects on the physician's role in helping families to remain intact under the pressure of end-of-life decisions (page 1197).[3]

The emotionalism and rancour that swirled around the Schiavo case underscores a wider societal duty borne by the medical and scientific community. This is to remain alert to political and legislative tendencies that impose imprecise moral generalizations on the majority, at the expense of reason, scientific understanding and, not infrequently, compassion. — *CMAJ*

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English on previous page

Le sacré et le profane : la vie et la mort de Terri Schiavo

J'exhorte tous ceux qui honorent Terri Schiavo à continuer d'essayer de créer une culture de la vie où tous les Américains sont les bienvenus, valorisés et protégés, et en particulier ceux qui vivent à la merci d'autrui. L'essence de la civilisation réside dans le devoir qu'ont les forts de protéger les faibles. - George W. Bush, président des États-Unis, le 31 mars 2005.

[L]a réflexion idéologique conteste directement et explicitement la pensée politique. - Bernard Crick, *In Defense of Politics*, 5e rév., 2000.

Au cours des dernières semaines de Terri Schiavo, des étrangers du monde entier ont appris à reconnaître les photographies et les vidéos de cette femme lourdement handicapée au sourire que ses parents considéraient comme signe de reconnaissance et ses médecins, comme un réflexe sous-cortical. De l'avis des médecins et des avocats, la conscience que Terri Schiavo avait d'elle-même et sa vie ont pris fin en 1990, lorsqu'elle a été victime d'une arythmie cardiaque et d'une encéphalopathie corticale cérébrale massive qui l'ont laissée dans un état végétatif persistant. L'expression du visage, de même qu'un cycle sommeil–éveil d'apparence «normal», n'était qu'une des facettes de la cruauté de son état.

Les tragédies personnelles liées aux décisions en fin de vie ne dépassent pas normalement le cercle affligé des membres de la famille et des amis. En 1976, le cas de Karen Ann Quinlan a établi aux États-Unis le principe selon lequel la famille peut avoir préséance sur l'État dans les décisions en fin de vie. Après une longue lutte publique, les parents de Mme Quinlan ont été autorisés à débrancher le respirateur qui maintenait cette jeune femme comateuse dans un semblant impitoyable de vie. En dépit de multiples appels interjetés devant les tribunaux, l'affaire Schiavo n'a créé aucun précédent juridique important aux États-Unis. Il se pourrait toutefois que la mort très publique de Mme Schiavo enclenche des changements législatifs visant à satisfaire l'élément conservateur de la société qui aimerait transformer toutes les questions épineuses en belles théories d'une «culture de la vie».

Le problème avec les slogans de tout acabit, c'est qu'ils obscurcissent les questions complexes que l'on doit étudier clairement. Ainsi, le slogan «culture de la vie» obscurcit les distinctions importantes entre toute une gamme de questions d'éthique allant des décisions en fin de vie, ce qui inclut l'aide au suicide, jusqu'à l'accès à l'avortement, en passant par la recherche sur les cellules souches et le clonage. De nombreux commentateurs ont considéré la lutte pour le «droit de vivre» visant à prolonger l'existence pitoyable de Mme Schiavo comme une campagne anti-avortement «déguisée». Même le président des États-Unis a utilisé son cas comme prétexte pour faire progresser le programme de son gouvernement en formulant ses condoléances à l'intention des «familles» Schiavo dans les mêmes termes qu'il a utilisés pour décrire la «guerre au terrorisme». C'est ce même gouvernement qui attend impatiemment de s'attaquer à d'autres questions métaphysiques en légiférant au sujet de la recherche sur les cellules souches et de l'avortement, et qu'on a aussi accusé de fonder la composition de comités consultatifs scientifiques nationaux sur les opinions religieuses et morales des scientifiques en question[1].

Peu d'entre nous pourraient honnêtement affirmer que nous préférerions que les gouvernements et les tribunaux n'aient jamais à intervenir dans des questions comme la dignité de la vie et son caractère sacré, et n'exercent jamais une influence protectrice dans ces questions. Il semble toutefois y avoir peu de doute qu'en Amérique du Nord, l'idéologie et la religion ont commencé à déformer sérieusement le type de dégagement de consensus qui appartient dûment à la politique démocratique.

Où se retrouvent les médecins dans de tels débats? La médecine est une profession profane et scientifique qui doit quand même faire face aux enjeux sacrés de la naissance, la vie et la mort. Dans la pratique, les médecins doivent mettre de côté leurs propres croyances et s'en remettre à l'autonomie morale de chaque patient — ou transférer le soin de ce patient à quelqu'un qui puisse se conformer à cette éthique profane. L'affaire Schiavo nous aura au moins enseigné une leçon pragmatique, soit que les médecins font bien d'encourager les patients à discuter de leurs préférences en fin de vie avec les membres de leur famille et leurs proches longtemps avant ce qu'ils pourraient imaginer comme l'heure de leur mort. En aidant les familles à faire face à cette issue, peu importe quand elle surviendra, le Code de déontologie de l'AMC affirme que les médecins doivent «déterminer dans la mesure du possible les désirs de votre patient au sujet de la mise en œuvre, du maintien ou de l'interruption des traitements essentiels au maintien de la vie». Dans ce numéro, Glenys Godlovitch et ses collaborateurs relatent une affaire peu connue dans le contexte de laquelle un tribunal de l'Alberta a aidé une famille à prendre une telle décision dans un contexte paisible (page 1172)[2]. Dans son commentaire, Charles Weijer formule des réflexions sur le rôle que jouent les médecins en aidant les familles à demeurer intactes face aux pressions exercées par les décisions en fin de vie (page 1197)[3].

L'émotion et la rancœur qui ont entouré l'affaire Schiavo mettent en évidence l'obligation sociétale plus étendue qui incombe aux milieux médicaux et scientifiques. Ils doivent surveiller les tendances politiques et législatives qui imposent des généralisations morales floues à la majorité, au détriment de la raison, de la compréhension scientifique et, assez souvent, de la compassion. — *JAMC*

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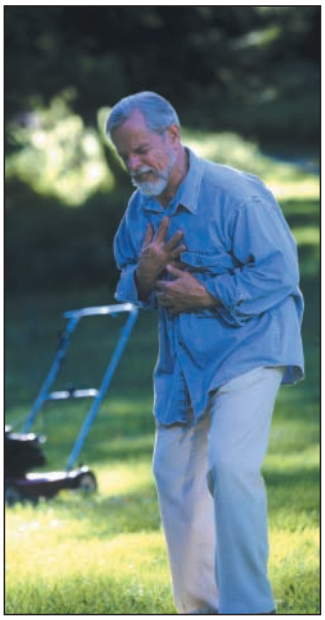
Class effect of statins in elderly patients

Statins are used in the secondary prevention of acute myocardial infarction (AMI). Since they belong to the same drug class, they are generally thought to be therapeutically equivalent. However, evidence supporting this assumption has been limited, and prescribing practices suggest that some statins are preferred over others. Zhou and colleagues compared the effectiveness of 5 commonly prescribed statins in a head-to-head retrospective analysis of data for over 18 000 elderly patients who had AMI and who filled a prescription for a statin within 90 days after discharge. They found that the 5 statins were equally effective for secondary prevention after AMI. However, the costs of statins differ, as Wright points out in a related commentary, which gives physicians an opportunity to reduce costs to patients and the health care system while still achieving optimal health outcomes for their patients.

See pages 1187 and 1195



Corbis Canada

Effets des catégories de statines chez les patients âgés

Les statines sont utilisées pour la prévention secondaire de l'infarctus aigu du myocarde (IAM). Comme elles appartiennent à la même catégorie de médicaments, on croit en général qu'elles s'équivalent sur le plan thérapeutique. Les données probantes à l'appui de cette hypothèse sont toutefois limitées et les habitudes d'établissement d'ordonnances indiquent que l'on préfère certaines statines plutôt que d'autres. Zhou et ses collaborateurs ont comparé directement l'efficacité de cinq statines prescrites couramment au cours d'une analyse rétrospective de données portant sur plus de 18 000 patients âgés ayant subi un IAM et qui ont fait remplir une ordonnance de statine dans les 90 jours de leur congé d'hôpital. Les chercheurs ont constaté que les cinq statines ont la même efficacité pour la prévention secondaire après un IAM. Les coûts des statines diffèrent toutefois, comme le signale Wright dans un commentaire connexe, ce qui permet aux médecins de réduire les coûts pour les patients et le système de santé tout en produisant des résultats optimaux pour la santé de leurs patients.

Voir pages 1187 et 1195

Coronary artery bypass grafting in elderly patients

With our elderly population increasing, more and more people 80 years of age and older are being referred for coronary artery bypass grafting (CABG). Baskett and colleagues took a closer look at outcomes of elderly Canadians undergoing this procedure and provide additional evidence for eventual informed policy-making. They found that people in this age group represented 5% of patients undergoing CABG over a 5-year period. These patients had more comorbid conditions and a higher acuity level than younger patients, and a higher overall mortality. The mortality decreased over the study period for both older and younger patients, but the risk of postoperative stroke did not change among the older patients. The authors conclude that advanced patient age should not on its own deter a decision to perform CABG if there is a clinical need for it and that older patients undergoing elective procedures may experience outcomes equivalent to those of younger patients.

See page 1183

Le pontage aortocoronarien chez des patients âgés

À mesure que la population vieillit, de plus en plus de personnes de 80 ans et plus sont référées pour un pontage aortocoronarien (PAC). Baskett et ses collaborateurs, qui ont analysé de plus près les résultats chez des Canadiens âgés subissant cette intervention, fournissent des données supplémentaires sur l'établissement éventuel de politiques éclairées. Ils ont constaté que les personnes de ce groupe d'âge comptaient pour 5 % des patients ayant subi un PAC sur une période de cinq ans. Ces patients avaient plus de problèmes comorbides, leur cas était plus lourd que celui de patients plus jeunes et leur taux général de mortalité était plus élevé. La mortalité a diminué pendant la période d'étude chez les patients plus âgés autant que chez les plus jeunes, mais le risque d'accident vasculaire cérébral postopératoire n'a pas changé chez les patients âgés. Les auteurs concluent que l'âge avancé d'un patient ne devrait pas à lui seul dissuader de décider de procéder à un PAC si le patient en a besoin sur le plan clinique et que les patients âgés qui subissent des interventions électives peuvent obtenir des résultats équivalents à ceux de patients plus jeunes.

Voir page 1183

Chronic systemic inflammation, weight loss and exercise

Persistent low-grade inflammation, as indicated by elevated levels of circulating inflammatory markers such as C-reactive protein, interleukin-6 and tumour necrosis factor-α, is a strong risk factor for several chronic diseases, including cardiovascular disease, diabetes and osteoarthritis. As Nicklas and colleagues explain in their review article, dietary weight loss and increased physical activity may be effective therapies for reducing overall chronic inflammation. Research has shown that levels of circulating inflammatory markers are elevated in people with total and abdominal obesity and that they are decreased after weight loss. The same effect has been observed in association with physical activity. Although the mechanisms by which weight loss and exercise reduce inflammation have yet to be explained, their beneficial effects have been confirmed.
See page 1199

Inflammation systémique chronique, perte de poids et exercice

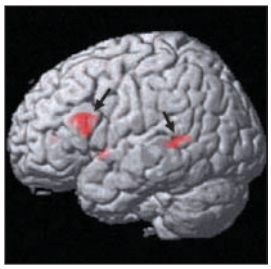
Une inflammation persistante peu importante, indiquée par des concentrations élevées de marqueurs inflammatoires en circulation, comme la protéine C-réactive, l'interleukine-6 et le facteur de nécrose des tumeurs α, constituent un important facteur de risque pour plusieurs maladies chroniques, y compris les maladies cardiovasculaires, le diabète et l'arthrose. Comme Nicklas et ses collaborateurs l'expliquent dans leur article de critique, la perte de poids liée à l'alimentation et une augmentation de l'activité physique peuvent constituer des thérapies efficaces pour réduire l'inflammation chronique générale. La recherche a démontré que les concentrations de marqueurs inflammatoires en circulation sont élevées chez les personnes qui ont de l'obésité totale et abdominale, et qu'elles diminuent après une perte de poids. On a observé le même effet associé à l'activité physique. Même si les mécanismes par lesquels la perte de poids et l'exercice réduisent l'inflammation restent à expliquer, leurs effets bénéfiques sont confirmés.
Voir page 1199

In Synopsis

Secko describes the exciting implications of the recent discovery of 2 genes that influence the virulence of ***Cryptococcus neoformans*** **infection** (page 1174). In Practice, Burneo and McLachlan discuss when surgery should be considered for **temporal lobe epilepsy** (page 1175). Weir and Flegel provide information on the diagnosis, management and prevention of ***Clostridium difficile*** **infection** (page 1178). Baerlocher and Detsky comment on a randomized study of whether **coronary revascularization** before elective major vascular surgery is beneficial (page 1180). Wooltorton reports on a possible association between the use of **eczema drugs and an increased risk of cancer** (page 1179). Sharma describes a case of a patient who coughed up a **metastatic malignant fibrous histiocytoma** (page 1182).

Synopsis

Secko décrit les répercussions excitantes de la découverte récente de deux gènes ayant un effet sur la virulence de l'**infection à *Cryptococcus neoformans*** (page 1174). Dans la chronique Dans la pratique, Burneo et McLachlan discutent du moment où il faudrait envisager la chirurgie dans des cas d'**épilepsie temporale** (page 1175). Weir et Flegel présentent de l'information sur le diagnostic, la prise en charge et la prévention de l'**infection à *Clostridium difficile*** (page 1178). Baerlocher et Detsky commentent une étude randomisée visant à déterminer si la **revascularisation coronarienne** avant une chirurgie vasculaire majeure élective présente des avantages (page 1180). Wooltorton décrit un lien possible entre l'utilisation de **médicaments contre l'eczéma et un risque accru de cancer** (page 1179). Sharma décrit le cas d'un patient qui a expectoré en toussant un **histiocytome fibreux malin à métastases** (page 1182).



Pediatric clinical trials registry

Although the need to register clinical trails in a publicly accessible register has been considered for years,[1,2] it has only recently become a major issue. After the much-publicized situation regarding withheld data on the use of selective serotonin reuptake inhibitors in children, various groups, including the International Committee of Medical Journal Editors (ICMJE),[3] have acted to increase awareness of the need for trial registration and to put pressure on pharmaceutical companies to register all trials.

Although a single, all-inclusive, worldwide register would be optimal, disciplines such as pediatrics need special attention. The well-known difficulties of conducting studies in young patients, along with the limited economic returns to pharmaceutical companies for pediatric drugs, have led to a scarcity of pediatric studies and therefore a scarcity of knowledge about drug safety and efficacy in children. The lack of scientifically evaluated medicines for children has been recognized as an area that requires correction.[4,5] Legislation to increase the number of clinical trials for children has been introduced in the United States[6] and is planned for Europe. To facilitate pediatric research, promote more network-based studies and identify areas where research is needed, an international register of clinical trials of drugs in children (both planned and under way) has been established, the DEC-net (Drug Evaluation in Children) register (www.dec-net.org).

Researchers, health professionals, sponsoring agencies and the public will be able to search DEC-net for information on trials specific to children. The register, supported by the European Union and currently operating as a 3-year feasibility study, was activated in 2004 and is run by groups of researchers from 4 countries: Italy, France, Spain and the United Kingdom.[7] It fits the criteria outlined by the ICMJE,[3] is available free of charge, allows for data correction and updating, and is designed for use by the general public as well as health care professionals. The DEC-net register is the only pediatric, population-oriented trial register set up to receive information from a variety of sources (ethics committees, national health agencies, universities, national and international medical societies, hospitals, physicians, industry and spontaneous reporters). The register complies with the criteria of the *meta*Register of Controlled Trials (an international register of registers run by Current Controlled Trials; see http://controlled-trials.com/mrct), to allow future collaboration.

We agree with the ICMJE that clinical trial registers will be most useful if they are designed to include all possible trials from any country in the world. For pediatric research, the DEC-net register meets this goal.

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Cardiovascular risk in patients with type 2 diabetes

There is no doubt that aggressive control of common risk factors is of paramount importance in the management of diabetic patients with atherosclerotic disease to prevent cardiovascular morbidity and mortality. In assessing management of such patients, Lauren Brown and associates[1] identified the study cohort between 1991 and 1996 and followed the patients until 2000; however, the evidence for the standard therapies they evaluated (regarding antiplatelet agents,[2] angiotensin-converting enzyme [ACE] inhibitors[3] and statins[4]) did not become available until at least 2000. In other words, evidence published during or after the year 2000 was applied to data collected up to 2000; thus, it is no surprise that management was suboptimal relative to current recommendations.

It would have been preferable for the authors to have used the 1998 guidelines for management of diabetes[5] in evaluating the care provided to these patients. I acknowledge that their findings would probably have been similar, as it takes a few years to implement such guidelines (by which time they may have been changed or be undergoing revision). None of the therapies listed above was strongly recommended for cardiovascular protection in the 1998 guidelines. In fact, the UK Prospective Diabetes Study,[6] published at the same time, highlighted the importance of effectively controlling both blood glucose and blood pressure to improve microvascular and macrovascular complications and did not favour one agent over the other (β-blocker versus ACE inhibitor).

Since then, however, evidence has accumulated, and the 2003 Canadian guidelines[7] make appropriate recommendations about these therapies.

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Lauren Brown and associates[1] observed low use of therapies with proven benefit for the prevention of cardiovascular events in patients with type 2 diabetes, both with and without atherosclerotic disease. We are conducting a similar study analyzing use of acetylsalicylic acid (ASA), statins, β-blockers and angiotensin-converting enzyme (ACE) inhibitors (or equivalent) in a cohort of 407 high-risk patients attending the Lipid/Cardiovascular Risk Reduction Clinic at St. Paul's Hospital in Vancouver. These patients have a history of vascular disease (coronary, peripheral or cerebral) with or without diabetes.

Data on the patients' lipid profile and use of the 4 medications at the time of the initial visit to the clinic (between 1984 and 2004) and their most recent visit (between November 2003 and July 2004) have been collected (Table 1). The use of these medications will also be prospectively evaluated at the next scheduled visit.

We are also trying to examine differences in medication use in a subgroup of 178 patients with diabetes from the same cohort: 54 with established coronary artery disease (CAD) and 124 without clinical evidence of CAD. Preliminary data were obtained from the most recent follow-up visits (with an average of 60 months between the first and the most recent visit). We found no significant differences in the use of ASA and statins between the 2 groups; however, the rate of treatment with β-blockers and ACE inhibitors was significantly higher among patients with CAD than among those without CAD. Although the difference in β-blocker use was not unexpected, we

Table 1: Use of proven cardioprotective agents in a cohort of high-risk patients: preliminary results

	No. (and %) of high-risk patients *n = 407*			No. (and %) of diabetic patients* *n = 178*		
Agent	First visit *n = 407*	Most recent visit *n = 402*	*p* value	With CAD *n = 54*	Without CAD *n = 124*	*p* value
ASA	194 (48)	302 (75)	< 0.001	39 (72)	81 (65)	0.22
Statins	158 (39)	328 (82)	< 0.001	44 (81)	99 (80)	0.80
β-Blockers	108 (27)	127 (32)	0.11	23 (43)	13 (10)	< 0.001
ACE inhibitors	143 (35)	284 (71)	< 0.001	45 (83)	80 (65)	0.012

CAD = coronary artery disease, ASA = acetylsalicylic acid, ACE = angiotensin-converting enzyme.
*Data obtained during most recent visit.

were surprised by the low use of ACE inhibitors or equivalent for patients who had diabetes but no clinical evidence of CAD.

These preliminary results indicate that there is room for improvement in implementing treatment guidelines in clinical practice. The overall use of cardioprotective medications was suboptimal at the initial visit, although use had increased significantly by the time of the most recent visit (Table 1). However, the use of ACE inhibitors remained suboptimal among diabetic patients without CAD, a result similar to the data presented by Brown and associates.[1] We agree that multidisciplinary cardiovascular risk reduction programs are needed to improve quality of care in high-risk patients.

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Competing interests: None declared.

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C. difficile: Will lessons be learned?

Laura Eggertson[1] reports that "there were 7004 cases of [*Clostridium*] *difficile* across Quebec from Apr. 1, 2003, to Mar. 31, 2004, and 1270 people died." Additional data in her article reveal a staggering increase in both morbidity and mortality due to *C. difficile* from 2001 to 2003,[1] yet the provincial government only recently intervened with policies to aggressively control the outbreak. Moreover, some health care professionals have reported a lack of sufficient resources to effectively control the outbreak.[2] This state of affairs raises 2 issues: first, how health care institutions effectively intervene when a pathogen manifests in a community and, second, the allocation of resources to achieve desired social goals.

The fact that, until recently, reporting of hospital-acquired infections to health care authorities was not required points to both structural and procedural shortcomings within our health care institutions. The recent establishment of province-wide surveillance and infection-control committees is intended to rectify the structural deficiencies, although the effectiveness of these measures remains unknown. In addition, procedural interventions appear to have been underused, both clinically and interpersonally. Clinically, health care professionals should have been informed by a provincial nosocomial infection control committee about the technical means of controlling the outbreak. This advice should have been based on the best evidence available and should have been provided as soon as possible after the increase in incidence was noted.[3–5] At an interpersonal level, patients or their representatives should have been informed of the increased risks and patient groups should have been engaged in consultation and decision-making.

Yet these structural and procedural interventions cannot be undertaken without the addition of the resources needed for their implementation. If hospitals have to redirect existing scarce resources from other services to combat *C. difficile*, overall quality of care could decline.

But the saddest lesson from the *C. difficile* outbreak has been exposure of the lack of planning and coordination in the face of a virulent form of a known infection. I hope the lessons of the *C. difficile* epidemic serve as a grave warning in case of future outbreaks of new pathogens.

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Influenza vaccine for all?

I find it interesting that, a few weeks after celebrating the achievements of the Cochrane Collaboration,[1] *CMAJ* published a systematic review[2] and a recommendation statement from the

Canadian Task Force on Preventive Health Care[3] on preventing influenza in the general population (and the authors of the systematic review were quoted in the lay press as endorsing universal vaccination[4]), when a Cochrane review of the topic[5] already exists.

The Cochrane systematic review,[5] alluded to but not cited by Joanne Langley and Marie Faughnan,[2] concludes that "[i]nfluenza vaccines are effective in reducing serologically confirmed cases of influenza. However, they are not as effective in reducing cases of clinical influenza and number of working days lost. Universal immunisation of healthy adults is not supported by the results of this review."

Langley and Faughnan[2] state that their goal was to determine the efficacy of the vaccine, not the efficacy of a universal vaccination program. Yet it appears that they, and the task force, endorse such a strategy, without evidence related to a variety of ancillary considerations that they identify (including economic costs, vaccine procurement and public acceptability).

Something is missing here. Was the *CMAJ* systematic review not the compelling piece of evidence leading to the task force's endorsement of universal vaccination? Was the conclusion of the Cochrane Collaboration wrong? Is there evidence of cost-effectiveness, and have procurement issues been sorted out? Just how many systematic reviews do we need on a particular topic?

R.A. Fisher, the pioneering methodologist for randomized trials and the most influential statistician of the 20th century,[6] envisioned controlled trials (and, by extension, systematic reviews and meta-analyses) as an essential technique to reduce the interpretive variability of study results. I wish he and Archie Cochrane were still around to help us sort this out.

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[One of the authors and the chair of the CTFPHC respond:]

As systematic reviews and meta-analyses have become established as methods for evidence-based decision-making, reviews on similar questions have been published, sometimes with discordant results. Recommended approaches to reconciling these differences include determining if the results truly differ or if the variation arises from the interpretation of the results.[1] Ross Upshur notes that different conclusions on vaccination of the general public were reached by the Canadian Task Force on Preventive Health Care (CTFPHC)[2,3] and the Cochrane Collaboration.[4] In this case, the reviews covered different populations (healthy adults and children in the CTFPHC review, healthy adults only in the Cochrane review) and considered different interventions (vaccines and neuraminidase inhibitors in the CTFPHC review, vaccines only in the Cochrane review). There were also differences in methods: CTFPHC reviews are systematic qualitative reviews,[5,6] whereas the Cochrane reviews are generally quantitative reviews.[4,7] As noted in the Methods section and Fig. 1 of our review,[2] we reviewed the Cochrane database to find primary trials that might not have been identified in our literature search. The trials that

were judged acceptable were not identical in the 2 reviews.

Perhaps the most important difference between the 2 reviews is in the interpretation of cumulative evidence for influenza vaccination in healthy people. The Cochrane reviewers concluded that the efficacy of inactivated influenza vaccines (the type of vaccine that is available in Canada) was 70% (95% confidence interval 56% to 80%) in healthy adults, but thought that this was insufficient evidence to support general vaccination.[4] The CTFPHC concluded that vaccination was a moderately effective intervention to reduce influenza in adults and children, without evidence of harm, and recommended it.[3] The clinical significance of a 70% reduction in influenza virus infection will likely be of variable importance to patients and their families, clinicians and other health care providers, and payers. The ultimate decision to offer influenza vaccination rests with those who must balance the broader issues of universal programs, such as the practicability of vaccinating large populations in a short period of time, public acceptance, vaccine procurement and the value of this intervention relative to other health prevention or treatment interventions.

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Earning our patients' trust

A recent editorial in the *CMAJ*[1] used notorious British family physician and serial murderer Harold Shipman as an example of how "professional malfeasance" wrought by physicians has eroded public confidence in physicians. While I could not agree more that public confidence and trust in physicians are the cornerstones of the physician–patient relationship, I challenge your assertion that "confidence in physicians is waning."

Physicians in Canada continue to be described as very trustworthy[2] in surveys designed to measure how much various professionals are trusted by the public. Being identified as one of the most trustworthy professions, along with nurses and pharmacists, is not an honour either bestowed or received lightly.

Canadian advocacy and regulatory bodies have reaffirmed the need for maintaining the highest possible ethical standards, physician competence and lifelong learning. Perhaps most importantly, a new era of openness and transparency has begun, with increased public representation on the governing councils of the colleges of physicians and surgeons and regular, publicly accessible reports on disciplinary actions and investigations.

The Shipman case represents a tragic episode in the history of medicine, and as physicians we all recoil at the horror and pain this individual

caused. However, raising the spectre of a mass murderer in relation to Canada's system of medical self regulation is inaccurate and unduly alarmist.

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DOI:10.1503/cmaj.050358

Gagner la confiance de nos patients

Dans un éditorial récent du *JAMC*[1], on utilise Harold Shipman, médecin de famille britannique et tueur en série notoire, comme exemple des «méfaits professionnels» causés par des médecins qui ont eu pour effet de miner la confiance du public envers la profession. Je ne saurais insister suffisamment moi-même sur le fait que la confiance de la population envers les médecins constitue la pierre angulaire de la relation médecin–patient, mais je conteste néanmoins votre affirmation selon laquelle la «confiance dans les médecins est à la baisse».

Les médecins du Canada sont toujours décrits comme étant très dignes de confiance[2] dans les sondages conçus pour mesurer la confiance que le public accorde à diverses professions. Être identifié à l'une des professions les plus dignes de confiance, en même temps que les infirmières et les pharmaciens, ce n'est pas un honneur que l'on accorde ou reçoit à la légère.

Les organismes canadiens de représentation et de réglementation ont affirmé qu'il faut maintenir les normes les plus rigoureuses possibles d'éthique, la compétence des médecins et l'acquisition continue du savoir. Le plus important, peut-être, c'est qu'une nouvelle ère d'ouverture et de transparence s'est ouverte avec la représentation accrue du public aux conseils de régie des collèges des médecins et chirurgiens et la publication de rapports périodiques, accessibles au public, sur les sanctions disciplinaires et les enquêtes.

L'affaire Shipman représente un épisode tragique de l'histoire de la médecine et comme médecins, l'horreur et la douleur causées par cette personne nous répugnent à tous. Évoquer le spectre de l'auteur d'une série de meurtres à l'égard du système d'autoréglementation de la médecine au Canada, c'est cependant à la fois erroné et indûment alarmiste.

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Letters submission process

CMAJ's enhanced eLetters feature is now the portal for all submissions to our letters column. To prepare an eLetter, visit www.cmaj.ca and click "Submit a response to this article" in the box near the top right-hand corner of any *eCMAJ* article. All eLetters will be considered for publication in the print journal.

Letters written in response to an article published in *CMAJ* are more likely to be accepted for print publication if they are submitted within 2 months of the article's publication date. Letters accepted for print publication are edited for length (usually 250 words) and house style.

Corrections

In a recent News item,[1] the sentence "Studies have shown that patients initially lose between 35%–60% of baseline body weight and maintain weight reductions of approximately 16% after 8 years" should have read "Studies have shown … after 10 years."

Reference

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DOI:10.1503/cmaj.050360

The following DOI was mistakenly omitted from a recent item[1] in the Analysis section of the journal: DOI:10.1503/cmaj.050370.

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DOI:10.1503/cmaj.050374

In a recent research paper,[1] the corresponding author's email address should have read jasoon@interchange.ubc.ca.

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INFECTIOUS DISEASE

Feds to stockpile antivirals as pandemic "speed bump"

A longer version of this article was posted Mar. 23, 2005, at www.cmaj.ca

The federal government has generated an ambitious plan to stockpile massive quantities of antiviral drugs in readiness for a potential influenza pandemic, to buy scientists precious time to produce a vaccine to fight the new strain.

However, the high cost and limited supply of the most effective drug means Canada will be able to obtain only 30 million of the 221.6 million doses officials believe they will need to treat the 684 000 Canadians most at risk of dying from the virus or who provide essential public services.

The National Antiviral Conference in Winnipeg on Mar. 21 and 22 focused on the use of antiviral drugs to fight an influenza pandemic, which the Public Health Agency of Canada (PHAC) estimates could kill up to 58 000 Canadians (*CMAJ* 2004;170:785-6). The conference confirmed a federal–provincial plan to stockpile as many as 20 million individual doses of oseltamivir (Tamiflu) and another 10 million doses of other antiviral drugs.

Conference delegates questioned how effective antiviral agents would be in a pandemic. Dr. Joel Kettner, Manitoba's chief public health officer, said they have never been tested in full-blown pandemic conditions.

In a best-case scenario, antiviral drugs would prevent infection in some groups, while helping others weather the virus with reduced critical symptoms, said Dr. Theresa Tam, PHAC associate director of immunization and respiratory infections. Assuming manufacturers have the 6- to 7-month window required to develop a vaccine, these drugs could help Canada avoid widespread death and disruption to the economy, she said (*CMAJ* 2005;172:623).

In a worst-case scenario, where the strain of influenza that emerges does not lend itself to rapid vaccine development, and infection rates rise to 1918 levels, this small stockpile would likely provide no comfort. Still, the worst case is not an excuse for sitting still, Tam said. "The only thing more difficult than planning for an emergency is having to explain why you didn't," she added.

Stockpiling antivirals is expensive. Each pill costs $2.50 and an infected person would require about 10. Prophylactic treatment could run to 42 doses. It would cost $75 million to provide 30 million doses.

The drugs are also in short supply; oseltamivir (Tamiflu), the most effective antiviral agent, is produced by a single manufacturer.

The drugs must be started within 48 hours of the onset of symptoms. Neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza) hold the greatest potential to control the spread of a virulent new strain of influenza, said Dr. Frederick Hayden, head of infectious diseases at the University of Virginia. Any new strain is more likely to have built up resistance to older inhibitors, including amantadine (Symmetrel) and rimantadine (Flumadine), making them less desirable to stockpile. These drugs also have a higher prevalence of side effects, some severe, said Hayden.

Most conference delegates agreed that 30 million pills might buy researchers just enough time to develop an effective vaccine. "It's a matter of how much insurance you want to buy, and how much insurance can you afford," said Jill Sciberras, a PHAC senior epidemiologist.

The Public Health Agency of Canada has developed a priority list of groups who would draw from the national stockpile for treatment or as prophylaxis (see Box). — *Dan Lett*, Winnipeg

Priorities for distributing antiviral drugs in an influenza pandemic

1. Treatment of people admitted to hospital with influenza
2. Treatment of ill health care workers and key decision-makers
3. Prophylaxis of frontline health care workers and key health decision-makers
4. Treatment of people at high risk in the community
5. Prophylaxis of remaining health care workers
6. Outbreak control among high-risk residents in institutions
7. Prophylaxis of high-risk people admitted to hospital for illnesses other than influenza
8. Prophylaxis of people at high risk in the community

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GOVERNMENT LEGISLATION

UK rejects compulsory mental health treatment

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Attempts to overhaul mental health law in England and Wales suffered a withering blow last month when a Joint Parliamentary Committee described the draft bill as "fundamentally flawed" and sent it back to committee.

The British Medical Association condemned the bill, which proposed new powers for compulsory treatment and assessment of outpatients in the community setting. These include powers to compel patients to make themselves available for assessment and to reside at specified locations. The BMA advised the committee to "tear the proposals up and start again."

The plans are aimed at better protecting the public from people with dangerous and severe personality disorders. Over the past few years several murders carried out by people with severe mental illness have provoked furious calls for firmer control of dangerous patients.

The Joint Parliamentary Committee that was set up to scrutinize the bill stated that the plans would "force too many people into compulsory treatment" and that it "places too great an emphasis on protecting the public from a small minority of dangerous mentally ill people."

It said it feared that the proposed powers could be used to enforce treatment on people who are a "nuisance" but who don't pose any risk to the public.

In a statement to *CMAJ*, the UK Department of Health wrote that it would review the committee's report carefully. "However … any legislation must ensure that there is a proper balance between protecting the rights and lives of our citizens alongside the rights of the individual." — *Colin Meek*, Wester Ross, Scotland

DRUG SAFETY

National consumer drug safety network launched

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Citing the recent withdrawal of refecoxib (Vioxx), members of a new national consumer network say Health Canada and Canadian doctors are failing in their duty to protect the public from harmful drugs.

"The evidence is clear, something is broken in the system and we should get busy and fix things," BC family physician Dr. Warren Bell said at the Mar. 18 Vancouver conference that gave birth to the network PharmaWatch/PharmaVeille.

Bell is a board member of the previous PharmaWatch, a Vancouver-based advocacy group spearheading the new organization which aims to involve the public in every stage of Canada's drug regulation process.

The other two founding groups are DES Action Canada, which was formed in 1982 in response to serious adverse reactions to DES (diethylstilbestrol), and l'Union des consommateurs, a Montréal-based consumer group that has launched a class action suit against Pfizer, the maker of celecoxib (Celebrex).

Although the conference focused on how to improve direct consumer reporting of adverse drug reactions, participants said consumers must also be part of other stages, including drug approvals and postmarket surveillance.

"We think citizens have a right to be involved in the approval process," said PharmaWatch and network head Colleen Fuller.

"The public should have full access to information about clinical trials being conducted, the reasons why a drug has been approved or not approved. And that means the government has to open the doors to people, and citizens have to step forward themselves."

Dr. James Wright, managing director of the Therapeutics Initiative at the University of British Columbia, illustrated the inadequacy of the current system through the example of COX-2 inhibitors.

In early 2001 Wright published information from a refecoxib trial showing that the drug was associated with an increase in life-threatening events (*CMAJ* 2002;167:1131-7).

"The regulators are passive," says Wright.

The network hopes to create a bilingual Web-based source of drug information; help Canadians play an active role in developing public policies that reduce the harmful effects associated with prescription drugs, including working for a ban on direct-to-consumer advertising; support equitable access to safe medicines and non-drug therapies; and encourage consumer reporting of adverse drug events.

Health Minister Ujjal Dosanjh recently announced Health Canada's new commitment to greater transparency and increased consumer involvement in decision-making about drug safety (*CMAJ* 2005;172:733). — *Alicia Priest*, Victoria

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ACCESS TO DRUGS

Patent-drug price board to review guidelines

The tribunal in charge of regulating drug prices is reviewing its guidelines in light of an increase in the price of 35% of all patented drugs last year.

In a Mar. 9 discussion paper, the Patented Medicine Prices Review Board (PMPRB) outlined concerns that price stability could be under some "strain" and asked for comments by May 9.

"The proportion of drug [price] increases is somewhat out of the norm," says Barbara Ouellet, PMPRB's new executive director. "It created questions in our minds over whether this is unique."

The board will not know until later this spring what the price increases translate into in dollar figures.

Operating at arm's length from government, the PMPRB is a quasi-judicial tribunal created in 1987 to regulate the price of patented drugs sold in Canada. Under current guidelines, manufacturers cannot increase prices above the consumer price index.

Rx&D, Canada's Research-based Pharmaceutical Companies, refused to comment on the discussion paper until it sends its comments to the board.

The paper presents 3 possible frameworks, the first being to maintain the status quo.

The second calls for changes to the Patented Medicine Regulations (1994) requiring manufacturers to notify the board in advance of any price change so it can calculate whether they fall within the guidelines. Currently, manufacturers are obliged to inform the board within 6 months of a price change.

Although this is presented as a proposal, the PMPRB has already applied for this amendment to the Patented Medicine Regulations, with comments due Apr. 15.

The third framework requires patentees to apply in advance of a price change, like the second framework, and to also justify the increase. "The PMPRB would then make a determination on both the appropriateness of the increase and then on the extent of the increase allowed up to a non-excessive maximum," the paper states.

Ouellet says she expects numerous submissions. The board will recommend action to the government.

Canadian drug prices have been stable since 1998 and are now comparable with 6 European countries. In 1987, Canadian prices were 23% higher than the median international prices. However, retail spending on drugs increased 10.5% in 2002 (to $18.4 billion). — *Barbara Sibbald*, CMAJ

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News @ a glance

Schiavo ruling: An extraordinary intervention in a family fight over whether to remove a comatose woman's feeding tube saw the US Congress pass a law requiring a Federal Court judge to hear the case. Despite rulings by 19 Florida judges in lower courts, and the Supreme Court's refusal to hear an appeal, Congress convened a special Palm Sunday session and interrupted a recess to pass the bill. President George W. Bush rushed back from his ranch in Texas to sign the legislation. The new law allowed Terri Schiavo's parents to ask a Federal Court judge to reinsert the feeding tube that Schiavo's husband Michael had removed 3 days earlier. The judge ruled against Schiavo's parents, and she died Mar. 31. She had been in a coma for 15 years, following brain damage after a heart attack. "In cases like this one, where there are serious questions and substantial doubts, our society, our laws, and our courts should have a presumption in favor of life," Bush said in a statement. Groups representing the Christian Right joined Schiavo's parents in lobbying politicians to keep her alive. — *Laura Eggertson*, CMAJ

Sunbed risks: Sunbed use increases the risk of skin cancer, particularly among people under 18, warns the WHO. Studies have shown that young people who get sunburns have an increased risk of developing melanoma later in life. More recently, a link has been found between the use of sunbeds and cancer (*J Nat Cancer Inst* 2003;95:1530-8). Each year, there are 132 000 cases of malignant melanoma and over 2 million cases of other skin cancers worldwide. WHO warns that these rates are increasing and advises regulatory authories to adopt stricter controls on the use of sunbeds. One in 3 cancers worldwide is skin-related; in the US the rate is 1 in 2. Health Canada's recently revised guidelines for tanning equipment prohibit their use by children under 16 and recommend new warning labels (see image below). France and California have prohibited people under age 18 from using sunbeds.

Applying pressure: Millions of Canadians who use home blood pressure monitoring devices may be endangering their health if they are not properly instructed in how to read the machines. Dr. Thomas Wilson, a researcher with the Canadian Heart and Stroke Foundation, estimates that these machines are used by a third of urban Canadians with high blood pressure. In his study (www.heartandstroke.ca), only about half of the 80 participants were able to measure their blood pressure within 5 mm of mercury. Only 7 people had been instructed in the monitors' use at the time of purchase. The study looked at several parameters to do with measurement, such as whether or not subjects knew they should rest for 2 minutes minimum before taking their blood pressure (90% didn't know). — *Tim Lougheed*, Ottawa

Breast best: Healthy, full-term babies should receive only breast milk for the first 6 months, advises the Canadian Paediatric Society. Previously, the CPS had endorsed a range of 4 to 6 months. "There is evidence that the benefits increase with longer breastfeeding, particularly when the infant is exclusively breastfed for the first 6 months, stated Dr. Margaret Boland, chair of the CPS Nutrition Committee. Statistics Canada reports that 85% of mothers start breastfeeding, but only 19% do so exclusively for 6 months. The new CPS recommendations are consistent with those of the WHO.

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Alternative choice: Alternative medicines are increasing in popularity among Canadians, indicate new data from Statistics Canada. The latest figures from the Canadian Community Health Survey show that 20% of Canadians over age 12 — some 5.4 million people — used alternative health care services in 2003; up from 15% in 1994–95. The rate was higher among women (23%) than men (17%). About 11% of the 12-and-over population had consulted a chiropractor (the most common form of alternative care), 8% a massage therapist, 2% an acupuncturist and 2% a homeopath or naturopath. Use rose with income, likely due to the fact that many types of alternative care are not publicly funded. Twenty-six percent of individuals in the highest household income group used alternative care in 2003, compared to 13% of those in the lowest income group. — Compiled by *Barbara Sibbald*, CMAJ

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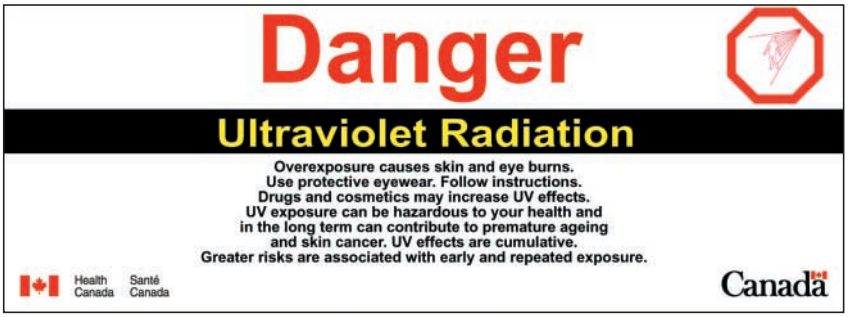

Health Canada

New litigation limit leads to storage woes

As provincial governments across Canada tweak their regulation of malpractice lawsuits, physicians aren't worried about heading to the courtroom, they're angry about spending extra time and money storing patient records.

"I haven't seen anything get doctors this animated in quite some time," says Marcus Davies, spokesman for the Saskatchewan Medical Association.

As of May 1, Saskatchewan is extending the time limit for filing malpractice suits from 2 years post-treatment to 15 years. For underage patients, the malpractice clock doesn't begin to tick until the patient reaches 18. To protect themselves in the event of litigation, doctors across the province will have to maintain patient records longer.

Doctors will "need storage space, digitalization, and time spent managing those files. They have to ensure aproper chain of custody on every file. We think that the government didn't really think this through," says Davies.

"We have to ask: What was broken with the previous system? There were no people being denied access to proper recourse."

BC, Alberta, and Ontario have already increased their limitation periods to 6, 10 and 15 years respectively. The Saskatchewan legislation sets common limits for 3 professions: engineers, architects and physicians.

The Canadian Medical Protective Association says the changes won't increase liability or unduly burden physicians. It currently advises physicians to retain records for a minimum of 10 years after the last entry or the patient reaches the age of majority.

"We don't see any reason to change that," says Associate Executive Director, Dr. William Beilby.

Given that the old statutes were flexible and uncertain, Beilby also sees some benefit in having a definitive litigation cap.

Kenneth Ready, a Regina lawyer who has tried over a dozen malpractice cases, says the new legislation likely won't create an influx of new litigants.

"If they think they have a claim, they act on it pretty quickly," says Ready.

He adds that the longer time limits may reduce the number of frivolous lawsuits. Previously lawyers were sometimes forced to file claims before fully investigating whether they were valid or not. — *Michelle Catton*, Ottawa

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ANALYSIS

LIFE DECISIONS

Discontinuing life support in comatose patients: an example from Canadian case law

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The type and extent of medical intervention that is appropriate for patients in a persistent vegetative state is a matter of painful moral and legal debate, as the Terri Schiavo case in the United States has recently shown. Every day, in intensive care units, families are faced with difficult decisions with regard to life-sustaining interventions that are therapeutically futile. Such situations are especially difficult when the patient has given no advance directive to guide family members and physicians. Many physicians are aware of the Sawatzky case, in which a woman challenged a physician's "do not resuscitate" order in her husband's chart.[1] Less well known is a case brought to the Surrogate Court of Alberta in 1999, in which the court approved the discontinuance of life support for a comatose, dependent adult with no advance directive.[2]

Robert Kenneth Durksen, a 47-year-old RCMP officer, suffered severe brain injury in a plane crash in June 1999. He was comatose after the injury and required intravenous hydration and nutrition to remain alive. Three months later he remained comatose. At his family's request, a public guardian was appointed as his substitute decision-maker under the terms of the Dependent Adults Act. The appointment of a public guardian was unusual given the existence of family members, but those closest to Const. Durksen preferred that a public guardian be the legal decision-maker rather than one of them. The governing principle of the Dependent Adults Act is to serve the best interests of the individual concerned, taking into account his or her known views, values and wishes. Specifically, the public guardian had to determine whether continued intravenous hydration and nutrition were in the patient's best interest.

No advance directive had been made by the patient. The public guardian consulted with the family, health care team members and the local clinical ethics committee. After some initial lack of consensus, the family and the patient's common-law partner became united in the belief that he would want his life support to be discontinued. However, given that the Dependent Adults Act is silent on the question of discontinuing life support, the public guardian was reluctant to authorize the discontinuance and applied to the court for advice and direction. The court was asked whether the public guardian could legally consent to discontinuance of hydration and nutrition or refuse such treatment on behalf of Const. Durksen and whether a court review was required.

The court's deliberations hinged on 2 questions and the connection between them. First, did the existing legislation allow the public guardian to give proxy consent to discontinue or refuse life-sustaining interventions? Second, did the principle of sanctity of life prejudge what could be determined as being in a person's best interest?

The court held that a court-appointed guardian lacked the power to authorize discontinuance of life support for a person with no advance directive and required the court's approval. The court's decision in this case was to grant the application to discontinue nutrition and hydration and to approve the proposed termination of all measures except purely palliative ones.

In making this determina-

Practical implications of the Alberta court decision in the Durksen case

Ethical points

- Sanctity of life is not an absolute value in the determination of appropriate health care for an incompetent patient
- Maintenance in a persistent vegetative state is not a benefit to the patient
- Appropriateness in health care depends on the facts of a given case
- The best interest of a patient may be met by discontinuance of all interventions except for palliative measures designed to allow a patient to die peacefully, with the greatest dignity and the least pain, suffering and distress
- Artificial hydration and enteral feeding were not distinguished from artificial respiration and seemingly do not have different legal significance from artificial respiration for discontinuance

Procedural points

- There is a limitation in the powers of a court-appointed guardian. Where there is no advance directive, the guardian as a proxy decision-maker cannot consent to discontinuance nor refuse commencement of life-sustaining interventions without court approval
- The court has inherent power to review, advise and direct in such matters
- Application to court for approval of a palliative care plan involving discontinuance of life support should be built upon prior medicolegal and ethical consultations

tion, the court took a pragmatic yet sensitive approach. The starting-point was that court review is essential in the absence of an advance directive: the public guardian cannot act alone. On the substantive issue, the decision indicated the need to address the particular facts involved. With no reported Canadian cases with similar facts, the court considered several factors. These included the English House of Lords decision in *Airedale NHS Trust* v. *Bland* (1993), which concerned a 17-year-old comatose survivor of the Hillsborough soccer disaster, who had been kept alive on life support for approximately 3 years. As his legal representatives, his parents went to court to get permission to authorize discontinuance of his life support. The decision in that case held that the "existence in a persistent vegetative state is not a benefit to the patient." However, incapacity to benefit does not address the "sanctity of life" issue. Again, the Alberta court adopted the position taken in *Bland*, namely that the sanctity of life is not an absolute principle. The court took the view that life is sacred, not in the sense of bare existence, but in a personal sense: how that patient construes a meaningful life — their life as they see it and how they wish to live. Lack of sufficient quality of life relative to the patient's known values will affect the rightness of a proxy decision about a person. At the same time, the Alberta court also found that a desire to die was not sufficient to warrant a medical intervention solely to bring about death; here, the court cited the Supreme Court of Canada decision in *Rodriguez* (1993), the case of the BC woman with amyotrophic lateral sclerosis who unsuccessfully sought court approval for physician-assisted suicide.

The Alberta court took into account the extensive consultation of medical and ethical experts and family. It also took into account hearsay evidence from family and friends to identify the patient's values and outlook on life for one in his condition. Const. Durksen had attended the scene of many injuries and fatal accidents and had talked to colleagues about his views. The anecdotal evidence from family and friends indicated that, were he able to do so himself, Const. Durksen would have refused continued life support in his condition. Overall, the court held that the patient's circumstances made it fitting to order the discontinuance of all but palliative care.

Discontinuance of life support for a patient is, and will continue to be, one of the most emotionally difficult situations faced by family, caregivers and health care professionals. It involves intensely personal deliberations about intensely interpersonal matters: what we mean to each other and what we mean to ourselves, and how best to deal with and respond to the monumental change in circumstances. When differences in outlook emerge, those involved risk becoming prey to public lobbying, as seen recently in the Schiavo case. The similarities in circumstances between her case and that of Const. Durksen are striking: both patients were comatose; both were represented by a court-appointed guardian; neither had a living will; and both were in a condition with no realistic prospect of significant improvement or recovery. The essential difference is that Const. Durksen's family found a way to reach consensus in their beliefs about what was best for him and what he would want for himself. If there is a lesson to be learned, it is surely that, in each case, had there been a living will, there would have been no need for a court hearing, and no publicity.

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Acknowledgments: We would like to acknowledge the understanding of those members of Const. Durksen's family who have assented to the dissemination of the information surrounding his case in this article. Although this has been a theoretically accessible decision, it has gone more or less unnoticed and has not been included in the usual law reports to date. The hope is that the present disclosure might assist people facing hard decisions in similar situations.

We thank senior staff, especially Darrel Koller, at the Office of the Public Guardian (Alberta) for assisting in the preparation of this article. We also thank Robert Bissett, with the law firm of Stringam Denecky, Barristers and Solicitors, who prepared an excellent brief of law and made the application on behalf of the Office of the Public Guardian.

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ANALYSIS

SCIENCE AND MEDICINE

Light as a defence against fungal infection

Fungi love the dark, and one day we may be able to turn this fact against them to fight fungal infections. New research suggests that the way in which the fungus *Cryptococcus neoformans* detects light plays a role in its virulence. Two genes controlling light responses in *C. neoformans* were recently discovered by Alexander Idnurm and Joseph Heitman, who found that deleting either gene reduced the virulence of the fungus.[1] The finding suggests that light-based therapies may have a role in treating fungal infections.

Virulence factors

C. neoformans is a well-known opportunistic pathogen. It normally infects people with compromised immune systems, such as organ transplant recipients and AIDS patients. In fact, it is endemic in Africa and Southeast Asia, infecting upward of 30% of AIDS patients.[2] The fungus has a number of virulence factors (e.g., a polysaccharide capsule, melanin synthesis, various enzymes); when the genes encoding these factors are mutated, virulence is diminished.

Idnurm and Heitman have now identified *C. neoformans*' light-sensing proteins as another virulence factor. A pair of proteins that sense blue light have been well studied in the fungus *Neurospora crassa*.[3] Idnurm and Heitman identified genes in *C. neoformans*, named *BWC1* and *BWC2*, that produce similar proteins; mutation of these genes allowed the pathogen to mate in the presence of light (Fig. 1). As well, they found that organisms with mutated *BWC1* were also sensitive to ultraviolet light, whereas wild-type strains were not.

Interestingly, the researchers also demonstrated that *C. neoformans* strains with mutations in either *BWC1* or *BWC2* gene were less virulent. For instance, mice inoculated with wild-type *C. neoformans* died within 30 days; however, mice inoculated with strains lacking either of the 2 light-sensing genes survived an average of 44 days. The finding suggests that the light-sensing proteins, although not essential for virulence, influence the speed with which the pathogen kills its host.

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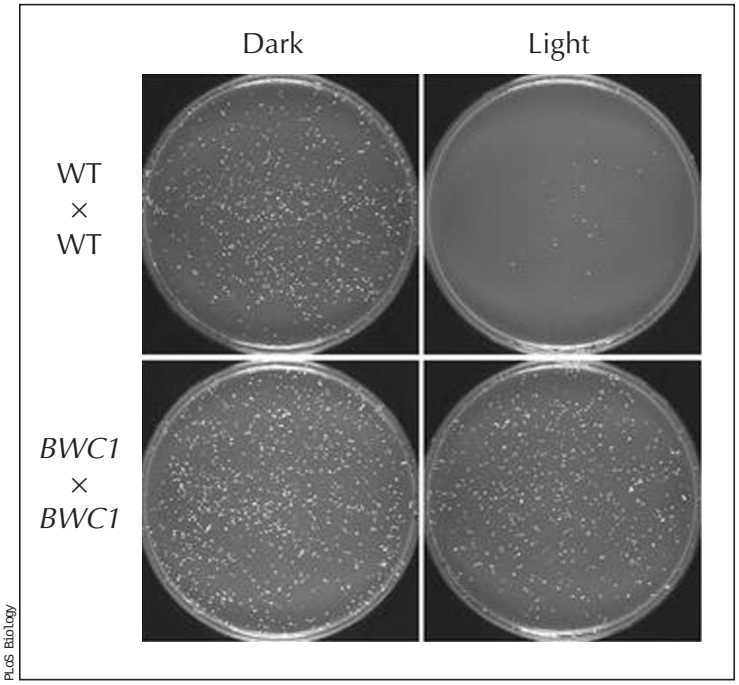

Fig. 1: The effect of exposure to blue light on fusion rates of wild-type (WT) and *BWC1*-mutated *Cryptococcus neoformans* cells. Light inhibited fusion in wild-type strains but not in *BWC1* mutant strains.[1]

Light therapy for fungal infections?

Idnurm and Heitman suggest a teleological rationale for *BWC1* and *BWC2*: the ability to sense darkness in an animal host may induce virulence factors that allow the pathogen to colonize the host. This hypothesis is still far from being confirmed, but it does suggest that the effects of light on other *C. neoformans* virulence factors, such as its polysaccharide capsule, should be studied further.

Idnurm and Heitman's work also brings up the intriguing possibility of using light therapy for the treatment of fungal infections. Light therapy already has some uses in clinical settings: vitiligo is commonly treated with ultraviolet radiation to repigment the skin. In recent years targeted phototherapy systems, which deliver light only to affected regions, have been developed.[4] If light is found to generally inhibit the virulence of pathogenic fungi, a combination of targeted light therapy and antifungal drugs could be a promising new treatment for fungal skin and nail infections. — *David Secko*, Vancouver

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When should surgery be considered for the treatment of epilepsy?

THE CASE: A 45-year-old right-handed man was admitted to hospital for evaluation of seizures that had begun when he was 10 years old but were not responding to treatment. The events were characterized by an initial butterfly sensation in his stomach, sometimes associated with a bad taste in his mouth, déjà vu and a diffuse tingling sensation lasting less than 30 seconds. About half the time, these symptoms would progress to loss of awareness, during which he would stare, smack his lips, drool, rub his leg with his right hand and flex his left arm in a rigid dystonic posture. These spells occurred 2 to 10 times a month and were more frequent during times of stress. The seizures were never completely controlled despite the use of numerous antiseizure medications, including phenytoin, phenobarbital, valproate, carbamazepine, primidone, topiramate, clobazam and levetiracetam. The patient was also taking paroxetine for depression related to the impact of his epilepsy on his ability to work and drive. He had had 2 brief febrile convulsions on the same day at 2 years of age but had no subsequent convulsions. His father had a history of grand mal seizures of unknown cause. The patient's physical examination was unremarkable, but he felt that his short-term memory was not as good as it had been at college.

Previous electroencephalograms (EEGs) over the years had demonstrated right temporal spikes, and previous MRI scans showed signs in the right hippocampus consistent with mesial temporal sclerosis (Fig. 1, arrow). Continuous EEG monitoring revealed seizures arising from the right temporal lobe. A formal neuropsychological evaluation was compatible with impaired memory mechanisms in the right mesial temporal structures but with notably intact memory in the left temporal lobe. Functional MRI for language localization indicated left hemisphere dominance (Fig. 2, arrows). A right temporal lobectomy in the form of a selective amygdalohippocampectomy was performed. The patient has been seizure-free since and continues to take low-dose carbamazepine therapy.

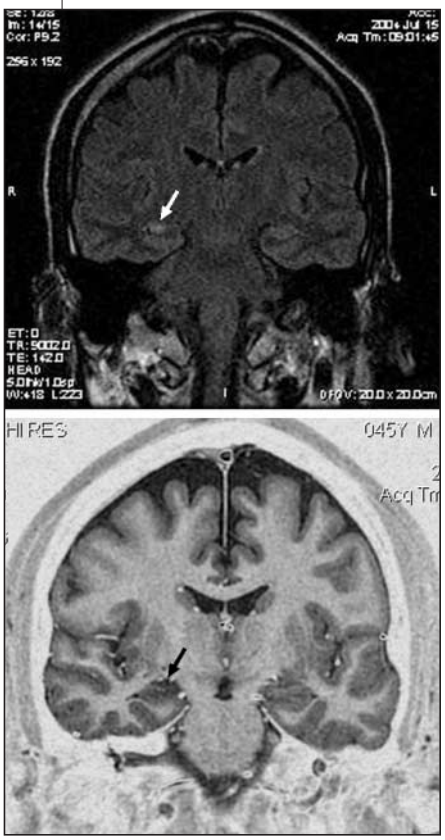

Fig. 1: Top: Coronal section of MRI of the brain on FLAIR (fluid-attenuated inversion recovery) sequence, showing high signal changes in the right hippocampus (arrow). **Bottom:** Coronal section of the same MRI on IR (inversion recovery) sequence, showing evidence of atrophy of the right hippocampus (arrow). The combination of these findings is diagnostic of mesial temporal sclerosis.

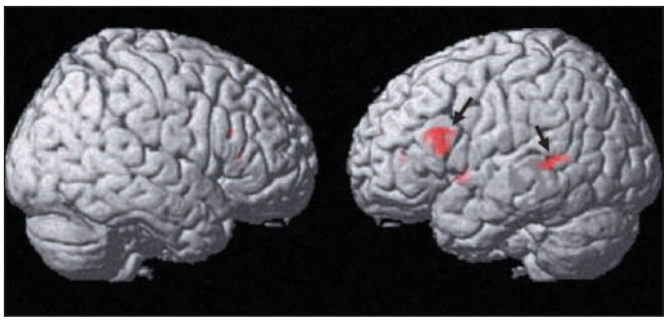

Fig. 2: Three-dimensional view of patient's brain. Areas of activation (Broca's area and Wernicke's area, arrows) for language are seen during mapping using functional MRI.

Epilepsy is a chronic disease characterized by the risk of recurrent seizures that afflicts about 200 000 Canadians at any one time. In Canada the prevalence is 5.6 per 1000 population, with some variation depending on age.[1] Seizures are completely controlled in about two-thirds of those with epilepsy,[2] but an estimated 50 000 Canadians continue to have medically uncontrolled refractory seizures. According to the World Health Organization, disability due to epilepsy accounts for about 1%

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of the global burden of disease, as measured by disability-adjusted life-years, which ranks epilepsy just after some psychiatric problems such as affective disorders and alcohol dependence. The global burden of epilepsy is comparable to that of breast and lung cancer.

In about half the cases, epilepsy is considered idiopathic and is characterized by generalized seizures influenced primarily by genetic factors. The remainder involve focal seizures from a cortical lesion. Our case illustrates the most common form of intractable focal or partial epilepsy, mesial temporal lobe epilepsy (TLE). The cause was mesial temporal sclerosis, the usual pathological substrate of TLE. Although this type of epilepsy often responds poorly to treatment with antiepileptic medication, surgery offers an opportunity for complete seizure control in many instances.

TLE due to mesial temporal sclerosis is a well-defined epileptic syndrome of partial seizures, localized anteromesial temporal lobe abnormalities on EEG, memory dysfunction, and hippocampal atrophy or sclerosis on MRI. The mean age of seizure onset in patients with mesial temporal sclerosis is typically during the second or third decade of life. Patients often have a history of febrile seizures early in life. Ictal features characteristic of TLE include epigastric (rising sensation, nausea, butterflies), emotional (fear) or psychic (déjà vu) auras; decreased behavioural activity with unresponsiveness and staring; clouding of consciousness; oroalimentary (lip smacking, chewing) or manual (picking, rubbing, walking) automatisms; and autonomic (pallor) phenomena.

Because TLE with mesial temporal sclerosis is refractory to antiepileptic medications in more than 90% of patients with the condition, early surgical intervention is now advocated. No longer a treatment of last resort, surgical therapy after 1 or 2 antiseizure drugs have been tried will alleviate seizures in at least 70% of cases, as compared with no more than 5% of cases if another drug is added.

However, epilepsy surgery appears to be grossly underused. Our patient waited 35 years before referral to an epilepsy centre. In Canada, of an estimated 20 000 people with intractable epilepsy who are candidates for surgery, only 352 underwent surgical treatment during a recent 1-year survey.[3] Similarly, in the United States, it is estimated that only 1500 patients undergo such surgical procedures each year. Many clinicians who care for patients with epilepsy are still uncertain about the efficacy and safety of surgical procedures and still view surgery as a last resort for patients with intractable epilepsy, even though the efficacy of surgery has been well demonstrated.

In addition to the many observational studies of the impact of surgical management, including those by Wilder Penfield and colleagues at the Montreal Neurological Institute more than 70 years ago, the only randomized, controlled trial of epilepsy surgery to date was done in London, Ont., by Wiebe and associates.[4] The evidence from that study alleviated any doubt about the efficacy of surgical treatment in temporal lobe epilepsy both for controlling seizures and for improving quality of life. Furthermore, the extensive preoperative investigation now carried out in epilepsy surgery centres limits any unwanted impact of surgery on normal brain function. Concerns that surgery may result in adverse effects on memory, language, behaviour and emotion must be weighed against the potential consequences of continued disabling seizures on these functions. The disruption of the limbic system caused by recurrent temporal lobe seizures is often associated with both memory impairment and behavioural problems that in some cases may be progressive. Although hippocampal resection can impair memory, it has long been known that the memory deficits related to continued complex partial seizures may actually be reversed, and overall cognitive function improved, if seizure-induced dysfunction of the contralateral hippocampus is eliminated by temporal lobe surgery. In general, the psychological and social consequences of disabling complex partial seizures that develop over time in many people with epilepsy have a much more negative impact than any adverse effects of surgical treatment. This is clearly indicated by patients' own reports in the form of standardized, health-related quality-of-life measures. Finally, uncontrolled seizures are associated with a not inconsequential mortality far greater than that associated with any form of epilepsy surgery.

There are 2 main surgical treatments for TLE with seizures arising from mesial temporal structures. Standard anterior temporal resection includes resection of up to 6.5 cm of the anterior nondominant (usually right) temporal lobe and 4.5 cm of the dominant temporal lobe, sparing the language area. Usually such resections encompass the amygdala and at least 1.0–3.0 cm of the hippocampus, where short-term memory resides. The second procedure is selective amygdalohippocampectomy, as was used in our patient. It is a limited removal of the hippocampal formation and amygdala, sparing the anterior and lateral temporal neocortex. Although no definitive comparative studies have been done of these 2 operations, they are likely equally effective in controlling seizures, and there is evidence that suggests the more limited procedure may have less impact on neuropsychological function.

Although TLE with mesial temporal sclerosis is the most common surgically treated seizure disorder, there are other focal epilepsy syndromes amenable to surgical management. More accurate diagnosis through multidisciplinary assessments in epilepsy monitoring units and improvements in neuroimaging

have allowed more patients to be considered for surgical treatment. An example of improved neuroimaging is high-resolution MRI techniques that detect subtle malformations of cortical development. A variety of other functional techniques may help to locate areas of epileptogenesis in patients without visible structural lesions. Among these techniques are functional MRI, single photon emission computed tomography (SPECT) scanning, and magnetic source imaging (MSI). Localization of seizure activity using continuous EEG recording from the scalp or from implanted intracranial electrodes, however, remains the mainstay of investigation of potential candidates for surgery.

This case highlights the lack of an early adequate referral of a patient with intractable or refractory epilepsy.[5] Box 1 outlines some general considerations for surgical management and referral to an epilepsy centre. Patients with seizures whose condition does not improve after 2 to 3 adequate trials of antiseizure medications may benefit from referral to an epilepsy centre, especially if there are signs that the patient has a surgically treatable condition such as temporal lobe epilepsy.

Box 1: When to consider referral for presurgical investigation of epilepsy

- Seizures have been uncontrolled for at least 2 years
- Adequate trials of at least 2 antiseizure drugs have failed to control seizures
- Seizures are controlled but with unacceptable medication side effects
- Seizures are disabling to patient
- Patient is psychologically prepared for surgery
- Patient is not at high risk of surgical complications
- Patient has symptoms or signs of focal seizures
- Electroencephalogram shows focal abnormalities
- Lesion is evident on MRI

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PRACTICE

PUBLIC HEALTH

Protecting against *Clostridium difficile* illness

Background and epidemiology: A gram-positive, anaerobic bacterium that is common in the environment, *Clostridium difficile* is transmitted by the fecal–oral route. Its resistant spores are ingested, survive passage through the stomach and ultimately reside in the colon.[1] Antimicrobial therapy disrupts the ecosystem of stool flora, which fosters *C. difficile* overgrowth.

Clinical symptoms range from none (asymptomatic carriage) to watery diarrhea to life-threatening pseudomembranous colitis. The incidence of *C. difficile* carriage, about 1%–3% among healthy adults, is higher among hospital employees and those working with susceptible patients. The rate increases to about 20% with antibiotic use. As many as 31% of high-risk patients in hospital are colonized with *C. difficile*, with only a subset becoming symptomatic.[1]

C. difficile–associated diarrhea tends to become a problem in hospitals, nursing homes and other long-term care facilities. Disease severity depends on the pathogenicity of the strain as well as the individual patient's risk factors: use of antibiotic therapy (particularly macrolides, third- and second-generation cephalosporins, clindamycin and quinolones, but also including flagyl and vancomycin),[2] advanced age, underlying illness (especially inflammatory bowel disease), institutional setting; and immunodeficiency due to HIV infection or chemotherapy. Recent outbreaks in Canada, the United Kingdom and the United States suggest that infections are more common than had been suspected, or that new strains have emerged that are more invasive or pathogenic.[3]

Various strains of *C. difficile* possess multiple virulence factors that aid in adherence and colonization, such as flagellar proteins, surface-layer proteins and surface-exposed adhesion proteins. Pathogenic strains of *C. difficile* express 1 or 2 large exotoxins, conventionally identified as A and B — although emerging epidemiologic data also point to a bivalent protein, yet to be fully characterized, that is associated with more severe forms of the illness.

Oligosaccharide receptors for toxin A are expressed on the apical membranes on intestinal epithelia; a toxin B receptor has yet to be identified. Purified toxin A shows enterotoxic and proinflammatory activity. The A and B toxins appear to act synergistically when together: toxin A degrades the integrity of epithelial cells, allowing entry of the more potent cytotoxin B.[1] The magnitude and kinetics of the host's IgG response to toxin A appears to have an important role in the clinical outcome of *C. difficile* infection. Individuals in whom the development of circulating antitoxin A IgG antibodies after primary infection is not prompt are likelier to experience more severe symptoms and recurrent diarrhea.[1]

Clinical management: Diagnosis is generally based on the detection of toxin A or B in stool filtrates. Because of its quick turnaround and ease of use, a toxin-specific enzyme-linked immunosorbent assay (ELISA) is often useful. Detecting cytotoxin B in diarrheal stool filtrates by means of tissue-culture cytotoxicity assay is considered the "gold standard" for diagnosis, but results for such tests may take up to 3 days.

Treatment typically involves cessation of the offending antibiotic, initiation of oral metronidazole or vancomycin therapy, and fluid replacement.[1] In severe cases the colon may perforate, necessitating colectomy. In a recently published series of cases from Quebec,[2] 25.4% of patients with *C. difficile* (68/298) who had an elevated leukocyte count or creatinine level experienced complications (megacolon, perforation, shock or colectomy); of these, 19% died within 30 days of diagnosis.

Prevention: Active and passive immunization (with intravenous immune globulin therapy) is undergoing evaluation for use in the treatment of relapsing cases of *C. difficile*.[1]

Preventing nosocomial transmission of *C. difficile* depends on careful attention to isolation and barrier precautions, cleaning of the physical environment all through the symptomatic period of the disease, and handwashing.[4] Correct handwashing involves a 2-minute scrub with soap to remove the surface layer of skin oil (which holds spores), followed by hand-drying with a disposable paper towel.

After a series of *C. difficile*–associated deaths in Quebec, the provincial government responded by introducing more intensive surveillance, and the Public Health Agency of Canada (see www.phac-aspc.gc.ca/c-difficile) initiated a 6-month surveillance study in teaching hospitals across the country.

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CMAJ

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Eczema drugs tacrolimus (Protopic) and pimecrolimus (Elidel): cancer concerns

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Reason for posting: Many patients with eczema, or atopic dermatitis, are prescribed the topical immunomodulators tacrolimus and pimecrolimus. The drugs are often given to people for whom the potential side effects of topical corticosteroids (e.g., systemic absorption, skin thinning, telangiectasia) are a concern. However, the US Food and Drug Administration (FDA) recently reviewed the safety of these agents and warned that they may be associated with a risk of cancer.[1]

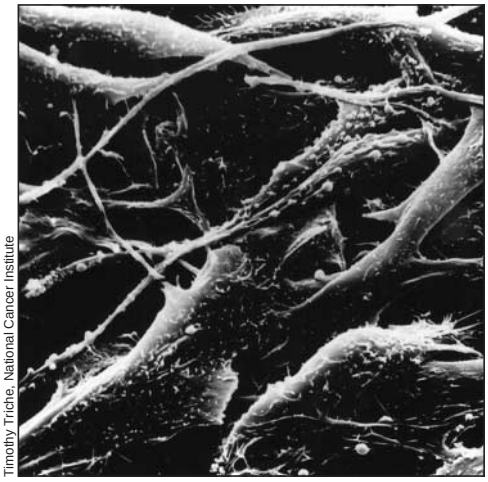
The drugs: Tacrolimus and pimecrolimus bind and inactivate calcineurin (a calcium- and calmodulin-dependent serine and threonine phosphatase) and may act by inhibiting T-lymphocyte activation, down-regulating numerous interleukins, interferon-γ, granulocyte-macrophage colony-stimulating factor and tumour necrosis factor-α, and affecting the function of mast cells, basophils and Langerhans cells.

Both agents are more effective than placebo in treating atopic dermatitis. Tacrolimus (0.03% and 0.1% preparations) is more effective than mild topical steroids, and the 0.1% preparation is as effective as more potent topical steroids.[2] In contrast, pimecrolimus is less effective than potent steroids (0.1% betamethasone valerate), but its efficacy relative to mild corticosteroids is unclear.[2]

Common adverse effects include mild, local, temporary burning or pruritus, and users may have increased risk of local varicella-zoster virus infection, herpes simplex infection and eczema herpeticum. Children under the age of 2 receiving topical pimecrolimus had higher rates of respiratory tract infections than children receiving the placebo.[1]

Lymphadenopathy, usually transient and related to underlying infections, has been reported. However, patients taking systemic tacrolimus (as an immunosuppressive agent after liver and organ transplantation) have reported lymphomas and solid organ tumours, possibly because their defences against cancer have been suppressed.[3] Only small amounts of the drugs are usually absorbed through the skin; however, some children given topical tacrolimus have blood levels of the drug similar to those given its systemic form.[1]

Animals (mice, rats, monkeys) given high doses of the drugs topically or orally have a risk of cancer that is dependent on both the duration and dose of the drug.[1,3] Long-term safety trials involving humans have not been done.



Timothy Triche, National Cancer Institute

Melanoma

Causative associations are uncertain, but the FDA is also reporting the cases of several patients in whom cancer developed after drug use. For tacrolimus, 19 cases of cancer were reported, involving 16 adults and 3 children under the age of 16. The cancers were diagnosed 21–790 days after the start of therapy (the median time to diagnosis was 150 days). Nine cases involved lymphomas, and 10 involved skin

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tumours (7 at the site of the drug application). Tumour types included squamous cell carcinoma, cutaneous sarcoma and malignant melanoma. For pimecrolimus, 10 postmarketing cases of cancer were reported, involving 4 children (3 less than 6 years of age) and 6 adults. Of the 10 cases, 6 involved cutaneous tumours and 4 were lymphomas. Diagnoses were made 7–300 days after treatment was started (median time to diagnosis was 90 days).

What to do: As second-line agents, these drugs should be used only if other therapies (topical corticosteroids, emollients) are ineffective or inappropriate. They should not be used by patients with weakened or compromised immune systems, by children under the age of 2 or by patients with active viral skin infections. Short-term or intermittent use is advised. Unfortunately, atopic dermatitis is an uncomfortable, common and chronic condition. Patients should be warned of the potential cancer risk and carefully monitored clinically when taking the drugs. Any patient with nonresolving lymphadenopathy should be appropriately investigated. The lowest concentration of the drugs needed to control a patient's symptoms should be used. Unnecessary and potentially harmful ultraviolet exposure (from the sun and tanning beds) should be avoided.

Eric Wooltorton
Associate Editor, *CMAJ*

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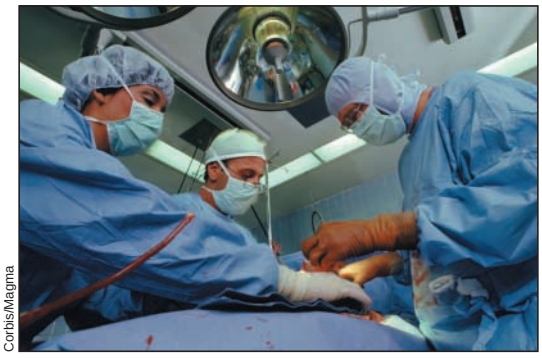
IN THE LITERATURE

Does coronary revascularization before major vascular surgery decrease mortality?

McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351(27):2795-804.

DOI:10.1503/cmaj.050289

Background: Evidence gathered over the last 30 years has permitted stratification of patients undergoing noncardiac surgery into categories of high, intermediate and low cardiac risk[1–3] and clarified the effectiveness of medical interventions, principally β-blockers, in reducing perioperative complications.[4] However, until now, the benefit of preoperative coronary revascularization (through percutaneous angioplasty or bypass surgery) has not been studied in a randomized trial. Guidelines recommend conservative management for patients with stable coronary artery disease and low-risk coronary anatomy,[5] but practice variation occurs. This randomized trial is therefore an important addition to an evidence-based approach to the management of such patients.



Corbis/Magma

Design: This study enrolled 510 patients from 18 US Veterans Affairs medical centres (98% male) between 1997 and 2003. Subjects were scheduled for elective vascular surgery (33% for an expanding abdominal aneurysm, 67% for symptomatic arterial occlusive disease of the legs). To receive cardiac catheterization, patients had to be deemed at increased risk of perioperative cardiac complications by a cardiologist. Those who had angiographic evidence of stenosis greater than 70% in at least 1 coronary artery were eligible. Exclusion criteria included severe coexisting illness, previous revascularization without evidence of recurrent ischemia, stenosis greater than 50% of the left main coronary artery, a left ventricular ejection fraction of less than 20% and severe aortic stenosis. Patients were randomly assigned to coronary artery revascularization (CAR) before surgery or to no revascularization. Percutaneous coronary intervention was performed on 59% of the patients and coronary artery bypass surgery on 41%. The primary end point was long-term mortality, with a minimum follow-up of 1 year and a median follow-up of slightly over 2.5 years.

Results: Of the study patients, 74% demonstrated a moderate or large reversible defect on stress imaging or were considered to be at intermediate or high cardiac risk according to the criteria of Eagle[5] or Lee and associates.[2] Before vascular surgery, there were 10 deaths in the CAR group and 1 death in

the no-CAR group. However, 30-day mortality was similar in both groups (3.1% and 3.4% respectively). At a median of 2.7 years after randomization, mortality was 22% and 23% for the CAR and no-CAR groups respectively (relative risk 0.98, confidence interval 0.70–1.37). There were no differences in 30-day postoperative myocardial infarction rates between the 2 groups. Patients assigned to CAR had a significant delay before receiving their vascular surgery procedure. An attempt to identify whether high-risk subjects within the study group might benefit more from CAR revealed no significant findings.

Commentary: This large and well-designed randomized study provides strong evidence in support of the recommendation against prophylactic coronary revascularization in patients with stable coronary artery disease scheduled to undergo elective major vascular surgery.

The limitations of this study include its lack of generalizability given the predominance of male patients and exclusion of patients with known left main coronary artery disease, severe aortic stenosis and left ventricular dysfuntion. Further, although the study included patients who would be deemed high risk using clinical risk scores, it lacked sufficient power to determine whether the intervention would help them. Finally, the trial lacked long-term follow-up. As the authors note, previous work has shown that bypass surgery is superior to percutaneous intervention after 5 years among patients with multivessel disease and diabetes. It is possible that high-risk patients scheduled to undergo preoperative vascular surgery, particularly those with diabetes, may benefit from surgical revascularization. Confirming this would require a much more specific randomized trial.

Practice implications: The results of this study support current guidelines by providing strong evidence that prophylactic coronary revascularization before elective major vascular surgery does not improve long-term survival of patients with stable coronary artery disease. Clinicians should be reassured that patients with apparently stable coronary artery disease, who are appropriately treated with β-blockers, antiplatelet agents, angiotensin-converting-enzyme inhibitors and statins, do not require preoperative revascularization. Despite the plethora of coronary screening tests available for such patients, physicians should also be reassured that their clinical judgement may still be the most important tool in determining stability of coronary artery disease and which, if any, patients must be screened and by what method.

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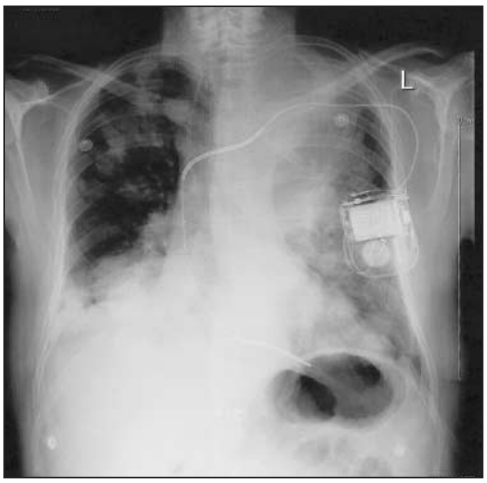
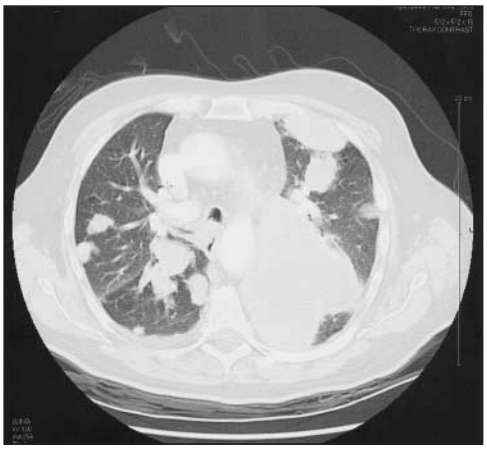
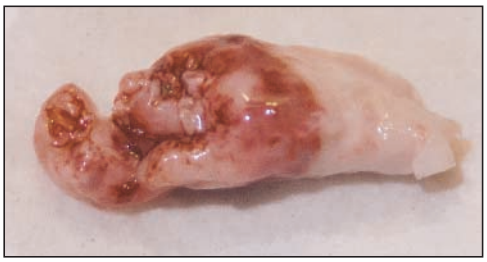
Spontaneous expectoration of lung tumour mass

DOI:10.1503/cmaj.045195

A 57-year-old man noticed a painless bluish mass enlarging on top of his right foot. Fine-needle aspiration and excisional biopsy showed a high-grade giant-cell variant of malignant fibrous histiocytoma. Because he had recurrence of the tumour at the initial excision site within 2 months, the patient opted for below-knee amputation without adjuvant radiation therapy. The surgical resection margins were free of tumour cells.







Unfortunately, the patient had increasing shortness of breath on exertion within 4 months after amputation. A chest CT showed bilateral pulmonary nodules consistent with metastases. He was admitted to hospital 5 months after the onset of shortness of breath for anthracycline-based chemotherapy. However, his left ventricular ejection fraction decreased, and therapy was switched to an ifosfamide-based regimen. Despite this, serial imaging showed enlarging nodules in the lung (Fig. 1 and Fig. 2), and hemoptysis developed 16 months after the start of chemotherapy. Along with bright red blood, the patient coughed up solid masses up to 5 cm in length (Fig. 3). Biopsy of the expectorated masses confirmed the radiologic diagnosis of metastatic malignant fibrous histiocytoma to the lung. The patient died in hospital within 2 months after the onset of hemoptysis.

Malignant fibrous histiocytoma is the most common soft-tissue sarcoma in adults,[1] occurring most often in the lower extremities. The tumour contains both histiocyte and fibroblast-like cells. There are many histologic subtypes, around which there are controversies in the literature. Variants include fibrous, giant-cell, myxoid and inflammatory.[2] The lung is the most common site of distant metastasis. Conservation surgery striving for negative margins along with adjuvant radiation therapy is the treatment of choice for local disease.[1] Distant metastasis, larger primary tumour (> 5 cm) and high-grade tumour are all negative prognostic factors.[3]

Originally described by Mackenzie in 1886,[4] expectoration of large fragments of lung tumour is rare.[5] It has been described in cases of endobronchial primary lung cancer and metastases from renal cell and colon carcinomas, osteogenic sarcoma and malignant melanomas.[5] More recently in the era of AIDS, coughing up sections of tumour has been seen in patients with Kaposi's sarcoma and lymphoma.[6] Spontaneous expectoration of metastatic malignant fibrous histiocytoma is exceptionally rare.

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Outcomes in octogenarians undergoing coronary artery bypass grafting

Roger Baskett, Karen Buth, William Ghali, Colleen Norris, Tony Maas, Andrew Maitland, David Ross, Rand Forgie, Gregory Hirsch

Abstract

Background: Although octogenarians are being referred for coronary artery bypass grafting (CABG) with increasing frequency, contemporary outcomes have not been well described. We examined data from 4 Canadian centres to determine outcomes of CABG in this age group.

Methods: Data for the years 1996 to 2001 were examined in a comparison of octogenarians with patients less than 80 years of age. Logistic regression analysis was used to adjust for preoperative factors and to generate adjusted rates of mortality and postoperative stroke.

Results: A total of 15 070 consecutive patients underwent isolated CABG during the study period. Overall, 725 (4.8%) were 80 years of age or older, the proportion increasing from 3.8% in 1996 to 6.2% in 2001 (p for linear trend = 0.03). The crude rate of death was higher among the octogenarians (9.2% v. 3.8%; $p < 0.001$), as was the rate of stroke (4.7% v. 1.6%, $p < 0.001$). The octogenarians had a significantly greater burden of comorbid conditions and more urgent presentation at surgery. After adjustment, the octogenarians remained at greater risk for in-hospital death (odds ratio [OR] 2.64, 95% confidence interval [CI] 1.95–3.57) and stroke (OR 3.25, 95% CI 2.15-4.93). Mortality declined over time for both age groups (p for linear trend < 0.001 for both groups), but the incidence of postoperative stroke did not change (p for linear trend = 0.61 [age < 80 years] and 0.08 [age ≥ 80 years]). Octogenarians who underwent elective surgery had crude and adjusted rates of death (OR 1.31, 95% CI 0.60-2.90) and stroke (OR 1.59, 95% CI 0.57-4.44) that were higher than but not significantly different from those for non-octogenarians who underwent elective surgery.

Interpretation: In this study, rates of death and stroke were higher among octogenarians, although the adjusted differences in mortality over time were decreasing. The rate of adverse outcomes in association with elective surgery was similar for older and younger patients.

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The population is rapidly aging, and an increasing number of octogenarians are being referred for coronary artery bypass grafting (CABG).[1,2] Previous single-centre reports from Canada[3–5] and from abroad[1,2,6–8] have concluded that elderly patients undergoing cardiac surgery have worse outcomes than younger patients. In addition, these studies have reported higher costs and slower recovery for octogenarians undergoing CABG, a finding that has generated debate over the appropriate use of health care resources.[1,5,7,9]

It has become increasingly clear that the results of CABG among octogenarians, although worse than among younger patients, are better than for percutaneous coronary interventions or medical therapy alone when the extent of the patient's coronary disease is such that revascularization with CABG is indicated.[10,11] Similarly, the superior results of percutaneous coronary intervention relative to medical therapy in elderly patients with coronary disease will likely continue to increase the total number of octogenarians undergoing coronary angiography, which in turn will probably increase the number of patients being referred for CABG.[10,12] Contemporary outcomes for octogenarians undergoing CABG in Canada have not been well described. If we are to have an informed debate and determine appropriate policy, it is important for these outcomes to be known.

We aimed to describe the characteristics and outcomes of patients 80 years of age and older undergoing CABG in Canada and to compare their outcomes with those of younger patients. In addition, we examined changes in results over time.

Methods

The study group included all consecutive patients undergoing isolated CABG from 1996 to 2001 at 4 Canadian centres (in Edmonton, Calgary, Saint John and Halifax). Patients undergoing CABG associated with heart valve repair or replacement, resection of a ventricular aneurysm or other surgical procedures were excluded. All patient data were collected prospectively according to definitions provided in the Society of Thoracic Surgeons database.[13] Data for the following variables were collected: age, sex, year of surgery, centre, urgency (elective, urgent [medical condition dictates that the patient must remain in hospital until surgery can be performed] or emergent [the clinical condition requires that surgery be performed without delay]), ejection fraction, diabetes, chronic obstructive pulmonary disease, hypertension, preoperative renal insufficiency, congestive heart failure, history of cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, reoperative surgery and critical left main stenosis. The outcomes of interest were in-hospital death and stroke, the latter defined as a new, permanent neurologic deficit.

Basic χ^2 and t tests were used to compare the prevalence of preoperative risk variables in octogenarians and non-octogenari-

ans, as well as the incidence of death and stroke. Rates of death and stroke were predicted for various patient groups and compared over time by means of analysis of variance. Trends in outcomes over time were compared with the Cochran–Mantel–Haenszel test (p trend). Logistic regression techniques were used for multivariate analysis and for the calculation of adjusted rates of the outcomes for octogenarians and younger subjects.[14] Age was used as a categorical variable, with patients under 70 years of age as the reference group (other categories: 70–74 years, 75–79 years, 80 years or older). Ethics approval was obtained from all centres involved in this study.

Results

From 1996 to 2001, a total of 15 070 consecutive patients underwent isolated CABG at the 4 centres; of these, 725 (4.8%) were 80 years of age or older. Compared with the younger patients, the octogenarians had a significantly greater burden of comorbidity and more urgent presentation at surgery (Table 1). In particular, a greater proportion of the octogenarians had renal insufficiency, cerebrovascular disease, peripheral vascular disease, critical left main stenosis and heart failure. The only risk factor with greater prevalence in the younger age group was diabetes mellitus (Table 1).

The proportion of patients undergoing CABG who were octogenarians increased over time, from 3.8% in 1996 to 6.2% in 2001 (p for linear trend = 0.03).

The crude rate of death was higher among the octogenarians (9.2 v. 3.8%; $p < 0.001$). In multivariate analysis, age of at least 80 years was significantly and independently associated with increased odds of death (odds ratio [OR] 2.64, 95% confidence interval [CI] 1.95–3.57) (Appendix 1). The overall adjusted mortality (for all years combined) was significantly higher for the octogenarians (6.65% v. 3.92%; $p < 0.001$). Over time, the crude mortality decreased in both age groups. After adjustment for differences in patient populations over time, mortality declined significantly over the period of the study (for patients less than 80 years of age, p trend < 0.001; for patients 80 years of age and older, p trend < 0.001) (Fig. 1). The gap in adjusted mortality between the older and the younger patients appeared to narrow over time (Fig. 1).

Postoperative stroke occurred in 4.7% of the older patients and 1.6% of the younger patients ($p < 0.001$). Overall, the older patients had a significantly greater risk of stroke (multivariate analysis: OR 3.25, 95% CI 2.15–4.93) (Appendix 1). In contrast to the rate of death, the crude incidence of stroke did not change significantly over the period of the study, ranging from 2.4% to 7.8% among the older patients and from 1.2% to 1.8% among the younger patients. Multivariate analysis indicated no significant change in the incidence of stroke over time for either older or younger patients (p = 0.61 and 0.08 respectively for trend over time) (Fig. 2). For all years combined, the adjusted stroke rates were 1.7% for the younger patients and 3.3% ($p < 0.001$) for the older patients. However, there was marked variation from year to year in the adjusted stroke

Table 1: Comparison of patient characteristics for octogenarians and non-octogenarians

Variable	< 80 yr *n = 14 345*	≥ 80 yr *n = 725*	*p* value
Sex (% female)	3092 (21.6)	264 (36.4)	< 0.001
Urgency			< 0.001
Elective	6332 (44.1)	181 (25.0)	
Urgent	7364 (51.3)	484 (66.8)	
Emergent	635 (4.4)	59 (8.1)	
Ejection fraction, %			0.80
< 30	650 (4.5)	31 (4.3)	
30–50	3776 (26.3)	201 (27.7)	
> 50	9151 (63.8)	458 (63.2)	
Missing	768 (5.4)	35 (4.8)	
Comorbid conditions			
Diabetes mellitus	4212 (29.4)	179 (24.7)	0.007
COPD	1653 (11.5)	88 (12.1)	0.62
Hypertension	8624 (60.1)	446 (61.5)	0.47
Congestive heart failure	1709 (11.9)	166 (22.9)	< 0.001
Preoperative renal insufficiency	486 (3.4)	71 (9.8)	< 0.001
Cerebrovascular disease	1382 (9.6)	127 (17.5)	< 0.001
Peripheral vascular disease	1928 (13.4)	141 (19.4)	< 0.001
Previous MI	8349 (58.2)	456 (62.9)	0.01
Other factors			
Reoperative surgery	691 (4.8)	50 (6.9)	0.01
Critical left main stenosis	3236 (22.6)	227 (31.3)	< 0.001

Note: COPD = chronic obstructive pulmonary disease, MI = myocardial infarction.

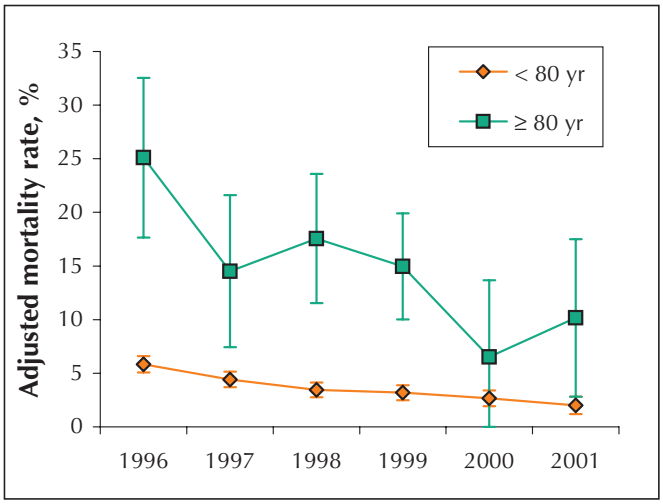

Fig. 1: Adjusted mortality over time (with 95% confidence intervals). For patients less than 80 years old, p for linear trend < 0.001; for those 80 years of age and older, p for linear trend < 0.001. The rates were adjusted for the following variables: centre, sex, urgency, presence of diabetes, preoperative renal failure, ejection fraction, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, heart failure, previous myocardial infarcation, redo surgery, left main disease; age and year of surgery were excluded.

rate for the older patients (Fig. 2).

Our data demonstrated that surgery was urgent or emergent for a large proportion of the octogenarians and that the rate of death in this group was higher than we had expected or predicted from the data. A comparison of crude outcomes stratified by age and urgency of surgery showed a marked interaction between these 2 variables (Table 2). The octogenarians had only a slightly greater risk for adverse events when undergoing elective surgery than the younger patients (3.9% v. 2.9% for death, 1.9% v. 1.2% for stroke). In contrast, the octogenarians requiring urgent CABG had a substantially greater rate of death than those undergoing elective surgery (10.3% v. 3.9%), as well as a markedly greater stroke rate (5.4% v. 1.9%) (Table 2). In a multivariate analysis using an interaction term for age group and urgency, octogenarians undergoing elective CABG had only a slightly, and nonsignificantly, greater risk of death (OR 1.31, 95% CI 0.60–2.90) or stroke (OR 1.59, 95% CI 0.57–4.44) than non-octogenarians undergoing elective surgery (Table 3).

Interpretation

The proportion of patients undergoing CABG who were 80 years of age or older increased steadily over the period of this study. We also found that octogenarians who were undergoing isolated CABG had more comorbidities and greater clinical acuity than non-octogenarians. Rates of death were higher among the octogenarians, but decreased over time in both age groups, and there was evidence that the gap in outcomes between groups was decreasing. Risk-adjusted rates of postoperative stroke, meanwhile, remained generally steady over time, at higher levels among octogenarians than among non-octogenarians.

Notably, however, the greater risk of death and stroke for octogenarians was most pronounced among patients undergoing urgent procedures, whereas the differences were smaller for patients undergoing elective surgery.

Collectively, these findings highlight that CABG surgery for elderly patients is increasing in Canada and that operative mortality is decreasing. Our analysis stratified by surgical urgency demonstrates that CABG can be performed electively in octogenarians with outcomes approaching those of younger patients, which suggests that advanced patient age should not, in isolation, deter a decision to perform CABG when other clinical factors dictate a need for the procedure.

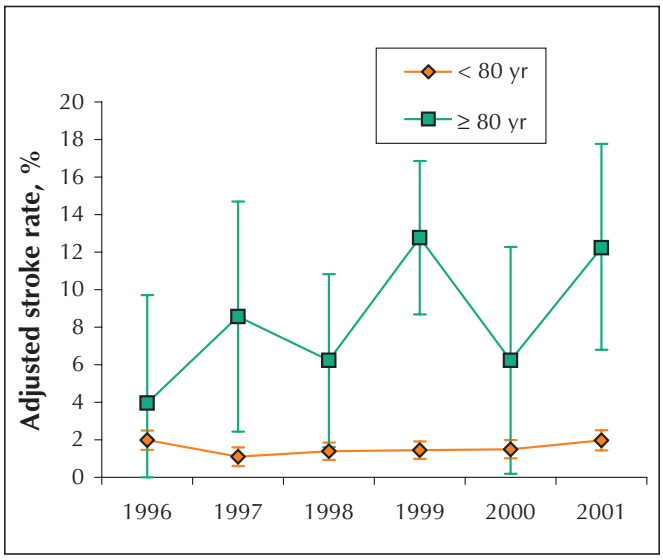

Fig. 2: Adjusted stroke rates over time (with 95% confidence intervals). For patients less than 80 years old, *p* for linear trend = 0.61; for those 80 years of age and older, *p* for linear trend = 0.08. The rates were adjusted for the following variables: centre, sex, urgency, presence of diabetes, preoperative renal failure, ejection fraction, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, heart failure, previous myocardial infarction, redo surgery and left main disease; age and year of surgery were excluded.

Table 2: Rates of death and stroke among patients, by age, related to the urgency of surgery

	Urgency; % of patients		
Age group, yr	Elective	Urgent	Emergency
Death			
< 70	2.2	2.9	9.8
70–74	3.8	4.9	16.5
75–79	6.6	6.8	16.9
All < 80	2.9	3.9	12.1
≥ 80	3.9	10.3	17.0
Stroke			
< 70	1.0	1.1	2.6
70–74	1.7	2.9	1.6
75–79	2.1	4.4	4.5
All < 80	1.2	1.9	2.7
≥ 80	1.9	5.4	6.8

Table 3: Adjusted* risks of death and stroke among patients, by age, according to the urgency of surgery

	Urgency; OR (95% CI)		
Age group, yr	Elective	Urgent	Emergency
Death†			
< 80	Reference	1.02 (0.84–1.24)	2.83 (2.90–3.85)
≥ 80	1.31 (0.60–2.90)	2.48 (1.74–3.52)	3.19 (1.45–6.99)
Stroke‡			
< 80	Reference	1.42 (1.06–1.89)	2.06 (1.19–3.58)
≥ 80	1.59 (0.57–4.44)	3.31 (2.04–5.36)	4.09 (1.36–12.29)

Notes: OR = odds ratio, CI = confidence interval.
*The following variables were included: sex, year of surgery, centre, ejection fraction, diabetes mellitus, COPD, hypertension, preoperative renal insufficiency, congestive heart failure, cerebrovascular disease, peripheral vascular disease, previous MI, reoperative surgery, critical left main stenosis, age–urgency interaction term.
†*C* statistic = 0.77.
‡*C* statistic = 0.72.

In a recent study from Hamilton, Ont., results for octogenarians were not worse than those for patients 70 to 79 years of age.[3] However, in contrast to the present study, the number of octogenarians was small (n = 71), and the patients' risks were generally lower than for the younger comparison cohort. In addition, the octogenarians accounted for only 3% of all patients from the centre, which indicates that this group of octogenarians was probably highly selected and of low surgical acuity.

The current study had a number of important limitations. Even with more than 15 000 patients and more than 700 patients who were octogenarians, the statistical power to assert that there was no significant difference in outcomes among elective patients was limited. However, the differences were relatively small for these patients and, overall, appeared to be diminishing over time.

In addition, this study included only patients who actually underwent CABG and did not compare outcomes in those with disease who underwent medical therapy alone or percutaneous coronary interventions. It has become clear from other research that elderly patients derive a substantial benefit from revascularization in terms of quality of life, reduction in major cardiac events and mortality.[10,12]

A more detailed examination of octogenarians undergoing urgent (i.e., nonelective) CABG, as well as the clinical management of these patients before surgery, is warranted to determine whether suboptimal timing of surgery contributes to the poor outcomes seen after urgent procedures.

This article has been peer reviewed.

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Competing interests: None declared.

Contributors: Roger Baskett was involved in the study design, data analysis and writing of the manuscript. Karen Buth designed and carried out most of the analysis and contributed to drafting the manuscript. William Ghali helped to design the study and analysis and contributed to drafting the manuscript. Colleen Norris and Andrew Maitland participated in data acquisition and interpretation. Tony Mass participated in the study design and data acquisition. David Ross was involved in the study design and data analysis; he also helped to draft the manuscript. Rand Forgie was involved in the study design and data interpretation. Gregory Hirsch was involved in the study design and data interpretation; he also helped in drafting the manuscript. All the authors were involved in revising the draft manuscript and gave final approval of the manuscript.

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Appendix 1: Variables in model for mortality and stroke

Mortality model (*C* statistic = 0.78)

Age (< 70 years, 70–74 years, 75–79 years, ≥ 80 years), sex, year of surgery, centre, urgency (elective, urgent, emergent), ejection fraction (< 30%, 30%–50%, > 50%), diabetes mellitus, chronic obstructive pulmonary disease, hypertension, preoperative renal insufficiency, congestive heart failure, cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, reoperative surgery, critical left main stenosis

Stroke model (*C* statistic = 0.75)

Age (< 70 years, 70–74 years, 75–79 years, ≥ 80 years), sex, year of surgery, centre, urgency (elective, urgent, emergent), ejection fraction (< 30%, 30%–50%, > 50%), diabetes mellitus, chronic obstructive pulmonary disease, hypertension, preoperative renal insufficiency, congestive heart failure, cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, reoperative surgery, critical left main stenosis

Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect

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Abstract

Background: Clinical trials have shown the benefits of statins after acute myocardial infarction (AMI). However, it is unclear whether different statins exert a similar effect in reducing the incidence of recurrent AMI and death when used in clinical practice.

Methods: We conducted a retrospective cohort study (1997–2002) to compare 5 statins using data from medical administrative databases in 3 provinces (Quebec, Ontario and British Columbia). We included patients aged 65 years and over who were discharged alive after their first AMI-related hospital stay and who began statin treatment within 90 days after discharge. The primary end point was the combined outcome of recurrent AMI or death from any cause. The secondary end point was death from any cause. Adjusted hazard ratios (HRs) for each statin compared with atorvastatin as the reference drug were estimated using Cox proportional hazards regression analysis.

Results: A total of 18 637 patients were prescribed atorvastatin (n = 6420), pravastatin (n = 4480), simvastatin (n = 5518), lovastatin (n = 1736) or fluvastatin (n = 483). Users of different statins showed similar baseline characteristics and patterns of statin use. The adjusted HRs (and 95% confidence intervals) for the combined outcome of AMI or death showed that each statin had similar effects when compared with atorvastatin: pravastatin 1.00 (0.90–1.11), simvastatin 1.01 (0.91–1.12), lovastatin 1.09 (0.95–1.24) and fluvastatin 1.01 (0.80–1.27). The results did not change when death alone was the end point, nor did they change after adjustment for initial daily dose or after censoring of patients who switched or stopped the initial statin treatment.

Interpretation: Our results suggest that, under current usage, statins are equally effective for secocondary prevention in elderly patients after AMI.

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Randomized controlled trials (RCTs) have shown that the use of statins after acute myocardial infarction (AMI) are effective in reducing the incidence of both fatal and nonfatal cardiovascular events.[1–8] Although these trials have significantly influenced post-AMI treatment,[9–12] it remains unclear whether all statins are equally effective in preventing recurrent AMI and death. Drugs in the same class are generally thought to be therapeutically equivalent because of similar mechanisms of action (class effect).[13–15] However, in the absence of comparative data, this assumption requires evaluation. Statins differ in multiple characteristics, including liver and renal metabolism, half-life, effect on other serum lipid components, bioavailability and potency.[16–19] These differences could potentially influence the extent to which the drugs are beneficial. Despite limited evidence in support of a differential benefit of statins for secondary prevention, preferential prescribing already occurs in practice and cannot be fully explained by the existing evidence or guidelines.[20] Comparative data of statins are thus required to inform health care decision-making.

A number of RCTs have directly compared statins using surrogate end points, such as lipid reduction,[21–23] markers of hemostasis and inflammation[24–26] or reduction in number of atherotic plaques.[27] However, the extent to which these results can be extrapolated to clinically relevant outcomes remains to be established. The newly released PROVE IT–TIMI 22 trial[28] was the first trial to compare 2 statins for cardiovascular prevention. The study showed that atorvastatin used at a maximal dose of 80 mg (intensive therapy) was better than pravastatin at a dose of 40 mg (standard therapy) in decreasing the incidence of cardiovascular events and procedures. The study was, however, conducted to show the benefit associated with increased treatment intensity. It did not compare the drugs by milligram-equivalent doses or by cholesterol-lowering equivalent doses. Moreover, no difference was detected when death alone or the combined outcome of death or AMI was evaluated. Other than the PROVE IT–TIMI 22 trial, few data are currently available from RCTs that compare statins for cardiovascular prevention.[29]

We conducted a population-based study to examine the relative effectiveness of different statins for long-term secondary prevention after AMI. We used retrospective cohorts of elderly patients prescribed statins after AMI in 3 provinces. Five statins were studied: atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin. The newest statin, rosuvastatin, was not available during the study period and was not considered in this study.

Methods

Three comparable AMI cohorts were created by using the linked hospital discharge databases and the physician and prescription claims databases in Quebec, Ontario and British Columbia. We used standardized inclusion and exclusion criteria as well as comorbidity information across provinces according to concurrent collaborations at the national level in cardiovascular outcome research.[30,31] Several validation studies have ensured the accuracy of coding in each province.[30,32,33]

Information regarding outpatient prescriptions and therapeutic procedures was obtained from the physician and prescription claims databases (the Ontario Drug Benefits database, the BC PharmaCare Program and the Régie de l'assurance maladie du Québec [RAMQ]). All patients aged 65 years and over receive free prescription coverage in Canada. Available prescription information included type, dosage, quantity and days of supply. Death information was obtained from provincial registry databases (Ontario Registered Persons, BC Vital Statistics and RAMQ). All data were linked by the patients' unique, encrypted health care insurance number.

Patients were included if they were 65 years or older, had their first recorded AMI-related hospital admission and were discharged alive between 1997 and 2001, and had their statin prescription filled within 90 days after discharge. All patients had AMI (ICD-9-CM[34] code 410) recorded as the most responsible diagnosis in the hospital discharge database (Canadian Institute for Health Information for Ontario and BC data, and Med-Echo [Maintenance et exploitation des données pour l'étude de la clientèle hospitalière] for Quebec data).

We excluded patients if they met any of the following criteria: the AMI was coded as an in-hospital complication; the AMI-related hospital admission was a transfer from another hospital (to avoid counting patients twice, yet all transfers related to the initial AMI admission were counted in the total length of hospital stay); the total length of hospital stay was less than 3 days (to exclude ruled-out AMI cases and those admitted only for procedures); the patient was discharged to a long-term care institution or a rehabilitation centre or moved out of the province; or the health care number was invalid. More details of the rationale for these criteria can be found elsewhere.[30,35]

Cohort enrolment began on Apr. 1, 1997, and ended on Mar. 31, 2001 (1 year before the end of the study to ensure a potential for at least 1-year follow-up for every patient). Follow-up for each patient was from the time of the first statin prescription (time 0) to the occurrence of a study end point or the end of the study period. On the basis of the first statin prescribed, 5 statin groups were formed (atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin). For statin usage patterns, we recorded the number of patients who switched or stopped the initially prescribed statin treatment. Stopping treatment was defined as discontinuation of the initial statin or the absence of a prescription for the initial statin 15 or more days after the end of the previous prescription. To indicate patient persistence on the treatment, we calculated the ratio of the total number of days supplied for the initial statin divided by the total number of follow-up days.

Patient demographic characteristics and comorbidities at discharge were determined from the hospital discharge databases. Comorbidities included coexisting cardiovascular and lung diseases, chronic kidney or liver conditions as well as diabetes mellitus, dementia and malignant disease. Concurrent use of major cardiac medications was also recorded. These drugs included β-blockers, angiotensin-converting-enzyme inhibitors, antiplatelet drugs (ASA, clopidogrel), calcium-channel blockers, diuretics, warfarin and digoxin. Use of statins during the year before the index AMI was included as a baseline covariate. Information was obtained regarding the in-hospital procedure performed (catheterization, percutaneous coronary intervention or coronary artery bypass graft surgery), length of hospital stay, time to first statin prescription, year of AMI, specialty of the treating physician (cardiologist, internist, general practitioner or other specialist), type of hospital (teaching or not), hospital volume, hospital location (urban or rural) and availability of cardiac catheterization facility in the hospital.

The primary end point was defined as a combined outcome of recurrent AMI or death from any cause, whichever occurred earlier. The secondary outcome was death from any cause.

Descriptive statistics were used to compare baseline patient characteristics between statin groups. A multivariate Cox proportional hazards model was used to assess the associations between type of statin used and time to study outcome. The proportional hazard assumption was assessed by a plot of log(–log(survival function)) versus time for both primary and secondary outcomes. The linearity assumption was assessed for continuous variables in the model, including age, length of hospital stay and time to first statin prescription. These variables were categorized if the linearity assumption was not met.

Analyses were performed in 2 ways. First, in an intention-to-treat analysis, patients were assumed to be taking the initial statin throughout follow-up. In a second analysis, patients were censored at the time of switching or stopping the initial statin. Adjusted hazard ratios (HRs) for each statin compared with the reference statin (atorvastatin) and 95% confidence intervals (CIs) were reported, with adjustment made for baseline characteristics and potential confounders. To examine the robustness of our results, we did several additional analyses. First, to assess the impact of statin dose, we adjusted for the initial daily dose of each statin by creating a binary variable "at or above target dose." We determined the target dose by referring to the cholesterol-lowering equivalent dose[21,36] as well as the dose tested in the large-scale RCTs of each statin for long-term cardiovascular prevention.[1,2,5,8,37–40] The target dose was set as 10 mg for atorvastatin and 40 mg for the other statins. The binary variable "at or above target dose" was subsequently adjusted in the Cox model. Second, results were stratified according to statin use (yes or no) before the index AMI to examine whether the effect depended on the history of statin use. Finally, to ensure that the results did not depend on the choice of the reference statin, a likelihood ratio test with 4 degrees of freedom (df) was performed with the hypothesis that all of the statins had the same effects.

We applied the same methods to the data from each of the 3 provinces. We then pooled the HRs for each statin (compared with atorvastatin) using a fixed-effects model, with weight being the inverse of the variance of the province-specific parameter estimate.[41] A test of heterogeneity was performed to examine the appropriateness of using a fixed-effects model to pool the estimates.[42]

Results

Of the 56 408 identified AMI patients, 18 637 (33.0%) had filled a prescription within 90 days after discharge for atorvastatin (n = 6420), pravastatin (n = 4480), simvastatin (n = 5518), lovastatin (n = 1736) or fluvastatin (n = 483).

The median follow-up was 2.3 (range 1–5, interquartile range 1.6–3.2) years.

A comparison of baseline demographic and clinical characteristics did not reveal any major differences across the statin groups (Table 1). Notable exceptions were that (a) lovastatin users tended to have more comorbidities and possibly a longer cardiac history, as suggested by greater use of diuretics and calcium-channel blockers and higher prevalence of congestive heart failure; and (b) fluvastatin was found to be prescribed more by general practitioners and less by cardiologists, and fluvastatin users were more often treated in rural hospitals and less often underwent revascularization procedures during the initial hospital stay. Nevertheless, a pattern of preferential prescribing of a particular statin to sicker or healthier patients did not emerge.

Table 1: Characteristics of elderly patients prescribed statins after acute myocardial infarction (AMI) in Quebec, Ontario and British Columbia

	Statin; weighted value*				
Characteristic	Atorvastatin *n = 6420*	Pravastatin *n = 4480*	Simvastatin *n = 5518*	Lovastatin *n = 1736*	Fluvastatin *n = 483*
Patient					
Age, median,† yr	72 (72, 72)	72 (71, 73)	73 (71, 73)	73 (72, 73)	72 (72, 73)
Sex, % male	59 (59, 62)	61 (59, 63)	61 (60, 64)	56 (50, 61)	57 (56, 59)
Comorbidity at baseline, %					
Hypertension	32 (27, 39)	31 (24, 37)	31 (29, 36)	32 (28, 41)	29 (26, 31)
Diabetes mellitus	25 (20, 27)	23 (19, 25)	23 (17, 24)	24 (20, 26)	25 (20, 29)
Congestive heart failure	20 (15, 21)	19 (13, 20)	20 (14, 22)	23 (17, 28)	18 (16, 22)
Cardiac dysrhythmia	15 (12, 18)	15 (12, 17)	15 (12, 18)	15 (13, 19)	13 (11, 16)
COPD	10 (6, 16)	11 (9, 17)	10 (9, 16)	11 (9, 16)	11 (6, 19)
Cerebrovascular disease	4 (1, 7)	5 (2, 8)	4 (2, 8)	5 (2, 8)	5 (2, 6)
Chronic renal failure	4 (1, 7)	5 (1, 7)	4 (1, 7)	4 (1, 9)	4 (1, 9)
Malignant disease	2 (1, 2)	2 (1, 2)	2 (1, 3)	2 (1, 2)	2 (1, 3)
Dementia	1 (1, 1)	1 (0, 1)	1 (0, 1)	1 (1, 1)	1 (0, 2)
In-hospital procedure					
Catheterization	30 (24, 47)	29 (21, 45)	28 (22, 42)	29 (17, 43)	26 (23, 33)
PCI	12 (8, 25)	12 (7, 22)	11 (6, 22)	12 (6, 23)	9 (5, 19)
CABG	4 (2, 11)	3 (1, 6)	4 (2, 8)	5 (2, 12)	5 (4, 6)
Length of hospital stay, median,† d	7 (7,9)	8 (7, 9)	8 (7, 9)	8 (7, 10)	8 (7, 9)
Cardiac medication (before first statin prescription)					
Nitrate	71 (62, 73)	71 (66, 74)	72 (68, 74)	69 (61, 74)	67 (66, 70)
β-Blocker	71 (65, 73)	67 (65, 67)	67 (62, 69)	63 (61, 64)	64 (55, 69)
ACE inhibitor	56 (45, 60)	52 (47, 55)	53 (45, 57)	49 (42, 51)	48 (42, 51)
Antiplatelet agent‡	54 (51, 64)	57 (54, 63)	54 (51, 61)	50 (47, 59)	55 (54, 57)
Diuretic	28 (22, 28)	28 (23, 29)	28 (23, 29)	33 (27, 35)	26 (23, 28)
Calcium-channel blocker	24 (22, 25)	24 (19, 24)	25 (19, 26)	30 (18, 35)	24 (22, 26)
Warfarin	12 (7, 16)	13 (12, 13)	13 (9, 13)	14 (11, 15)	14 (7, 20)
Digoxin	11 (9, 16)	12 (8, 14)	11 (10, 13)	14 (12, 17)	10 (6, 12)
Physician					
Cardiologist	39 (36, 48)	42 (37, 50)	40 (35, 48)	38 (34, 45)	27 (20, 32)
Internist§	35 (10, 41)	30 (9, 40)	36 (14, 43)	31 (10, 38)	35 (20, 44)
GP or other	26 (22, 41)	28 (23, 40)	24 (19, 37)	31 (21, 44)	38 (26, 41)
Hospital					
Teaching hospital	21 (5, 23)	17 (5, 20)	23 (7, 25)	21 (8, 27)	11 (4, 18)
Catheterization facility available	18 (14, 31)	23 (16, 37)	21 (18, 27)	25 (22, 34)	12 (10, 19)
Rural location¶	4 (4,6)	5 (4, 8)	4 (3, 6)	5 (5, 6)	11 (7, 15)

Note: COPD = chronic obstructive pulmonary disease, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery, ACE = angiotensin-converting enzyme, GP = general practitioner.
*Weighted proportion of patients, unless specified otherwise; numbers in parentheses represent the lowest and highest values for the 3 provinces.
†Weighted median; figures in parentheses represent the lowest and highest values for the 3 provinces.
‡Includes ASA and clopidogrel.
§Excludes cardiologist.
¶Defined as having 0 in the middle of the first 3 digits of the postal code (as per Canada Post definition).

Use of any statin within 1 year before the index AMI was similar for atorvastatin, pravastatin and simvastatin users but was more frequent among lovastatin and fluvastatin users (Table 2). No apparent delay in filling a first prescription was associated with any particular statin. The median duration of use of the initial statin during the first year of follow-up was similar across the statin groups (330–365 days) except for fluvastatin (307 days). This difference could be explained by the higher switching rates among fluvastatin users. On average, more than 85% of the patients in each group had initial statin prescriptions that covered at least 80% of the follow-up period.

The overall proportion of statin users who switched to a different statin during the first year of follow-up was low (7%), but increased to 21% by the end of follow-up. Among patients who switched, 55% switched to atorvastatin. Fluvastatin and lovastatin users had the highest rates of switching (Table 2). To assess whether switching to atorvastatin was related to a change in disease state, we examined the rates of hospital readmission because of cardiovascular causes and the rates of cardiac medication use from the first prescription to the time of switching and compared them between patients who switched to atorvastatin and those who switched to another statin. No significant difference in these rates was found. The overall proportion of patients who stopped statin treatment during follow-up was 11%, with similar percentages across the statin groups (Table 2).

In terms of the distribution of daily doses, we found that in most cases the statins were prescribed at their lower doses (10–20 mg) (Table 2), which are approximately equivalent in lowering cholesterol levels.[21] Very few subjects (0.7%) were prescribed the highest dose of each statin. For example, among the atorvastatin users, only 0.5% of them were prescribed an 80-mg dose. The proportion of patients who changed doses was low and was similar in the atorvastatin, pravastatin and simvastatin groups. The doses of fluvastatin and lovastatin changed less frequently (Table 2).

A total of 2924 patients either had an AMI or died. The unadjusted cumulative incidences of each outcome for each statin group are shown in Table 3. Patients in the lovastatin group appeared to be at higher risk of recurrent AMI or death compared with those in the other statin groups, although the difference was not statistically significant.

The results of the multivariate survival analysis are summarized in Table 4. Higher age, male sex and most major comorbidities were associated with increased risk, whereas cardiac procedures and use of some cardiac medications showed protection. Patients using diuretics, calcium-channel blockers and digoxin and patients who were using statins before the index AMI were at increased risk of AMI or death. This effect could be an indication of greater disease severity associated with use of these medications.[43] Hypertension did not appear to be a significant risk factor.

Table 2: Pattern of statin usage

Variable	Statin; weighted % of patients*				
	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Use of statin before index AMI†	33 (27, 37)	37 (32, 38)	35 (32, 40)	53 (37, 58)	42 (37, 50)
Time to first statin prescription after discharge, median,‡ d	3 (1, 4)	6 (1, 14)	3 (0, 15)	6 (0, 11)	9 (0, 12)
Duration of statin use in the first year, median,‡ d	364 (360, 365)	352 (330, 360)	360 (350, 365)	353 (330, 360)	307 (240, 342)
Persistence§	0.94 (0.87, 0.99)	0.94 (0.87, 1.00)	0.94 (0.87, 0.99)	0.94 (0.89, 1)	0.95 (0.88, 1)
Switched from initial statin					
During first year	3 (3, 3)	9 (8, 9)	6 (6, 7)	13 (12, 15)	17 (14, 23)
During follow-up	8 (8, 9)	29 (24, 31)	22 (22, 26)	41 (36, 43)	50 (42, 56)
Stopped statin treatment during follow-up	10 (9, 12)	10 (10, 12)	11 (10, 12)	12 (9, 13)	13 (10, 18)
Daily dose, median, mg¶	10 (10, 10)	20 (20, 20)	20 (20, 20)	20 (20, 20)	20 (20, 20)
Dose distribution					
10 mg	66	12	46	2	0.2
20 mg	28	71	47	82	75
40 mg	5	16	7	15	24
80 mg	0.5	0.6	0.4	1	0.8
Dose changed during follow-up					
Increased	13 (11, 14)	13 (11, 15)	13 (11, 14)	10 (10, 11)	11 (9, 11)
Decreased	5 (5, 6)	5 (4, 6)	6 (4, 6)	4 (3, 4)	3 (1, 4)

*Unless specified otherwise; numbers in parentheses represent the lowest and highest values for the 3 provinces.
†Any statin use within 1 year before the index AMI.
‡Weighted median; numbers in parentheses represent the lowest and highest values for the 3 provinces.
§Defined as the ratio of the total number of days supplied for the initial statin divided by the total number of follow-up days.
¶Median daily dose of statin initially prescribed after AMI. Starting and maintenance dose as recommended in the 2002 *Compendium of Pharmaceuticals and Specialties*: atorvastatin 10–20 mg; pravastatin 20–40 mg; simvastatin 10–40 mg; lovastatin 20–40 mg; fluvastatin 20–40 mg.

This could be due to the inclusion of anti-hypertensive medications in the risk adjustment model. A delay in initiating statin therapy appeared to be "protective"; however, this effect was due to a decreasing risk over time after discharge, which was independent of statin treatment effect. None of the physician and hospital characteristics was significantly associated with outcome. No apparent secular trend in the event rate was detected.

For all statins, the heterogeneity test of estimates (HRs) from the 3 provinces suggested a homogenous effect (all p values > 0.62, 2 df). The pooled adjusted HRs and 95% CIs for the combined outcome of recurrent AMI or death showed that each statin had similar effects when compared with atorvastatin (Fig. 1). Adjustment for initial daily dose of each statin according to whether it was "at or above target dose" did not materially change the results. Stratified analyses according to prior statin use did not affect the results, nor did restricting the outcome to death or censoring patients who switched or stopped the initial statin treatment. The likelihood ratio test confirmed the absence of any statistically significant difference in risk between patients prescribed different statins (p > 0.41, 4 df). Finally, we performed post hoc comparisons of (a) atorvastatin versus the other statins and (b) lovastatin versus the other statins. The latter comparison was done because the lovastatin group showed a slightly increased incidence of clinical end points. The results were unchanged in each comparison: HR for recurrent AMI or death was 0.98 (95% CI 0.90–1.07) for the comparison of atorvastatin with the other statins and 1.09 (95% CI 0.98–1.22) for the comparison of lovastatin with the other statins.

Interpretation

The results of our population-based study of commonly used statins suggest that individual drugs in the statin class exhibit a similar effect in reducing the incidence of recurrent AMI or death among elderly patients.

Individual statins have been shown in several studies to be of benefit in reducing the incidence of recurrent AMI and death among patients who have experienced an AMI. These studies included the 4S trial[1] (simvastatin), the CARE[2] and the LIPID trials[5] (pravastatin), and the GREACE[8] trial (atorvastatin). The benefit has also been evident in recent trials that enrolled subjects with and without prior cardiovascular diseases but who were at high risk of future cardiovascular events, including the HPS trial[38] (simvastatin) and the PROSPER trial[44] (pravastatin). In each trial, the statin was compared with a placebo. It is not evident whether the effect size observed across trials varied because of different trial characteristics or because the statins had truly different effects. The results of the PROVE IT–TIMI 22 trial suggested that a statin used at a high dose could provide additional benefits,[28] yet 80 mg of atorvastatin was not frequently prescribed in practice during our study period. Compared with the patients in our study, those in the PROVE IT–TIMI 22 trial were younger (mean age 58 years), mostly male (78%) and had less comorbidity and thus were more likely to tolerate a high dose of statin and experience the benefit. In our head-to-head comparison of 5 statins, we examined the relative effectiveness of the drugs in older patients with a more diverse risk profile, a population-based setting that is representative of daily practice.

Our study was a retrospective analysis of administrative databases, and thus several limitations merit discussion. First, because the patients studied were all receiving statin therapy, there is a lower likelihood of confounding by indication.[45] However, we could not control for all patient characteristics that may influence physicians' choice of statin. Unmeasured comorbidity as well as missing clinical data (e.g., cholesterol levels, location of MI) could confer residual confounding effects; however, there is no obvious reason that prescribing of different statins would be strongly influenced by these unmeasured characteristics. The analysis of available baseline characteristics did not suggest preferential prescribing of a particular statin to sicker patients. In addition, we controlled for the specialty of treating physician and the type of hospital, which could be associated with statin selection and intensity of therapy.

Table 3: Unadjusted cumulative incidence and rate of recurrent AMI and death from any cause during follow-up

	Statin; weighted value*				
Outcome	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Length of follow-up, median, yr	2.0	2.4	2.3	2.4	2.5
Recurrent AMI or death					
% of patients	19 (14, 21)	22 (16, 24)	23 (16, 25)	27 (20,31)	21 (17, 23)
Rate per 100 patient-years	11 (8, 12)	11 (7, 11)	11 (7, 11)	12 (9, 14)	10 (7, 10)
Death alone					
% of patients	13 (9, 15)	16 (10, 19)	16 (10, 18)	22 (12, 28)	13 (8, 17)
Rate per 100 patient-years	7 (5, 7)	7 (4, 7)	7 (4, 7)	9 (7, 10)	6 (4, 7)

*Weighted percentage of patients or weighted rate, unless specified otherwise; numbers in parentheses represent the lowest and highest values for the 3 provinces.

Table 4: Factors associated with recurrent AMI and death from any cause among elderly patients

Factor	Adjusted hazard ratio (and 95% CI)*
Statin prescribed initially	
Atorvastatin (reference)	–
Pravastatin	1.00 (0.90–1.11)
Simvastatin	1.01 (0.91–1.12)
Lovastatin	1.09 (0.95–1.24)
Fluvastatin	1.01 (0.80–1.27)
Baseline patient characteristics and comorbidities	
Age†	1.04 (1.04–1.05)
Male sex	1.19 (1.10–1.28)
Use of statin before index AMI‡	1.26 (1.16–1.36)
Length of hospital stay§	1.06 (0.98–1.15)
Time to first statin prescription¶	0.70 (0.64–0.77)
Hypertension	1.01 (0.93–1.09)
Diabetes	1.60 (1.46–1.75)
Congestive heart failure	1.51 (1.38–1.65)
Cardiac dysrhythmia	1.09 (0.98–1.20)
COPD	1.18 (1.06–1.32)
Cerebrovascular diseases	1.30 (1.12–1.51)
Chronic renal failure	1.71 (1.49–1.97)
Malignant disease	1.97 (1.59–2.44)
Dementia	1.29 (0.93–1.80)
In-hospital procedure	
Catheterization	0.76 (0.67–0.87)
PCI	0.60 (0.48–0.74)
CABG	0.33 (0.23–0.47)
Cardiac medication (before first statin prescription)	
Nitrate	1.00 (0.92–1.09)
β-Blocker	0.83 (0.77–0.90)
ACE Inhibitor	1.08 (0.99–1.16)
Antiplatelet agent	0.88 (0.82–0.94)
Diuretic	1.46 (1.34–1.59)
Calcium-channel blocker	1.21 (1.12–1.32)
Warfarin	1.03 (0.92–1.14)
Digoxin	1.28 (1.16–1.42)
Physician and hospital characteristics	
Cardiologist	0.98 (0.90–1.07)
Teaching hospital	1.08 (0.95–1.22)
Catheterization facility available	0.98 (0.87–1.10)
Hospital volume**	0.87 (0.41–1.85)
Year of index AMI admission	
1997–1998 (reference)	–
1998–1999	1.04 (0.95–1.15)
1999–2000	1.06 (0.95–1.18)
2000–2001	1.05 (0.92–1.20)

Note: CI = confidence interval.
*Adjusted hazard rates and 95% CIs for each statin (compared with atorvastatin) were calculated from the data for the 3 provinces and then pooled using a fixed-effects model, with weight being the inverse of the variance of the province-specific estimates.
†Effect of age was linearly related to the outcome, hence "Age" was modelled as a continuous variable.
‡Any statin use within 1 year before the index AMI.
§Length of hospital stay was dichotomized at 7 days; < 7 days was the reference category.
¶Time to first statin prescription since discharge was dichotomized at 30 days after discharge; < 30 days was the reference category.
**Hospital volume was dichotomized at the third quartile (Q3); Q1–Q3 was the reference category.

Second, unlike patients in RCTs, those in actual practice start statin treatment at different points after discharge and may experience more changes in use over time. Our analysis showed a similar time-to-first statin prescription across the 5 statin groups. This similarity reduced concerns about a potential initial survival advantage associated with a particular statin. In addition, patients were observed to have a high persistence on the statin initially prescribed. To account for switching and stopping treatment, we censored patients at the time they changed exposure status, and the results were unchanged. Nevertheless, the concern would be whether an excess proportion of this switching was related to worsening of clinical status. Our comparison of patients who switched to atorvastatin with those who switched to another statin by rates of hospital readmission and cardiac medication use before switching did not suggest a "channeling over time" due to a change of disease state.[46]

Third, the statins were used at low doses all within the range of starting and maintenance doses recommended in the *Compendium of Pharmaceuticals and Specialties*. These doses were comparable based on cholesterol-lowering equivalents.[21] Our adjustment for initial daily dose according to whether it was "at or above target dose" did not affect the results. This adjustment reduced the likelihood of confounding by dose. However, the lack of information on patients' cholesterol levels limited our ability to study the effect of statin dose on cholesterol levels. The observed pattern of prescribing low doses also limited our ability to compare statins at their upper dose limits. The accumulation of new data that reflect possible practice changes of prescribing statins at higher doses[28] will help to answer this question.

Fourth, our follow-up period was shorter than that in large-scale RCTs of statin therapy. However, the RCTs would have required a longer follow-up to see an effect because they enrolled only stable patients 3–6 months after AMI. Our study patients were included immediately after their discharge from hospital and thus were at higher risk of recurrent AMI or death. Early initiation of statin therapy after AMI has been found to be beneficial.[47] The PROVE IT–TIMI 22 trial, which enrolled patients within 10 days after experiencing an acute coronary syndrome and randomly assigned them to receive either standard or intensive statin therapy, observed a difference between the 2 treatment arms after 6 months and at the end of the trial (follow-up 1.5 to 3 years, mean 2 years).[28] Accordingly, our median follow-up of 2.3 years and maximum of 5 years is of reasonable length to detect possible differences in outcomes.

Fifth, because we studied all-cause mortality in an elderly cohort followed for several years, death from other causes may have been an issue. However, most of the deaths in the study population occurred relatively soon after the index AMI, and therefore we more than likely captured cardiac-related deaths. Also, we adjusted for major

morbid conditions in elderly patients, including dementia, malignant disease, congestive heart failure and chronic renal failure.

Sixth, we used prescription claims as a proxy for actual statin use. However, given that the data represented filled prescriptions instead of written prescriptions, and that the patients refilled their prescriptions regularly, it was likely that the patients were compliant.

Finally, although the conclusion toward the effect of lovastatin and fluvastatin should be more conservative because of the relatively low number of patients prescribed these agents, the point estimates of the relative effects between statins were all in the neighborhood of 1.0, and the accompanying 95% CIs were narrow. If we consider a range of 10%–20% relative difference in hazard ratios as the region of clinical equivalence, we have good evidence to declare equivalence among these statins.

In conclusion, our study provides evidence that, under current usage, statins are equally effective for the secondary prevention of AMI in elderly patients.

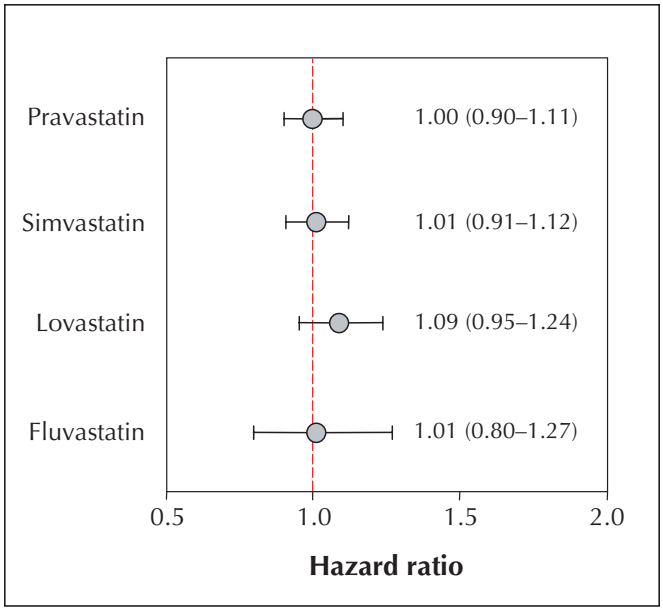

Fig. 1: Pooled adjusted hazard ratios and 95% confidence intervals (error bars) for the combined outcome of recurrent acute myocardial infarction (AMI) or death from any cause among elderly patients prescribed statin therapy after an AMI. Atorvastatin is the reference drug. Hazard ratios were adjusted for age, sex, statin use before the index AMI, hypertension, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, chronic renal failure, dementia, malignant disease, in-hospital procedures (catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery), cardiac medications (β-blockers, angiotensin-converting-enzyme inhibitors, nitrates, antiplatelet agents, calcium-channel blockers, diuretics, warfarin, digoxin, fibrates), specialty of treating physician, hospital type, length of hospital stay, time to first prescription and year of index AMI.

This article has been peer reviewed.

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Contributors: Zheng Zhou prepared the manuscript and, with Louise Pilote and Elham Rahme, was responsible for the study design and the analysis and interpretation of the data. Louise Pilote, Elham Rahme, Jack Tu, Karin Humphries, Michal Abrahamowicz, Mark Eisenberg and Peter Austin participated in the development of the study concept, the acquisition of data (Ontario data: Tu and Austin; Quebec data: Pilote, Rahme, Abrahamowicz and Eisenberg; BC data: Humphries) and critical revision of the manuscript for important intellectual content. Peter Austin contributed to the analysis of Ontario data. All of the authors approved the final version of the manuscript for publication.

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Are the benefits of statins a class effect?

James M. Wright

ß See related article page 1187

In general we have to be cautious about basing prescribing decisions on the results of cohort studies. When physicians prescribed hormone replacement therapy to postmenopausal women in the 1990s for the prevention of coronary artery disease, they made a mistake. That is because their decision was based on the Nurses' Health cohort study[1] and other cohort studies.[2] In 2002 the Women's Health Initiative randomized trial[3] demonstrated that, compared with placebo, combined estrogen–progestin therapy increased the risk of coronary artery disease (hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.02–1.63).

In some instances, however, cohort studies provide accurate findings, and it is reasonable to base prescribing decisions on them. I believe that the cohort analysis in this issue (page 1187) is one of those instances. The article by Zhou and associates[4] reports on the effectiveness of 5 statins in elderly patients in 3 Canadian provinces and provides good evidence that the important outcomes are the same for the different statins. This represents evidence in favour of a class effect for the statins. The reasons the findings of this cohort analysis are likely telling us the truth include the following: First, the 5 well-defined cohorts are remarkably similar in terms of comorbidities at baseline (see Table 1 in their article). Second, the outcomes of death and recurrent acute myocardial infarction (AMI) are easily identified in administrative databases and are those that matter to patients. Third, it is unlikely that there would be selection bias by physicians in choosing a statin. Fourth, the study was large enough to provide a precise estimate of the treatment effect (the 95% CIs are narrow and within a 10% range for pravastatin and simvastatin compared with atorvastatin). Finally, the results are consistent with those of indirect comparisons of different statins based on a systematic review of placebo-controlled randomized trials.[5]

The study by Zhou and associates provides critical information about how statins are prescribed in Quebec, Ontario and British Columbia. I was struck by the following findings: Only 33% of the patients with an AMI had filled a prescription for a statin within 90 days of discharge from hospital. Persistence with the statin was high among those who received it; only 11% who had filled a prescription for a statin stopped statin treatment during a median follow-up of 2.3 years. The median doses of statins prescribed were all at the lower end of the dose range (atorvastatin 10 mg, pravastatin 20 mg, simvastatin 20 mg, lovastatin 20 mg and fluvastatin 20 mg), which indicates that most physicians are conservative and cautious in prescribing these drugs. Very few patients had a dose increase or decrease.

I disagree with Zhou and associates on one important point. They conclude that the statin doses were similar based on cholesterol-lowering equivalents. That statement implies that the average magnitude of cholesterol-lowering effect in the 5 cohorts was similar. The authors mention that, since they did not have data on cholesterol measurements, it was impossible to directly answer that question. However, they ignore the fact that the median doses of the statins prescribed differ considerably in their ability to lower cholesterol. According to findings of a systematic review by Law and colleagues,[6] the expected average proportional reduction in low-density lipoprotein (LDL) cholesterol for the median doses taken by the patients in the study by Zhou and associates would be 37% for 10 mg of atorvastatin, 24% for 20 mg of pravastatin, 32% for 20 mg of simvastatin, 29% for 20 mg of lovastatin and 21% for 20 mg fluvastatin. This study, therefore, demonstrates that the benefit of statins is independent not only of which statin is prescribed, but also of the percentage reduction in LDL cholesterol over the range of 21%–37%. This confirms the findings in the largest statin trial to date, the Heart Protection Study, where the benefit expressed as relative risk (RR) was the same for the 3 tertiles of patients with different reductions in LDL cholesterol before randomization: less than 38% reduction (RR 0.78, 95% CI 0.71–0.85), 38%–47% reduction (RR 0.79, 95% CI 0.73–0.87), and 48% or greater reduction (RR 0.79, 95% CI 0.72–0.86).[7]

The results of Zhou and associates should not be extrapolated to the setting of primary prevention, where it is unclear whether the benefits of statins outweigh the harms.[8] The results probably can be extrapolated to patients with coronary artery disease other than a recent AMI and to patients with cerebrovascular disease or peripheral vascular disease. In the Heart Protection Study the treatment benefit of simvastatin was similar among patients with prior coronary artery disease (RR 0.79, 95% CI 0.74–0.85), those with prior cerebrovascular disease (RR 0.79, 95% CI 0.66–0.95) and those with prior peripheral vascular disease (RR 0.81, 95% CI 0.71–0.91).[7] It is also likely that the results are not specific for patients 65 years and older. In the Heart Protection Study the benefit among patients less than 65 years old (RR 0.77, 95% CI 0.71–0.83) was similar to that among older patients (RR 0.80, 95% CI 0.75–0.85).[7]

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The only exception to this extrapolation is perhaps for patients with acute coronary syndrome. In the recently reported PROVE IT–TIMI 22 randomized controlled trial,[9] 2 statins were compared at different cholesterol-reducing doses: at 30 days after the start of treatment, atorvastatin 80 mg and pravastatin 40 mg reduced LDL cholesterol by 51% and 22%, respectively. At 2 years, the event rate of the composite outcome of death from any cause or major vascular event was lower with atorvastatin than with pravastatin (22.4% v. 26.3%; HR 0.84, 95% CI 0.74–0.95). As can be appreciated by the wide confidence intervals and the fact that the findings from the PROVE IT–TIMI 22 trial contradict the evidence from the Heart Protection Study, these findings need to be confirmed.

Since in most settings of secondary prevention it does not appear to matter which statin is prescribed in terms of benefit, does it matter in terms of cost? In fact, the cost does vary widely depending on the statin, the dose and whether the tablets are split to reduce cost. Using 2005 BC Pharmacare data, I have compared the average cost of the most commonly used doses of statins in terms of whether the pills are taken whole or whether larger-dose tablets are halved or quartered (Table 1). For whole pills, fluvastatin 20 mg is the least costly. If patients are willing to cut larger-dose tablets into halves, simvastatin and pravastatin are the least costly; those willing to cut tablets into quarters will find that simvastatin is a bargain. Since the costs of drugs do not vary greatly between provinces, the costs in other provinces will be similar to those in British Columbia.

Table 1: Average cost of the most frequently dispensed statin doses in British Columbia

Generic (brand) name of statin	Daily dose, mg	Daily cost, $*		
		Whole tablet or capsule	Half tablet	Quarter tablet
Atorvastatin (Lipitor)	10	1.80	1.10	0.60
	20	2.25	1.20	0.60
	40	2.40	1.20	NA
Fluvastatin (Lescol)	20	0.85	NA	NA
Lovastatin (Mevacor)	20	1.15	1.05	NA
Simvastatin (Zocor)	10	1.20	0.75	0.35
	20	1.45	0.75	0.35
	40	1.45	0.75	NA
Pravastatin (Pravachol)	20	1.15	0.70	NA
Rosuvastatin (Crestor)	10	1.45	0.90	0.55

Note: NA = not applicable (fluvastatin capsules cannot be cut; required tablet sizes are not available).
*Average pill cost. Source: BC Pharmacare 2005 data.

In summary, this is an important cohort study that demonstrates that, among patients who have experienced an AMI, the incidence of recurrent AMI or death from any cause is similar for 5 different statins at doses that achieve different magnitudes of LDL reduction. This evidence provides physicians with an opportunity to reduce costs to patients and the health care system while still achieving optimal health outcomes for their patients.

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A death in the family

Reflections on the Terri Schiavo case

Charles Weijer

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Terri Schiavo, a 41-year-old Florida woman who was in a persistent vegetative state for the 15 years before her death on Mar. 31, 2005, was at the centre of a political, legal and media tempest over the removal of a feeding tube. Hyperbole has run high on both sides of the controversy. Religious conservatives have decried the removal of her feeding tube as a "mortal sin"; defenders of a "right to die" have claimed that "Congress will now go trampling into the most, private, personal and painful decisions families must make."[1] At the centre of the storm lay Terri Schiavo, her husband and her parents — all grievously struck by tragedy 15 years ago. Unable to agree on how to move forward, Schiavo's husband and parents sought remedy in the courts.

On Feb. 25, 1990, Terri Schiavo suffered a cardiac arrest caused by hypokalemia induced by an eating disorder.[2] Severe anoxic encephalopathy ensued. Several months after the incident, computed tomography revealed severe atrophy of both cerebral hemispheres, and electroencephalography showed no evidence of cortical activity. Clinically, Schiavo stabilized into a persistent vegetative state, a state of eyes-open unconsciousness with sleep–wake cycles in which patients are unaware of themselves or their environment. Despite the poor prognosis for meaningful neurologic recovery, standard and experimental therapies were administered, to no effect, for 3 years. Only then did her husband, Michael Schiavo, accept the diagnosis of her neurologists that her condition was irreversible. Recalling a statement that his wife had once made — "I don't want to be kept alive on a machine" — he refused further life-sustaining measures on her behalf.[2] However, her parents, Bob and Mary Schindler, never accepted the diagnosis of persistent vegetative state and vigorously opposed their son-in-law's decision. Seven years of litigation generated 30 legal opinions, all supporting Michael Schiavo's decision on his wife's behalf.[3]

Now that Terri Schiavo's life has drawn to a close, we might ask what lessons can be learned from this sad case. How ought decisions to be made on behalf of those in persistent vegetative states? How ought we to deal with families who disagree as to the right decision in these cases?

Adults capable of making their own decisions have an unfettered right in Canada and the United States to refuse unwanted medical treatment, including the provision of artificial nutrition and hydration.[3] When an adult is no longer able to make decisions for himself or herself, a surrogate decision-maker must take over that role. Although details of the law vary from province to province, the surrogate decision-maker is typically the spouse, adult child, parent or other close relation of the incapable patient. The law protects incapable adults by constraining the scope of surrogate decision-making. The surrogate must decide as the patient himself or herself would have decided, on the basis of previous statements or expressed values, or, should these not be known, in the best interest of the patient. Thus, consent or refusal by a surrogate decision-maker is in itself insufficient without a clear justification.

I have argued before in the pages of *CMAJ* that legitimate decisions on behalf of patients in a persistent vegetative state may differ from case to case.[4] Many — perhaps most — Canadians would not wish to have their life preserved by artificial means in a persistent vegetative state. When these wishes are expressed in a living will or in informal statements to family members or friends, or reflected more generally in the life values of the patient, the surrogate decision-maker may reasonably infer that the patient would not have wished his life prolonged by artificial means and accordingly refuse such treatment. Thus, as reflected by the unanimity of legal decisions, Michael Schiavo properly discharged his obligations as his wife's surrogate decision-maker when he refused the artificial provision of nutrition and hydration on the basis that she had stated to him in the past, "I don't want to be kept alive on a machine."

However, in some cases patients have a deep religious commitment to preserving life. Relying on a living will, previously expressed statements or the religious beliefs of the patient, the surrogate may with equal legitimacy decide in favour of continuing life-preserving interventions. Within the bounds of available resources, this decision also ought to be respected.[4] Most difficult are cases in which the wishes of the patient are unknown and a determination must be made purely in the best interests of the patient.

Bioethics commentary on the Terri Schiavo case has been, as one would expect, prominent in the media in re-

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cent weeks. The overwhelming message from bioethicists is that widespread use of living wills would prevent disputes like this from happening. For instance, Dr. Linda Emanuel said on *The NewsHour with Jim Lehrer* that "living wills are for everyone. They are analogous in many ways to a safety belt. They don't solve everything but they certainly minimize the damage."[5] Although living wills can usefully clarify the wishes of a patient who has become incompetent, they suffer from a number of limitations. First, living wills are limited by our inability to fully anticipate future medical circumstances. Such documents lack specificity, and therefore they require the assistance of family members to be interpreted. Just as Terri Schiavo's family disagreed as to the accuracy of the medical diagnosis, it is also possible that they would have disagreed as to how to interpret provisions in a living will in the event that Terri Schiavo had executed one. Second, only a minority of the population possess living wills. Although the case of Terri Schiavo will certainly inspire some to fill out living wills, it seems a safe bet that few in their second or third decade of life — the group most likely to survive grievous injury and enter a persistent vegetative state — will do so.

Bioethics commentators have missed an important moral question posed by the Terri Schiavo case, namely, how to deal with familial disagreement. Families commonly disagree over how best to care for a loved one, and no doubt there will be future cases in which families in similarly unfortunate circumstances are faced with the challenge of preventing disagreement or managing it when it occurs. Families share a bond in which each member has a duty to care for the others.[6] Legal solutions to cases of familial dispute are inherently divisive because they rest on the procedural solution of privileging one family member as "the decision-maker." Accordingly, they ought to be invoked only as a last resort. When a patient is incapable of directing his or her own care, regular meetings between the health care team and the family have a dual effect: they ensure that everyone has the same information, and they affirm the participation of all in the decision-making process. If a dispute arises, it is important to affirm the legitimate moral role played by all family members in seeking what is best for their loved one. Giving the family time to seek consensus on their own, trials of therapy with clear treatment goals, negotiation and arbitration can all be used to facilitate consensus. Some familial disputes will, in the end, require a legal solution. As the case of Terri Schiavo illustrates all too clearly, such solutions come at a potentially heavy cost: the double tragedy of a death in a family, and the death of a family.

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Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training

Barbara J. Nicklas, Tongjian You, Marco Pahor

Abstract

PERSISTENT LOW-GRADE INFLAMMATION, as indicated by higher circulating levels of inflammatory mediators such as C-reactive protein, interleukin-6 and tumour necrosis factor-α, is a strong risk factor for several chronic diseases. There are data indicating that decreasing energy intake and increasing physical activity may be effective therapies for reducing overall inflammation. Evidence is strong that circulating levels of inflammatory markers are elevated with total and abdominal obesity, possibly owing to a higher secretion rate of cytokines by adipose tissue in obese people. Moreover, very-low-energy dietary weight loss reduces both circulating markers of inflammation and adipose-tissue cytokine production. Data from several large population-based cohorts show an inverse association between markers of systemic inflammation and physical activity or fitness status; small-scale intervention studies support that exercise training diminishes inflammation. Dietary weight loss plus exercise is likely more effective than weight reduction alone in reducing inflammation. To date, data from randomized, controlled trails designed to definitively test the effects of weight loss or exercise training, or both, on inflammation are limited. Future studies are required to define the amount of weight loss needed for clinically meaningful reductions of inflammation; in addition, fully powered and controlled studies are necessary to clarify the effect of exercise training on chronic, systemic inflammation.

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The biologic cascade of events that form the body's natural defenses against injury or infection is a vital part of the immune system. Ordinarily, this process is an acute response resulting in rapid, major increases in inflammatory mediators released into the circulation.[1,2] In healthy, lean, non-elderly people, for example, blood concentrations of the acute-phase reactant C-reactive protein (CRP), which are normally less than 2 mg/L in men[3] and less than 2.5 mg/L in women,[4] can increase more than 1000-fold in response to infection or trauma.[2,5,6]

Typically, a CRP value of 10 mg/L or more is considered indicative of clinically significant inflammation.[7] However, recent evidence indicates that persistent elevations in circulating markers of inflammation, even when within the clinically normal range, are risk factors for cardiovascular disease in both middle-aged[8–13] and older[14–19] people. Recently, the US Centers for Disease Control and Prevention and the American Heart Association have stated that people with CRP values in the upper tertile of the adult population (> 3.0 mg/L) have a risk of cardiovascular disease that is double that of people whose CRP concentrations are less than 1.0 mg/L.[20] In addition to CRP, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), along with several other acute-phase reactant proteins, cytokines and cytokine-soluble receptors, are strongly associated with increased risk for several chronic diseases, including cardiovascular disease,[12,17,21,22] diabetes mellitus[23,24] and disability.[25,26] IL-6 and TNF-α are both stimulators of CRP release from hepatocytes.[27,28] It is not yet known which of these factors might be the most robust indicator of underlying inflammation, or whether the effects of these biomarkers are additive for risk prediction.

As illustrated in Figure 1, behavioural factors are associated with chronic, low-grade states of inflammation (as measured by slightly elevated inflammatory biomarkers), and therefore with the several chronic diseases that are associated with inflammatory states. Since the risk estimates associated with elevated inflammation appear to be linear (e.g., the CRP category cut-offs for assessment of cardiovascular disease risk[20] are low risk < 1.0 mg/L, medium risk 1.0–3.0 mg/L and high risk > 3.0 mg/L), behavioural interventions that produce even slight reductions in inflammation may have clinically significant benefits. A few pharmacologic interventions such as use of angiotensin-converting-enzyme inhibitors and statins decrease inflammation, as evidenced by lowered CRP concentrations in prospective clinical trials.[29–32] Moreover, there are very promising data suggesting that decreasing body weight and increasing physical activity are just as effective as medication for reducing overall inflammation. The published effects of behavioural interventions involving weight loss and exercise training on inflammatory markers are reviewed here.

Role of adiposity and weight loss in regulating inflammation

Evidence from observational studies

The association between excess adipose tissue (measured either indirectly by body mass index [BMI] or directly by body composition assessment) and elevated CRP concentrations[33–51] has been observed to hold for children,[36,40,45] elderly

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people[14,50] and people with metabolic syndrome,[49] diabetes[48] and heart disease.[52] In fact, obesity may account for a large portion of variation in circulating CRP concentrations; in a population-based study involving healthy, middle-aged women,[35] for example, BMI explained 30% of the variance in CRP concentrations. In an analysis[33] of the Third National Health and Nutrition Examination Survey, the proportion of people with a CRP level above 10 mg/L (the traditional clinical level suggestive of infection) was 20% in obese women, but only 4% in women whose weight was within the normal range. Obese participants were more likely than participants of normal weight to have an elevated CRP level, by an odds ratio of 2.13 for men (95% confidence interval [CI] 1.56–2.91) and 6.21 for women (95% CI 4.94–7.81).[33] Similarly, in a study involving 1929 middle-aged men and women,[49] 15% of obese participants had a CRP level above 10 mg/L, compared with only 3% of normal-weight people.

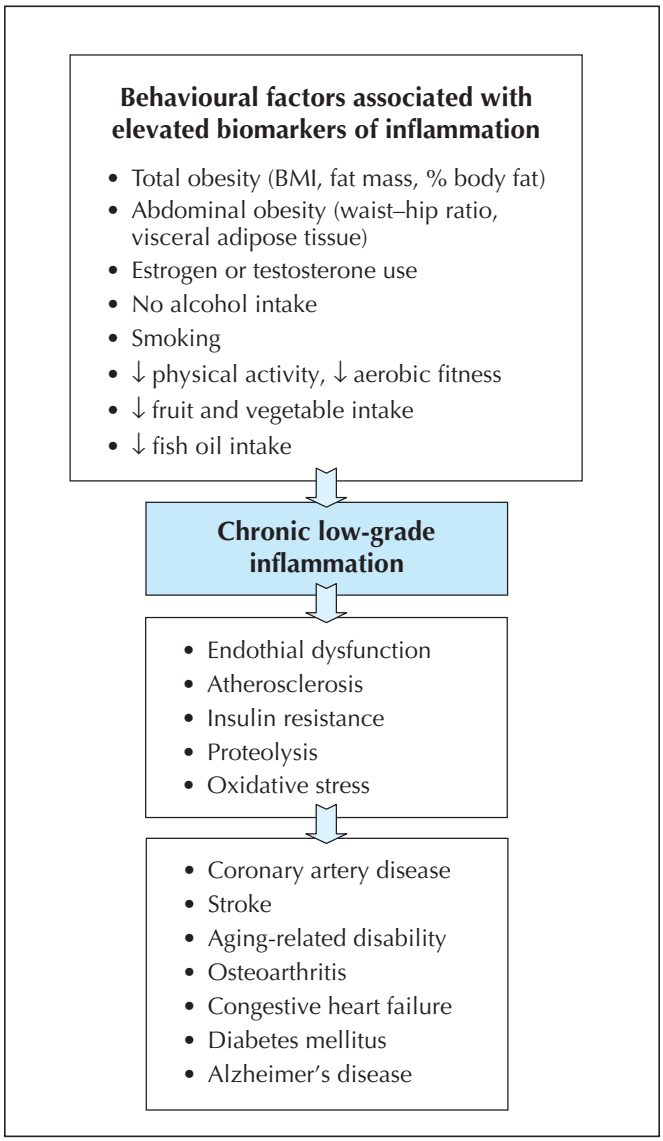

Fig. 1: Reported behavioural factors associated with chronic subclinical inflammation, and diseases and adverse health conditions for which inflammation is a risk factor. ↓ = decreased; BMI = body mass index.

Other inflammatory markers, including the cytokines IL-6,[34,53–60] TNF-α,[34,58,59,61–65] TNF-α receptors,[57,60,63,66–68] IL-8,[69,70] IL-18[56,58,59,71] and IL-1 receptor antagonist,[72,73] are elevated in obese people. Haptoglobin and serum amyloid protein A, both proteins involved in the acute-phase response to inflammation, have also been shown to circulate in higher concentrations in people with more body fat.[74–76] The sample sizes in these studies are smaller and typically not population-based, but across these studies the data are consistent. In an interesting study[63] involving identical twins discordant for obesity (the average difference in body weight between twin pairs was 18 kg), levels of TNF-α and soluble TNF-α receptor 2 (sTNFR2) were higher in obese than in lean twins, which suggests that obesity rather than other genetic factors is a major determinant of these inflammatory markers.

Lastly, there is some evidence from observational studies involving both men and women that, in addition to total body fat, visceral (abdominal) body fat may be an independent predictor of inflammatory markers.[37,38,43,44,64,77,78] In 2 studies[77,78] the amount of visceral fat was a better determinant of CRP levels than other measures of obesity, including fat mass. The location of body fat, independent of total amount, is therefore an important factor affecting chronic inflammation.

Adipose tissue is known to be a secretory organ producing cytokines, acute-phase reactants and other circulating factors.[79–81] The source of these "adipokines" is likely not the adipocyte itself, but the infiltration of inflammatory cells (macrophages) into adipose tissue.[82,83] In vivo release of IL-6 and TNF-soluble receptors from subcutaneous abdominal adipose tissue has been shown to correlate with BMI and body-fat proportion.[84] Moreover, TNF-α gene and protein expression in both subcutaneous and visceral adipose tissue are greater in obese than in lean people.[85,86] In one in-vitro study[87] TNF-α release from abdominal subcutaneous adipose tissue was 7.5-fold higher in tissue from obese (BMI 30–40 kg/m^2) than lean (BMI > 25 kg/m^2) subjects.[87] Ouchi and associates[81] reported not only that CRP is expressed in adipose tissue, but also that CRP and adiponectin mRNA levels are highly inversely related. (Adiponectin is a protein with anti-inflammatory properties.)

Thus, both in vivo and in vitro studies confirm that adipose tissue expression and release of cytokines are elevated in people with a higher adipose mass.

Evidence from intervention studies

The hypothesis that an expanded adipose-tissue mass contributes to an elevated state of chronic inflammation is corroborated by data (summarized in Table 1) showing that weight loss reduces inflammation. Several markers of inflammation, including CRP, IL-6, IL-18, TNF-α and TNF-α receptors, are reduced after weight loss achieved through short-term intense dietary restriction,[53,88–91]

Table 1: Summary of published data on the effects of weight loss on systemic markers of inflammation

Author group and year of publication	Participants and mean BMI, kg/m^2	Intervention for weight loss	Duration	Magnitude of weight loss	Effects on inflammatory markers
Intense, short-term dietary restriction					
Xydakis et al[91] 2004	40 obese adults with metabolic syndrome BMI 38.9 ± 1.0	600–800 kcal/d very-low-calorie diet	4–6 wk	7.0% of weight	CRP ↓ 14%; no change in TNF-α
Heilbronn et al[89] 2001	83 obese women BMI 33.8 ± 0.4	Low-fat (15%), 1360 kcal/d energy-restricted diet	12 wk	7.9 kg	CRP ↓ 26%
Gallistl et al[90] 2001	49 obese children BMI 26.7 ± 1.4	908–1194 kcal/d energy-restricted diet	3 wk	5.2% of BMI, 3.1% of fat mass	IL-6 ↓ 49%
Bastard et al[53] 2000	14 obese women BMI 39.5 ± 1.1	941 kcal/d very-low-calorie diet	3 wk	5.3% of BMI, 8.5% of fat mass	IL-6 ↓ 17%; no change in CRP, TNF-α
Bastard et al[88] 2000	17 obese women BMI 39.9 ± 1.6	941 kcal/d very-low-calorie diet	3 wk	5.0% of fat mass	sTNFR1 ↓ 8%; no change in sTNFR2
Longer-term behavioural changes					
Marfella et al[58] 2004	67 obese pre-menopausal women BMI 36.5 ± 1.8	1300 kcal/d energy-restricted diet, increased exercise	12 mo	13.4% of weight	CRP ↓ 44%; IL-6 ↓ 62%; TNF-α ↓ 31%; IL-18 ↓ 30%
Seshadri et al[94] 2004	78 obese adults, 86% with diabetes or metabolic syndrome BMI 43.5 ± 1.3	≤ 30 g/d low-carbohydrate diet, *or*	6 mo	8.5 kg	CRP ↓ 12%
		500 kcal/d deficit energy-restricted diet	6 mo	3.5 kg	CRP ↓ 7%
Monzillo et al[93] 2003	24 obese healthy and diabetic adults BMI 36.7 ± 0.9	500 kcal/d deficit energy-restricted diet and moderate-intensity exercise	26 wk	7.0% of weight	IL-6 ↓ 41%; no change in TNF-α
Bruun et al[70] 2003	19 obese men BMI 38.7 ± 0.7	1000–1480 kcal/d energy-restricted diet	16 wk	14.7% of weight	IL-6 ↓ 24%; TNF-α ↓ 29%; IL-8 ↓ 30%
Tchernof et al[42] 2002	25 obese post-menopausal women BMI 35.2 ± 1.0	1200 kcal/d American Heart Association Step II diet	14 mo	15.6% of weight, 25% of fat mass, 36.4% of visceral fat	CRP ↓ 32%
Ziccardi et al[43] 2002	56 obese women BMI 37.2 ± 2.2	1300 kcal/d energy-restricted diet, increased exercise	12 mo	12.6% of BMI	IL-6 ↓ 47%; TNF-α ↓ 31%
Esposito et al[92] 2002	40 obese women BMI 36.4 ± 2.0	1300 kcal/d energy-restricted diet, behavioural and nutritional counselling	12 mo	12.4% of BMI	IL-18 ↓ 41%
Dandona et al[62] 1998	38 obese women BMI 35.7 ± 0.9	925–1150 kcal/d energy-restricted diet and increased aerobic exercise	1–2 yr	12.3% of weight	TNF-α ↓ 24%
Medication use or weight-loss surgery					
Vendrell et al[57] 2004	34 morbidly obese BMI 49.6 ± 1.0	Gastric bypass	6 mo	30% of weight, 62% of fat mass	IL-6 ↓ 59%; sTNFR1 ↓ 15%; no change in sTNFR2
Valsamakis et al[99] 2004	21 obese women BMI 46.0 ± 1.9	10–15 mg/d sibutramine	6 mo	5.4% of weight	CRP ↓ 10%
Laimer et al[65] 2002	20 obese women BMI 41.6 ± 1.2	Adjustable gastric banding	1 yr	27% of weight, 45% of fat mass	CRP ↓ 70%; no change in IL-6
Randomized, controlled trials: intervention group (versus control group)					
Esposito et al[56] 2003	120 obese women BMI 35.0 ± 2.3 (v. BMI 34.7 ± 2.4)	1300–1500 kcal/d energy-restricted Mediterranean-style American Heart Association Step I diet (v. normal diet)	2 yr	14.7% of weight (v. 3.2% of weight)	CRP ↓ 34%; IL-6 ↓ 33% (v. no changes in CRP, IL-6)
Nicklas et al[97] 2004	316 older adults BMI 34.5 ± 5.4 (v. BMI 34.2 ± 5.0)	Behavioural counselling to achieve and keep a 5% weight loss (v. normal diet)	18 mo	5.1% of weight (v. 1.8% of weight)	CRP ↓ 3%; IL-6 ↓ 11%; sTNFR1 ↓ 2%; no change in TNF-α (v. no changes)

Note: ↓ = decreased, BMI = mean body mass index ± standard error of the mean, CRP = C-reactive protein, IL = interleukin, TNF = tumour necrosis factor, sTNFR = soluble TNF-α receptor.

lated in subcutaneous adipose tissue after 28 days on a very-low-energy diet that resulted in a 6-kg loss of fat mass.[73] In another study involving obese women,[53] 3 weeks on a very-low-energy diet (3.9 GJ/d, 5% drop in BMI) reduced IL-6 protein content in subcutaneous abdominal adipose tissue by 22%, with a corresponding 15% decrease in circulating levels. Interestingly, moderate dietary restriction (a deficit of 2.5 GJ/d for 10 weeks, for a 7.5% weight loss) reduced IL-6 mRNA in abdominal adipose tissue by 35% and its secretion rate by 30%, but decreased circulating IL-6 levels by only 6%.[100] Moreover, weight loss through caloric restriction reduced TNF-α gene[87,101,102] and protein expression[87] in, and TNF-α release from, abdominal adipose tissue.[102]

The effects of weight loss on adipose-tissue expression or secretion of CRP[81] are still unreported. More studies are needed to determine whether reductions in adipose-tissue production of inflammatory biomarkers is one mechanism by which weight loss reduces overall chronic inflammation.

Role of physical activity and fitness in regulation of inflammation

Evidence from observational studies

Although acute bouts of exercise are well known to increase concentrations of pro-inflammatory cytokines and acute-phase reactants,[103] chronic (regular, long-term) physical training may reduce basal concentrations of inflammatory markers. Table 2 summarizes the data from cross-sectional observational studies, which show an inverse association between markers of systemic inflammation and physical activity and fitness status.[50,104–112] Several studies of large population cohorts, including the British Regional Heart Study,[106] the Third National Health and Nutrition Examination Survey,[108,111] the Cardiovascular Health Study,[105] the men's Health Professionals Follow-up Study,[109] the Nurses' Health Study II[109] and the Health, Aging and Body Composition Study (Health ABC),[50] provide evidence for an inverse, independent dose–response relation between plasma CRP concentration and level of physical activity in both men and women.

This relation does not seem to alter with age: Of the 5888 participants in the Cardiovascular Health Study,[105] those older and younger than 72 years showed similar associations; and among people 70–79 years old enrolled in Health ABC,[50] trends for decreased IL-6, TNF-α and CRP concentrations were linear with increasing amounts of reported exercise. In the British Regional Heart Study,[106] even moderate physical activity (i.e., some vigorous activity at least once per week) in middle-aged men was associated with a 37% reduction in the number who had a high CRP concentration (> 4.27 mg/L). The relation was similar in men with and without prior heart disease.[106] A dose-

Table 2: Summary of published data on associations between systemic markers of inflammation and physical activity or fitness

Author group and year of publication (study name)	No. of participants (sex ratio)	Age, yr	Association between physical activity and inflammatory markers	Independent of obesity?
Colbert et al[50] 2004 (Health, Aging and Body Composition Study)	3075 (49% male)	70–79	↑ min/wk exercise ⇒ ↓ CRP, IL-6, TNF-α ↑ non-exercise PA ⇒ ↓ CRP, IL-6	Yes, for IL-6 only
Albert et al[112] 2004 (Pravastatin Inflammation/CRP Evaluation [PRINCE])	2833 (61% male)	60 ± 12	↑ frequency of PA ⇒ ↓ CRP in men only; no PA–CRP relationship in women	Yes
Jankord et al[114] 2004	12 men	60–74	Very active ⇒ ↓ IL-6; less active ⇒ ↑ IL-10	Not assessed
Pischon et al[109] 2003 (HPFS and NHS II)	HPFS: 405 men NHS: 454 women	40–75 25–42	↑ metabolic equivalent-hours/wk ⇒ ↓ CRP, IL-6, sTNFR1, sTNFR2	No
Reuben et al[110] 2003 (MacArthur Studies of Successful Aging)	870 (47% male)	70–79	↑ recreational activity ⇒ ↓ CRP, IL-6 ↑ house or yard work ⇒ ↓ CRP, IL-6	Yes
King et al[111] 2003 (NHANES III)	4072 (50% male)	>17	Jogging or aerobic dancing >12 times/mo protective for CRP >3 mg/L	Yes
Rawson et al[113] 2003	109 (57% male)	49 ± 12	CRP not related to current physical activity or to physical activity during previous year	No
Wannamethee et al[106] 2002 (British Regional Heart Study)	3810 men	60–79	↑ volume of PA ⇒ ↓ CRP (no PA ⇒ 2.29 mg/L; vigorous PA ⇒ 1.54 mg/L)	Yes
Church et al[107] 2002 (Aerobics Center Longitudinal Study)	722 men	51 ± 10	↑ cardiorespiratory fitness ⇒ ↓ CRP	Yes
Abramson et al[108] 2002 (NHANES III)	3638 (51% male)	>40	More frequent exercise ⇒ ↓ CRP	Yes
Geffken et al[105] 2001 (Cardiovascular Health Study)	5888 (42% male)	≥65	↑ kcal/wk of physical activity ⇒ ↓ CRP	Yes
Taaffe et al[104] 2000 (MacArthur Studies of Successful Aging)	880 (47% male)	70–79	↑ h/yr moderate–strenuous PA ⇒ ↓ CRP, IL-6	Yes

Note: ↑ = increased, ⇒ = led to, HPFS = Health Professionals' Follow-up Study, NHANES III = Third National Health and Nutrition Examination Survey, NHS II = Nurses' Health Study II, PA = physical activity; other symbols and abbreviations as defined in Table 1.

longer-term behavioural changes involving reduced energy intake and increased physical activity,[42,43,54,58,62,92–94] approved medication use[95] or surgical gastric bypass.[57,64] Results for liposuction are contradictory: Although one such study[99] resulting in a mean weight loss of 3 kg found concentrations of IL-6, IL-18, TNF-α and CRP to be reduced after a 6-month period of weight stability, another[96] in which fat mass was reduced by 9.8 kg on average found IL-6, TNF-α and CRP concentrations to be unaltered 10–12 weeks after the surgery. The effects of weight loss through liposuction for reducing inflammation thus require further investigation.

Most of the dietary weight-loss studies showed the magnitude of decrease in inflammatory markers to be linearly related to the amount of weight lost. For example, when CRP concentrations were reduced from 3.1 mg/L (standard deviation [SD] 0.7 mg/L) to 1.6 (SD 0.8) mg/L in postmenopausal women who followed a 14-month individualized weight-loss program,[42] the reductions correlated with changes in body weight and fat mass. Decreases in CRP, IL-6, IL-18 and TNF-α in a group of premenopausal women after a 10% weight reduction correlated with changes in BMI but were more strongly related to changes in waist–hip ratio.[43,58] Those women were healthy, without diabetes or metabolic syndrome, and their mean reduction in CRP (from 3.4 [SD 0.7] to 1.9 [SD 0.2] mg/L) mimicked the mean reported in healthy women by Tchernof and coauthors.[42] In other studies, weight loss reduced CRP levels (from 5.0 [SD 0.5] to 4.3 [SD 0.5] mg/L) in women with metabolic syndrome,[91] and IL-6 concentrations (2.75 [SD 1.51] to 2.3 [SD 0.91] pg/mL) in women with insulin resistance.[93]

To date, only 2 randomized controlled trials[56,97] have examined the effects of dietary weight loss on inflammation. Esposito and coworkers[56] compared obese women enrolled in a behavioural counselling program designed to achieve a 10% weight reduction through monthly individualized advice on eating a low-energy Mediterranean-style diet and increasing physical activity with obese women in a control group who received no dietary advice. The 2-year intervention decreased BMI more in the women in the intervention group than in the control group (–5.2 v. –1.0 kg/m^2) and reduced serum concentrations of CRP, IL-6 and IL-18 to a greater degree as well. In the intervention group, the average CRP value decreased from 3.2 to 2.1 mg/L, and the changes in CRP, IL-6 and IL-18 were found to relate to changes in BMI. Because exercise was included in the behavioural weight-loss intervention tested in this study,[56] it is not possible to separate out the effects of the diet alone in producing these changes.

In a retrospective analysis of stored serum samples from a randomized clinical trial,[97] our earlier research team found that an 18-month diet-induced weight loss program resulted in significantly greater reductions in body weight (–5.1% v. –1.8%) and CRP, IL-6 and sTNFR1 concentrations than no weight-loss intervention in a control group of older, obese men and women with knee osteoarthritis (Fig. 2). Changes in sTNFR1, but not CRP and IL-6, correlated with changes in body weight. Although some of the participants randomly assigned to the weight-loss intervention were also randomly assigned to an exercise intervention, no interaction was found between weight loss and exercise training.[97]

In that prior study,[97] the decrease in CRP concentrations in people who underwent diet-induced weight loss was 1.54 mg/L on average, or 5.8%. In other studies, CRP values decreased 26% with a 10% weight loss[89] and fell 32%–34% with a 15%–16% weight loss.[42,56] These results suggest that there may be a dose–response effect between the degree of weight loss and its capacity to attenuate chronic inflammation. Unfortunately, no data are available on clinical manifestations of this decline in CRP concentrations, although a CRP reduction of about 15% after 1 year of statin use was shown to be associated with a lowered risk of coronary events.[98] Longitudinal studies are needed to determine whether a reduced incidence of cardiovascular disease and diabetes is associated with the decline in CRP concentrations seen with weight loss.

Mechanism of effect

One of the postulated mechanisms by which weight loss reduces circulating markers of inflammation is through a decrease in adipose-tissue cytokine production (Fig. 3). A handful of studies have investigated the effects of dietary weight loss on cytokine gene and protein expression in subcutaneous adipose tissue; most data indicate that local production of IL-6 and TNF-α is reduced upon weight loss. Recently, gene-expression profiling showed that pro-inflammatory genes were downregulated and anti-inflammatory genes upregu-

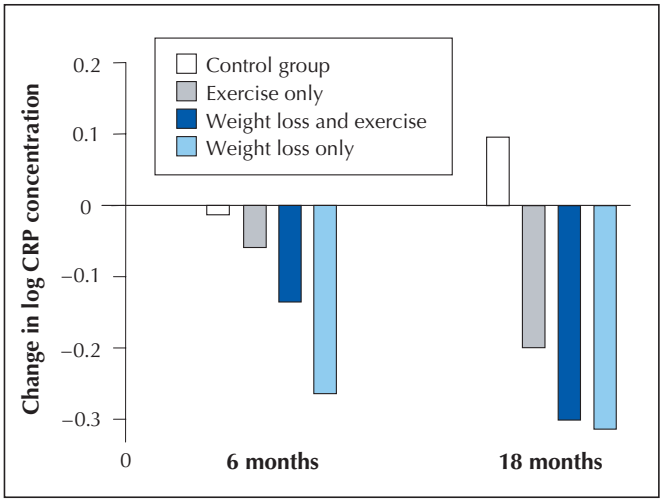

Fig. 2: Effects of 18 months of weight loss, exercise, or both upon mean CRP concentrations, adjusted for baseline BMI, baseline CRP level, sex and race. The treatment effect of dietary weight loss was significant compared with the control and exercise-only groups ($p = 0.01$). Modified from Nicklas et al (*Am J Clin Nutr* 2004;79:544-51), with permission.

response relation between CRP level and exercise was also seen at baseline in men, but not women, enrolled in the Pravastatin Inflammation/CRP Evaluation Study,[112] a finding that perhaps was confounded by the fact that the women were less likely than the men to be physically active.

In all of the studies described, the relations between inflammatory markers and physical activity were independent of differential levels of obesity. Contrary reports[109,113] do exist, but their results may reflect chance findings owing to their small samples.

Although CRP is the marker of chronic inflammation most frequently studied, both IL-6 and CRP concentrations have been shown in elderly men to be inversely correlated to reported amounts of moderate and strenuous exercise, even after adjustment for BMI.[104,109] Similar studies have shown this to be true for recreational activity and house and yard work[110,114] (although not consistently for IL-6[110]).

All of the studies mentioned relied on self-report to assess physical activity status. In a subsample of 722 men from the Aerobics Center Longitudinal Study, Church and

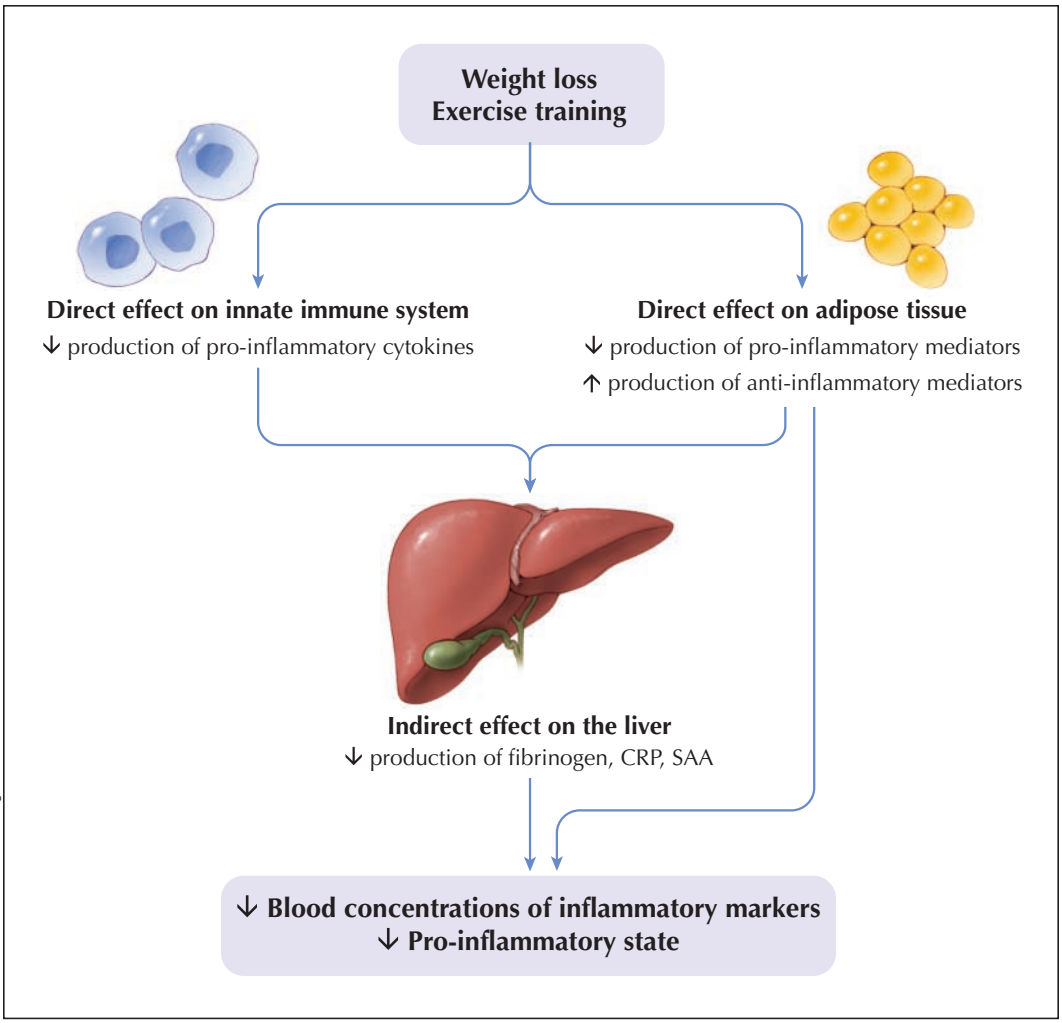

Fig. 3: Schematic of possible mechanisms by which weight loss and exercise training reduce sources of inflammation that lead to chronic activation of a pro-inflammatory state. Weight loss and increased activity affect the immune system by reducing the number of mononuclear cells in the peripheral blood, which are a source of pro-inflammatory cytokines (such as interleukins IL-6, IL-1β and IL-8; tumour necrosis factor-α and its receptors TNFR1 and TNFR2; and transforming growth factor TGFβ). A reduction in adipose tissue would not only reduce the volume of adipocytes and preadipocytes, but also decrease the number of endothelial cells and macrophages that reside there. These cells produce many pro-inflammatory mediators such as C-reactive protein (CRP), serum amyloid protein A (SAA) and cytokines. Weight loss and exercise may also increase the expression of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1ra) in these cells. The resulting circulatory changes could, in turn, cause the liver to contribute by decreasing its production of fibrinogen and other pro-inflammatory mediators.

collaborators[107] reported that plasma CRP is also inversely related, in a dose–response manner, to cardiorespiratory fitness measured directly on a treadmill. The odds ratio of men in the lowest quintile of fitness for having a high CRP concentration (> 1.84 mg/L) was 3.2 (95% CI 1.8–5.8), compared with men having higher fitness levels. Study investigators measured adiposity directly from the sum of skinfolds. Additional adjustments for body fat percentage and waist circumference did not alter the relation between CRP and cardiorespiratory fitness.[107]

Overall, data from observational studies show that the greater the volume of physical activity, the lower the risk of elevated levels of chronic inflammatory markers. Primarily, the relation between inflammation and physical activity is independent of obesity as measured by BMI. But since BMI is not a direct measure of body fat, the question remains, after adjustment for differences in total and abdominal adiposity, as to whether inflammation is associated with physical activity.

Evidence from intervention studies

Although no data from prospective randomized controlled trials exist to date to definitely conclude that long-term regular exercise training reduces chronic inflammation, several uncontrolled studies of exercise do show an effect on specific inflammatory markers. For instance, in patients with chronic heart failure, 12 weeks of aerobic exercise reduced TNF-α concentrations,[115] 6 weeks of cycle ergometry reduced sTNFR2 concentrations,[116] and 16 weeks of combined aerobic and resistance exercise training decreased levels of both TNF receptors (but not TNF-α itself).[117] In addition, exercise training for patients with intermittent claudication reduced CRP after 3 months.[118] CRP decreased after 9 months of training for a marathon in 10 of 12 male runners.[119] In overweight women, aerobic exercise training for 5 months decreased serum concentrations of TNF-α, sTNFR1 and sTNFR2,[120] and cycle ergometry for 12 weeks reduced TNF-α and sTNFR2 (but not sTNFR1) concentrations.[121] Moreover, levels of acute-phase reactants CRP and serum amyloid protein A (but not IL-6) decreased significantly in 20 postmenopausal women who completed a 14-day diet and aerobic exercise intervention as inpatients.[122] The magnitude of the CRP decrease (45%) in these women was not significantly related to the magnitude of weight loss (4%). In another study,[123] resistance exercise training decreased TNF-α (both mRNA and protein levels) in skeletal muscle of frail, elderly subjects, which suggests that resistance training is also a potential treatment for chronic inflammation.

All of these studies had a small number of participants, were conducted in populations with elevated inflammatory markers (i.e., patients with congestive heart failure or obesity) and had relatively short durations. One of the larger studies[124] to date, which incorporated a control group but did not randomly assign participants to groups, demonstrated that a phase II cardiac rehabilitation and exercise training program reduced median CRP concentrations by 41% (mean change from 5.9 [SD 7.7] mg/L to 3.8 [SD 5.8] mg/L; median change from 3.4 to 2.0 mg/L) in 235 patients with coronary artery disease, but CRP concentrations did not change in 42 who did not exercise (Fig. 4). Exercise training seemed to be more effective in those with the highest CRP concentrations; for example, the proportion of patients with a CRP value above 15 mg/L decreased from 9% to 1%. Stratification of the data according to use of statin therapy did not alter the results. Changes in CRP concentrations were unassociated with changes in body weight or percent body fat, which provided compelling evidence that the exercise training effect was independent of body fat loss.[124] Another earlier research team of ours[125] also found evidence for an independent effect of exercise training in postmenopausal women who underwent 6 months of dietary weight loss alone or in combination with aerobic exercise training. In this study, decreases in IL-6, sIL-6R and sTNFR1 differed significantly between the groups, with changes in sIL-6R and sTNFR1 concentrations inversely related to changes in aerobic fitness.[125] Another interesting study[126] was conducted specifically to determine the effects of a 6-month supervised, individualized aerobic exercise training program on the production of cytokines by mononuclear cells in men and women at high risk of ischemic heart disease. In the 43 people who completed the program, overall production of atherogenic cytokines (interferon γ, TNF-α and IL-1α) decreased by 58%, and the production of atheroprotective cytokines (IL-10, IL-4 and transforming growth factor TGFβ1) increased 36%. (Their mean CRP level was 35% lower after exercise training, but the difference was not statistically significant.[126])

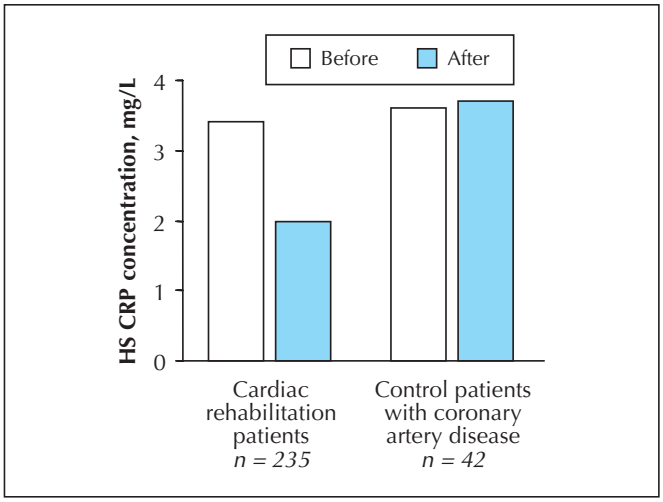

Fig. 4: Median changes in high-sensitivity (HS) C-reactive protein concentrations in patients with coronary heart disease after 19 weeks of follow-up (standard deviation 3 weeks) in cardiac rehabilitation compared with control patients with coronary artery disease. Reprinted with permission from Milani et al (*J Am Coll Cardiol* 2004;43:1056–61).

Only a few randomized controlled trials have been published that report the effects of an exercise intervention on inflammatory markers, and the data are conflicting. During a 6-year trial involving 140 middle-aged Finnish men,[127] CRP concentrations remained consistantly lower in the aerobic exercise group than in the control group, but the trend was not statistically significant ($p > 0.20$). In the weight loss and exercise trial[97] already described, our team also did not find an 18-month combined resistive and aerobic exercise training program to have a statistically significant effect on inflammatory biomarkers, although mean CRP values at follow-up visits tended to be lower in the intervention group than in the control group at both 6 and 18 months. Smaller studies[118,128] of shorter duration also hint that exercise training reduces inflammation compared with no exercise. In men with metabolic syndrome, 3 months of aerobic exercise decreased concentrations of monocyte chemoattractant protein-1 by 33% and IL-8 by 13%.[128] Although CRP levels in patients with intermittent claudication were significantly reduced after 3 months of a 12-month exercise training program compared with levels in control subjects,[118] CRP concentrations increased to baseline levels at the 6- and 12-month follow-up visits, perhaps because exercise in this study was unsupervised after the first 3 months. Interestingly, Gielen and associates[129] reported that exercise training did not reduce serum inflammatory markers in male patients with congestive heart failure but did reduce TNF-α, IL-6 and IL-1β gene expression in local skeletal muscle, relative to a control group. This suggests that exercise may elicit local anti-inflammatory effects that may or may not be evident in the systemic circulation.[129]

Additional data derived from randomized controlled studies are needed to provide definitive evidence that exercise training should be used as a treatment for chronic inflammation.

Summary

Persistent low-grade inflammation is emerging as an important contributor to the pathophysiology of several chronic diseases. Given the widespread deleterious health effects of an augmented inflammatory state, identification of therapies that reduce inflammation is critical. Yet, to date, there is little definitive evidence for therapies that can be used effectively to treat elevated markers of inflammation that are within the clinically normal range. As reviewed here, there are promising data suggesting that decreasing energy intake and increasing physical activity could be effective for reducing overall inflammation. But at present, data from randomized controlled trials conducted to determine the effects of weight loss or exercise training, or both, on inflammation are lacking. The mechanisms by which weight loss and increased physical activity reduce inflammation have yet to be elucidated.

Although weight loss is likely to emerge as an effective treatment for reducing inflammation, the magnitude of the effect and the weight loss needed to produce clinically meaningful results require delineation. On the other hand, the effects of exercise training in the absence of weight loss are unclear. Large-scale prospective studies are needed to definitively determine whether aerobic or resistive exercise training, or both, are effective in reducing inflammation.

This article has been peer reviewed.

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The Left Atrium

Playing Noah

Mourning dove
A play by Emil Sher
Directed by Lorne Pardy
Great Canadian Theatre Company, Ottawa
Feb. 16 –Mar. 6, 2005

Emil Sher's *The Mourning Dove*, which premiered at Ottawa's Great Canadian Theatre Company this winter, begins with sound: the sawing of wood, the wheeze of a respirator. A man is recreating Noah's ark, preparing a puppet play for his profoundly disabled daughter. Will she enjoy the show? Can there be any relief for her suffering? The sawing, we soon learn, is a correlative of the imminent and intolerable prospect of a saw on bone: doctors have planned a "salvage operation" on Doug's pain-wracked daughter.

The story is, in essence, the story of Robert Latimer and his daughter Tracy, whose life Mr. Latimer ended in 1993 by means of carbon monoxide poisoning. So familiar is this sad story to Canadians that few who see Sher's play (or who heard it in its earlier incarnation as a radio drama) will arrive without prejudice. But most will expect a re-opening of the case. Theatres bear something in common with courtrooms, for they subject human behaviour to a trial — by the audience, and by a cast of characters.

For Emil Sher, who discussed his script with me recently, there seems to be "very little conflict" to explore in the real Robert Latimer, who, he believes, is "absolutely rock-solid in his beliefs"; hence there is no ambivalence to examine in his choice. Perhaps this helps to explain why Timothy Webber (of *North of 60*) appeared rather aloof from his "Latimer" character; at least, I did not come away with a deeper sense of what his moment of choice *felt* like. Kate Hurman gave the audience more to work with as Sandra, Doug's doggedly upbeat wife, who makes "Team Tina" T-shirts for friends who have offered to help after the surgery. Sandra is practical, patient, ordinary — until the moment she returns from church to find her euthanized daughter. Sher holds back from moral judgement in this play, but I certainly felt one in the gunshot-loud slamming of a door as Sandra enters to confront her husband. There is no equivocation in this moment.

The ambiguity begins after this apparent point of no return. Doug, waiting for the judgement of society, evades the judgement of his wife in self-exile in his workshop. Sandra, alienated but no deserter, brings him blankets and food. She puts it to him that no one is questioning his motivation — only his choice. He has done what she herself once contemplated. In that choice they are divided. But why *did* she choose differently, Sandra wonders. Out of cowardice? Out of love? Which one of them was Tina's true protector?

As potent as this marital dynamic is, the most interesting dimension of the script is the character of Keith, a intellectually challenged young man who dotes on Tina and is a satellite member of the family. Ben Meuser's portrayal is wonderfully rich and well-studied, from his facial expressions to his mannerisms, speech and gait (a pity that a noisy stage amplified his heavy step to the point of caricature). Keith exhibits an unshakable literalmindedness, creating humour he does not intend. Although we are charmed and cannot miss the poignancy of his remarks ("Hippo doesn't want to go on the ark. Nobody knows how to speak hippo"), there is an inequality between Keith and Doug, as between Keith and the audience — at least superficially. Keith's realization that the "crazy talk" surrounding Doug's part in Tina's death is true provokes him to an eloquent anger in which it is plain that he perceives both his limitations and his worth. "I am never going to heal," he shouts. "Are you going to kill me, too?" Thus Keith asserts himself not only as Tina's proxy, but as his own advocate. In the writing, and in the quality of the performance, this character is at the centre of the play.

GCTC

Ben Meuser as Keith and Timothy Webber as Doug in *Mourning Dove*.

For all that, Keith is not Tina. Tina is a notable absence, represented offstage by Stephanie Burchell, who creates the sounds of the respirator. The other characters mime their interactions with her, caressing imaginary hair, speaking to an emptiness (until the end, when Tina "appears" as a vacant, accusatory wheelchair). I suspect that the impact and possibilities of this play would have been different had Tina been a bodily presence on stage — if she had not been an abstraction, a cipher, a moral puzzle, but had truly been "there" to challenge us. For the audience, as for Keith, the simple fact of her would leave no room for debate.

Anne Marie Todkill
CMAJ

Mourning Dove will be published this summer by Playwrights Canada Press (www.playwrightscanada.com).

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Room for a view

Fragments

So thoughtful of the geriatricians to invite the psychiatrists to dinner, even if I was the only one who could come out tonight. The restaurant is very nice, and the food is good. At my table are two geriatricians, a family physician with an interest in seniors, an anthropologist and the guest speaker, whose specialty is unclear to me. There are other tables in this private dining room, and the noise level makes it necessary to raise one's voice to be heard.

The speaker's topic was the ethics of dementia. I wonder, as I cut through the delicate flesh of caviar-topped scallops plated with sprigs of organic rosemary, how he managed to convince the pharmaceutical company to allow him to speak on such an esoteric subject. No irksome diagrams of cholinergic neurons to trouble the digestion. No complicated study protocols to decipher through the gentle fog of a glass or two of Pinot Noir.

I would like to be able to make intelligent conversation with the guest speaker. I try to think of something he might have said, some comment or fact that I could pick up on, but I can't come up with anything. I think I must have missed the point of this lecture — so completely, in fact, that now I am mired in a self-conscious silence.

Fortunately, the speaker is engaged in a vigorous debate with one of the geriatricians at the far end of the table. The topic is mild cognitive impairment and whether it represents the earliest stages of dementia

"Dr. So-and-So thinks ... "

"Really. When did he say that?"

"It was — let me think. It must have been last November. It was that conference in Ottawa. Help me out, when was that conference?"

"November."

"Right. November."

"He said that? I find that hard to believe."

And so on. This discussion has perked up the guest speaker. During his talk he had that fatigued, distracted, if-this-is-Wednesday-this-must-be-Halifax look that speakers get at the end of a tour.

I consider trying to start a conversation with the anthropologist across the table, but I have forgotten her name. It occurs to me that the three women at the table have said almost nothing during the meal. I suddenly remember a comment the speaker made about the importance of the humanities in medicine and seize upon it: I ask him what he sees as the role of stories in the study of dementia.

"Stories," he says thoughtfully, spearing a piece of haddock. He tells me about narrative medicine and how it is being used to teach medical students. I have read a bit about this. It contrasts with the traditional humanities approach, in which you read the classics, study poems and watch movies to enrich your practice of medicine. I ask him if he is a writer. Then I feel foolish: obviously he's a writer, he just finished telling us about all the medical books and articles he's written and about the time he was on Oprah.

But he just says, "No, I'm not a writer."

Seated to my left is another geriatrician whom I've known for over ten years, since he was a resident and I was a medical student. I remember being on call with him at the old Infirmary, sitting in the TV lounge and watching the first season of "Friends." I remind him of that and he smiles. Because I respect his opinion, I ask him whether he thinks that mild cognitive impairment is part of normal aging.

He tells me no, that as a geriatrician he doesn't believe there is such a thing as normal aging. He says that he thinks everything that happens as people get older is the result of a disease process, or the consequences of neglecting one's health in some way. If this could be prevented, then the slowing of the body and mind we associate with getting older would be eliminated, and we would just go on until the day of our death, when everything suddenly falls apart.

"Like the Deacon's one-horse shay," I say, spontaneously recalling the poem about a chaise that was constructed so that no part was weaker than the others. Because it couldn't break down in one place, it went on and on until it finally "went to pieces all at once." This is a perfect example of the kind of thing that sticks in my mind: fragments of old poems. They embed themselves in some especially resilient neurons and refuse to make room for more current information, like why the speaker disapproves of modern bioethics, or what the anthropologist's name is, or how the cholinergic system works.

I think of a patient I saw just that same morning, with moderately advanced dementia. She wrote a sentence for me: "My heart leaps up when I behold a rainbow in the sky." I had to look it up: Wordsworth.

So was it when my life began;
So is it now I am a man;
So be it when I shall grow old,
Or let me die!

The dinner ends, and the party breaks up. I shake hands with the guest speaker, and he tells me that I should keep up my interest in narrative medicine. I make a mental note to try to remember his name so I can look up some of his papers later. I climb the stairs leading from the private dining room and exit onto the street, where I start the questionably normal and darkly mysterious process of forgetting.

Lara Hazelton
Psychiatrist
Halifax, NS

DOI:10.1503/cmaj.050276

Room for a view

Lessons from history

Dear Colleagues,

I found the clue whilst traversing a recent Journal and brought it to the attention of an estimable Librarian. Employing his considerable powers of detection, he promptly unearthed the treasure itself: an operating Time Portal.

Suitably disguised, I passed through the portal to visit Central Canada in the winter of 1918. The locals, being Canadian, were reserved but friendly, although I have reason to believe that as a result of what they had just been through they were a little more talkative than usual. Grief for recent loss was mixed with a profound gratitude that the unprecedented wave of death had receded.

Prominent also was a sense of camaraderie and pride evident whenever they mentioned how so many, from teenager to grandmother, from nun to soldier, had pulled together to care, to help and to succour.

Those of us living now have important lessons to learn from these people of 1918. They had no effective treatment for the severe form of the disease caused by the influenza "bacillus" that had stricken so many of them; nor, I venture, do we. Although there was tantalizing mention of specific treatments, details were not forthcoming. However, they would certainly have had blankets and kind words and chicken soup with onions and garlic. Nowadays we have in addition a very small supply of oseltamivir, and perhaps there is also some benefit to be had from statins or ACE inhibitors. I found it particularly interesting that, in 1918, both the Connaught Laboratories at the University of Toronto and the Laboratories of Ontario's Provincial Board of Health were able to prepare vaccine, and fast, although there were worries about both effectiveness and safety.

Life was harder then. More human effort, as compared with now, was related directly to the production of food and shelter, and less to the maintenance of a social safety net. And yet there also seems to have been a reserve capacity and the ability and will to mobilize it quickly. As amazing as this seems to us today, regular hospitals were able to accommodate a large influx of extra patients, and it was even possible to assemble and staff emergency facilities: for example, in Montréal, 596 extra hospital beds were quickly established, staffed by nuns and brothers as well as by city-employed nurses and physicians. The load must have been staggering: despite a death rate that others have estimated at 1%–2%, in Montréal alone over 3000 people died in the 39 days ending November 7.

An enormous volunteer effort, aided by the police and firemen, worked long and hard to ensure that medical attendance, as well as food, fuel and clothing, was provided to those unable to pay for it.

The most effective pandemic control measures were in 1918 as they probably will be for us today: in preference to labour-intensive quarantine, the 1918 Boards of Health reduced exposure by disseminating advice to the public and summarily closing down all but essential services. This not only slowed down the spread of the virus through the population, but also freed up workers to help manage the epidemic, from bringing food and supplies to the sick — most of whom were of necessity at home — to transporting the bodies of the dead to temporary morgues in ice arenas and elsewhere.

I only hope that, when our time comes, we will be able to match the intelligence, energy co-ordination and cooperation of our forebears. Any of us involved in current-day planning will, I think, find inspiration in their example.

To that end, I have done my best to restore and refurbish the Time Portal for your use on *eCMAJ* so that, if you wish, you too can travel to our past.

I remain, your humble servant, etc.

Gillian Arsenault
Clinical Associate Professor
University of British Columbia
Vancouver, BC
Medical Health Officer
Fraser Health Authority
Maple Ridge, BC

DOI:10.1503/cmaj.050372

Quarantine

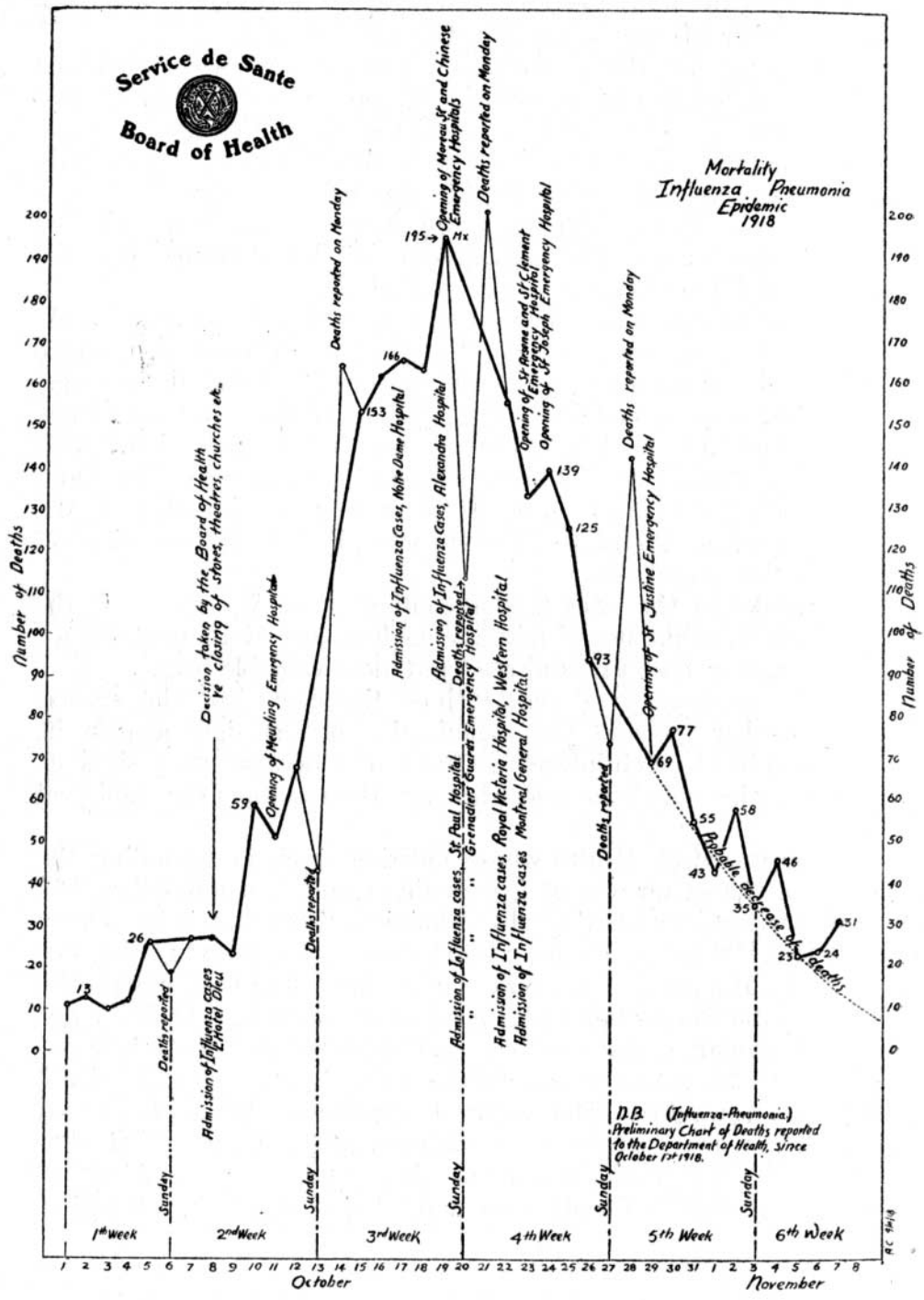
With respect to the closing of schools, churches, theatres and other public assemblages, each Medical Officer of Health or Local Board of Health has power to close such places if it seems desirable. The matter of placarding, and quarantining for this effection is regarded by the Provincial Board of Health of Ontario as being impracticable. The Board does not think such a law could be satisfactorily enforced for the reason that before the necessary measures (inspection, placarding, etc.) could be taken in respect to the thousands of homes, a great number of the cases would be well and the intolerable situation of keeping comparatively well persons in large numbers tied up would ensue. Under such a regulation many people with colds would be improperly quarantined, and in short the operation of the law would, as it has been in many of the States to the south of us, be a dead letter.

From: McCullough JWS. The control of influenza in Ontario. *CMAJ* 1918;8(11):1084

DOI:10.1503/cmaj.050403

The documents that Dr. Arsenault found on the other side of the Time Portal, including the graph reproduced on page 1215, were originally published in 1918 in the November and December issues of *CMAJ*. Read them online at www.cmaj.ca/cgi/content/full/172/8/965/DC1.

Past progressive



The Spanish Influenza in Montréal. From an article by S. Boucher, director of the city's Department of Health, in the December 1918 issue of *CMAJ*. The graph shows the peak in the number of deaths from influenza reported daily in Montréal during October and the first week of November. The cumulative number of deaths reported since the disease appeared in Montréal at the end of September was 3028. "From the beginning," Boucher reported, "the Department of Health took energetic means of combating the disease." By Oct. 8, with a total of 144 deaths reported, the Board of Health agreed on "the immediate closing of all places of public meeting, such as schools, theatres, dance halls, moving picture houses, concert halls, etc." Soldiers were confined to barracks. On Oct. 10, a new Board of Health consisting of physicians replaced the existing lay board. Further infection control measures were ordered, including the suspension of all church services. For the full article, see www.cmaj.ca/cgi/content/full/172/8/965/DC1. — *CMAJ*

DOI:10.1503/cmaj.050402

Deaths

Nécrologie

CMAJ welcomes obituaries submitted within 60 days of a death. Send to Kyle Rooks, kyle.rooks@cma.ca; fax 613 565-5471.

Ahsan-Uddin, Syed, Edmonton; University of Punjab (Pakistan), 1979; general surgery; FRCS(Glas.), LRCP, MRCS(Eng.), FRCSC; staff, Sturgeon Community Hospital & Health Centre. Died Nov. 21, 2004, aged 49.

Alway, Alan E., London, Ont.; University of Western Ontario, 1943; internal medicine; MSc, FRCPC; former Surgeon Lieutenant Commander, Armed Forces (Reserve) and Clinical Associate Professor of Medicine, University of Western Ontario. Died Oct. 31, 2004, aged 86; survived by his wife, Mary Lee, his children Ann, Mary and Pamela, and 6 grandchildren.

Berkeley, Joseph, Windsor, Ont.; University of Glasgow (Scotland), 1948; physical medicine and rehabilitation; ChB, DPH, FRCPC; staff, Hotel Dieu of St. Joseph, Metropolitan General Hospital and Windsor Western Hospital Centre; Honorary Lecturer, University of Western Ontario. Died Nov. 27, 2004, aged 84.

Bissell, Erwyn W., Edmonton; University of Alberta, 1950; plastic surgery. Died Nov. 7, 2004, aged 81.

Byrnes, Michael C., North York, Ont.; University of Toronto, 1960; psychiatry; DPsy, FRCPC; staff, Rouge Valley Health System – Centenary Health Centre. Died Nov. 1, 2004, aged 70.

Dietrich, Michael, Windsor, Ont.; University of Western Ontario, 1954; general pathology; former Chief Pathologist, Windsor Western Hospital Centre and staff, Grace Hospital. Died Nov. 17, 2004, aged 74.

Erian, Samir A., New Waterford, NS; Cairo University (Egypt), 1971; MB, BCh. Died June 8, 2004, aged 56; survived by his wife, Nadia, and his children Mina and Sara. "He was a valued member of the medical staff and his contribution to the medical care of the community was deeply appreciated and will be greatly missed."

Gordon, Aaron, Westmount, Que.; University of Toronto, 1946; pediatrics; former staff, Jewish General Hospital. Died Nov. 8, 2004, aged 87.

Hall, John G., Hamilton, Ont.; University of Toronto, 1943; psychiatry; DPsy, FRCPC; former staff, Henderson General and Hamilton Civic hospitals. Died Nov. 8, 2004, aged 86.

Hoffman, Harold J., Toronto; University of Toronto, 1956; neurosurgery; BSc, FRCSC, FACS; former Neurosurgery-in-Chief, Hospital for Sick Children and Professor of Surgery, University of Toronto. Died Nov. 14, 2004, aged 72; survived by his wife, JoAnn, his children Richard, Andrew and Leslie, and 6 grandchildren.

Ishii, Masatatsu, North Vancouver, BC; Keio Gijuku University (Japan), 1954; anesthesia; FRCPC; Assistant Director, Department of Anesthesiology, Calgary General Hospital. Died Nov. 5, 2004, aged 74.

MacDonald, William B., Edmonton; University of Saskatchewan, 1959; anesthesia; DABA, FACA, FRCPC; former staff, Department of Anesthesiology, Plains Health Centre & Pasque Hospital; Clinical Professor, Department of Community Medicine & Epidemiology, University of Saskatchewan; Deputy Minister, Saskatchewan Health. Died Nov. 3, 2004, aged 68.

MacDougal, J. Raymond (Ray), Kingston, Ont.; University of Toronto, 1953. Died Nov. 20, 2004, aged 87; survived by his children Suzanne, Peter, Nancy and Carol, and 9 grandchildren.

MacFarlane, Gordon N., Burlington, Ont.; University of Dublin (Ireland), 1937; general surgery; medical officer, Canadian Army and former Chief, Department of Surgery, Joseph Brant Memorial Hospital. Died Nov. 24, 2004, aged 92; survived by his wife, Irene, and his children Jennifer, Maureen, Kathryn, Elizabeth and Jamie, 13 grandchildren and 3 great grandchildren. "He was a kind and gracious man who had an abiding interest in all things relating to life and the human spirit. he was adored by his family and he will be deeply missed by all who knew him."

Moes, Charles A.F., Toronto; University of Toronto, 1946; radiation oncology; FRCPC; staff, Radiology Department, Hospital for Sick Children, and Professor Emeritus, University of Toronto. Died Nov. 7, 2004, aged 83; survived by his wife, Barbara, and his children William, Jane and Share.

Porter, Robert H., Burlington, Ont.; University of Western Ontario, 1955; CCBOM; former Assistant Vice President of Health & Safety, Bell Canada. Died Nov. 9, 2004, aged 75.

Shepherd, John T., Oakville, Ont.; University of Toronto, 1959; orthopedic surgery; FRCSC; staff, Joseph Brant Memorial Hospital and Halton Healthcare Services, Corp-Oakville Site. Died Nov. 19, 2004, aged 70.

Sheridan, Charles A., Mont-Royal, Que.; Queen's University, 1946; anesthesiology. Died Nov. 28, 2004, aged 87.

Sternberg, Ronald, Toronto; University of Toronto, 1975; family medicine; CCFP; active staff, Mount Sinai Hospital. Died Nov. 8, 2004, aged 53; survived by his children Emily, Jessica and Ashley.

Stewart, Gerald M., Lethbridge, Alta.; University of Calgary, 2000. Died June 23, 2003, aged 29.

DOI:10.1503/cmaj.050361

QUERY

I once lived the life of a paper-based creature. I wrote notes on multicoloured things called Stickies. I had a notepad to remind me about important events and items to follow up. I carried a pen. I wrote in things called charts whenever a patient came to see me.

This life made sense to me. Paper begat paper, which begat more paper. Papers were signed, sent, filed, shredded; papers were shuffled, left on my desk, left overflowing in my in-box. Letter size, legal size, Sticky-size. Paper was my comfort and delight.

Then came the electronic revolution. Promising an end to paper, Computer People came to preach about their "record." An Electronic Medical Record, to be precise; with it, any patient's life from birth to death could be recalled at the touch of a button. One day I was leafing though a luxurious, thick chart; the next I was struggling to type the name Deirdre with one finger while precious clinical time oozed away. When I entered a note about patient Deirdre or Donald, the computer would freeze and I'd lose all I'd written; mostly, I felt like throwing the contraption out the window and into the snow. (I never told this to the Computer People, who logged all my difficulties, poking at their PDAs with a little stick.)

The sad fact was this: the Computer People had convinced our clinic to "go electronic," and $100 000 later we were committed. There could be no return to paper from a regime of triple passwords that couldn't be a personal name, or contain more than one capital letter, three numbers or fewer than eight characters. To-Do pop-ups, Alert Actions, Electronic Signatures and Correspondence Control Centres must forever rule.

A handful of doctors quit our group practice in frustration. Inscrutable, the Computer People watched them go. Each time a colleague left, I wished I could pull out a particularly fat chart, toss it in the air and make the Computer People restore every single piece to order. Because that's how hard learning the new system felt for me. It is counterintuitive, a barrier between patient and doctor. Instead of sitting down, facing the patient and taking a history, we must interact with a computer screen. Already patients have complained that the doctor is "more interested in his computer than he is in me."

I think this secretly makes the Computer People happy. They patrol the clinic perimeter, available to address any "problems" — which they privately believe to reside with us, the users. (One can tell by their solicitude, their unruffledness.) Computer problems may bog down morning clinics, things may be brought to a standstill until a glitch is resolved, and they will never understand the urgency of a doctor behind schedule. They do not arrive winded. They glide in like emperors of the Internet. And because of these computer problems — ours or theirs? — all the doctors are behind schedule. Every day.

The Computer People are thus kept in demand.

— Dr. Ursus

Anson Liaw

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