Letters
Correspondance

An historical take on the physician's charter

Nuala Kenny and her colleagues have expressed concern that the CMA Charter for Physicians will be seen as self-serving.[1] On the face of it, I share this feeling. But when I place the charter in an historical context I am reassured. For the Charter is not just a product of the "current political and economic climate," but one more expression of the centuries of efforts to define the relationship between physicians and the society they serve.

One concern expressed about the charter is that it is a further example of the entitlement that too often bedevils our profession.[2] But compare the modest claim in the preamble to section III — "like all Canadians, Canadian physicians deserve fair treatment"[3] — to our 1868 Code of Ethics,[4] where we pronounced that "the benefits accruing to the public, directly and indirectly, from the active and unwearied beneficence of the profession are so numerous and important that physicians are justly entitled to the utmost consideration and respect from the community." As justification of this sentiment the code pronounced that "There is no profession from the members of which greater purity of character and a higher standard of moral excellence are required than the medical."

Our Code of Ethics has been strongly influenced by Thomas Percival's *Medical Ethics* (1803). Pellegrino[5] has described how Percival urged physicians to speak out when economics conflict with ethics. Percival's issues have a contemporary ring: he condemned overcrowded wards and warned that unwise economies in treatment might lead to the use of drugs of inferior quality. It is therefore quite appropriate for our present-day charter to assert that physicians must act as advocates for their patients.

Finally, the charter's assertion that physicians need to be paid for their work has an even longer record. In his 1955 Osler lecture at McGill, Edelstein[6] cited Aristotle's view that the function of medicine is to cause health, not wealth. But in *The Republic* Plato pointed out that there would be no benefit in a physician's work "unless pay is added to it," for the physician would consequently be unwilling to go to the trouble of taking care of the troubles of others.

There is a place for the charter. If society expects a great deal of its physicians then physicians must look for something in return. They are human and need their quid pro quo.

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[Two of the authors respond:]

Peter Warren makes the reasonable point that some issues raised in the CMA's Charter for Physicians[1] are not new. But this is quite beside the point. The existence of historical sources for contemporary issues does not argue for the Charter for Physicians as the solution.

Moreover, to take an historical view, Warren does not point out that a statement of rights on behalf of physicians, as opposed to the obligations typically found in a code of ethics, is unprecedented. We find the Charter for Physicians problematic for 2 reasons.

First, the Charter purports to be something it is not. We acknowledge that it uses the rhetoric of needs, but this language is misleading; the document is actually a statement of physician rights. Second, legitimate charters of rights are either for all citizens or for oppressed groups. Physicians are a powerful and wealthy professional group with neither need of nor legitimate claim to special rights. The only course left to entrench the claims found in the Charter would be a democratic process involving all parties — physicians, government, hospitals and patients — on an equal basis. Since the Charter for Physicians is a unilateral declaration, it has no force in a democratic society.

Warren, along with other respondents to our article,[2–5] fails to see that the Charter for Physicians does not serve well the goal of preserving the health care system. Sadly, it may further the public's perception that too many physicians in Canada are more committed to financial gain than to altruistic service.

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Studying the statins

There are several inaccuracies in Robert Herman's review of the statins.[1] First, he listed several inhibitors of cytochrome P-450 (CYP), including diltiazem and substances found in grapefruit juice and green tea, and labelled them all "potent inhibitors." Calcium-channel blockers have not been associated with an increase in myopathy in either controlled clinical trials or clinical practice.[2] Grapefruit juice, when taken in normal quantities in the morning, has minimal effects on the serum concentration of HMG–CoA reductase inhibitors following administration of lovastatin and has not been shown to have any clinically significant adverse effects.[3]

Second, Herman singled out lovastatin and simvastatin as being particularly likely to cause drug interactions by implying that active metabolites play no significant role. He noted that atorvastatin and cerivastatin are at least partially exonerated because "active ... metabolites of atorvastatin and cerivastatin contribute in large measure to their overall clinical activity." He concluded, "Thus, inhibition of first-pass metabolism of lovastatin and simvastatin could result in 10–20 fold elevations (oral availability increasing from 5% to 100%) in steady-state concentrations with a marked liability to drug toxicity." This is also inaccurate. Approximately 75% of the HMG-CoA reductase inhibitory activity of simvastatin results from 3 active metabolites. Therefore, measuring only the parent compound, such as simvastatin, grossly overestimates the overall interaction with CYP inhibitors.[2]

Editorialists Lori Shapiro and Neil Shear highlighted the statins as an example of a drug class in which not all members share similar drug interactions.[4] They stated, "To date, all reports of significantly increased rates of myalgia in patients receiving combination therapy with a statin and certain other agents involve simvastatin or lovastatin, the statins with the highest known metabolic dependency on the CYP3A4 pathway for elimination." This is simply not true; several cases of myopathy have been reported in patients taking pravastatin concomitantly with cyclosporine.[2] In addition, a significant increase in creatine kinase was documented in a patient taking nefazodone and pravastatin concomitantly, necessitating the discontinuation of nefazodone.[5]

Simvastatin has been well tolerated by millions of patients and has been shown to decrease coronary mortality by 42% in patients with high cholesterol levels and heart disease. Some drugs, such as niacin, fibrates and cyclosporine, increase the likelihood of myopathy with all statins. Other drugs, such as erythromycin, clarithromycin, the azole antifungals, nefazodone and other HIV protease inhibitors, increase the potential for myopathy when given concomitantly with statins metabolized by CYP3A4.

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1. Herman RJ. Drug interactions and the statins. *CMAJ* 1999;161(10):1281-6.
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[The author responds:]

The metabolism and action of simvastatin (and lovastatin) are complex.[1] The parent drug is without intrinsic activity. However, it is readily metabolized to simvastatin acid by nonenzymatic hydrolysis as well as by nonspecific esterases in the liver and other tissues. It is also metabolized through a parallel pathway by hepatic and intestinal CYP3A4. The fact that the CYP3A4 metabolites circulate in blood in much higher concentrations than simvastatin acid has led to speculation that they may account for as much as 75% of the overall HMG–CoA reductase inhibitory activity of the drug. However, simvastatin acid and other open-lactone metabolites are also capable of undergoing reversible lactonization in tissues and exist in an equilibrium between active acid and inactive lactone forms. The lactone forms, including the parent simvastatin, have partition coefficients of around 4.7. In animal experiments, myopathy has been linked to the more lipophilic derivatives.[2] Thus, the inactive lactones may be important in the distribution of the drug into tissues, where they are subsequently metabolized and have their effects on cells.

Inhibition of CYP3A4 results in a shift in simvastatin metabolism away from the hydroxylated metabolites toward simvastatin and simvastatin acid. This always produces a more lipid-soluble and more active drug–metabolite profile. The question is, by how much? One can measure the absolute levels of drug and metabolites in blood by quantitative chromatography or by the activity profile of mixed active and inactive drug using a bioassay. I quoted[3] the changes in simvastatin acid induced by itraconazole (19-fold), a potent CYP3A4 inhibitor, from a well-designed placebo-controlled crossover study.[4] In Ernest Prégent's opinion, the bioactivity profile (5.2-fold[4]) would have been more appropriate. One could argue that estimation of bioactive equivalent concentrations may be confounded by high levels of inactive metabolites in the presence of an inhibitor, or that bioactivity does not reflect differences in plasma protein binding or lipophilicity for mixtures of substrates. However, neither the quantitative nor bioassay method tells us unequivocally what is happening in the cell.

In my article I tried to emphasize the characteristics of a drug that may predispose it to a potentially serious drug interaction. Dose-dependent toxicity within or close to the therapeutic range and high first-pass metabolism are clearly associated with HMG–CoA

reductase inhibitors. Partly to make a teaching point regarding balanced inhibition and partly because of clinical interest in the drug, I tried to moderate these concerns with atorvastatin. In this case, there is a 1:1 relation between the active parent drug and the active hydroxy metabolites; the metabolites are as potent as or slightly more potent than atorvastatin itself; the differences in lipophilicity are much less than those with simvastatin; and the changes in concentration (a 3.3-fold increase in atorvastatin acid, a 1.6-fold increase in bioactivity) are within the usual dosing ranges for the drug.[5] One could not make the same concessions for simvastatin or lovastatin.

The issue regarding the interaction of calcium-channel blockers and statins has been addressed by others.[6] There is a major interaction (3.5–6.2 fold elevations in statin concentration) between diltiazem or verapamil and lovastatin or simvastatin.[7,8] The change in drug levels is about the same order of magnitude as the interaction of these drugs with erythromycin. Prégent would like us to believe that a recently published meta-analysis[9] adequately addresses concerns regarding concomitant use of these drugs with the statins and that their interactions are without clinical significance. However, these data came from studies designed to assess clinical efficacy and not adverse events, least of which would be drug interactions. There were no controls of the number or types of potential inhibitors used by patients (they reported aggregate data for calcium-channel blockers) and the numbers of events were far below those that would be required to show a difference, if any existed. In other words, the data are poor and are vastly underpowered to answer the question.

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[The editorialists respond:]

We thank Ernest Prégent for his comments about our editorial.[1] He is correct to point out that not all reports of significant rates of myalgia in patients receiving combination therapy with a statin and certain other agents have involved simvastatin or lovastatin. However, the reports with these particular HMG–CoA reductase inhibitors are often based mechanistically on their inhibition by a CYP3A4 inhibitor. The concept of differential susceptibility of the statins in terms of CYP3A4 inhibition still holds true.

The myopathy reported in patients receiving combination therapy with pravastatin and cyclosporine clearly is not based on inhibition of CYP3A4 metabolism. We all continue to learn as these drugs are used, and therefore interactions are often not recognized until years after clinical trials are completed. Adverse reports of large trials such as those discussed by Gruer and colleagues[2] are reassuring. However, the data do have limitations. This study was conducted when our understanding of cytochrome-mediated drug metabolism was in the early stages. Therefore, drug interactions may have been underrecognized. While the mechanism of cyclosporine–pravastatin interactions is not known, it could relate to interference with transport mediated by P-glycoprotein.[3]

We know that a few drugs, such as niacin, fibrates and cyclosporine, increase the likelihood of myopathy with *some*, not *all* statins as Prégent states. In the end, we all agree that the potential for myopathy increases when the most potent CYP3A4 inhibitors are given with statins metabolized by CYP3A4.

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Degrees of difficulty in ascertaining credentials

I am disgruntled to see the names of *CMAJ* authors published without the authors' degrees. I have always rapidly screened credentials to decide if, when, and in how detailed a fashion I would peruse an article. I know I can get used to this jarring change in the *CMAJ* but I disapprove of it.

If the purpose of the omission is to take the focus off the author and put it on the article, then the policy is having the reverse effect. I am now compelled first to turn to the end of the article to see who really is the author. Is it a clinical medical colleague? A basic scientist? A priest? A social worker? The head of an institute of alternative medicine? A freelance writer? (I'm not suggesting that these categories are mutually exclusive, nor that I wouldn't possibly be interested in articles by all such authors.)

Omitting degrees is a friendly, equi-

table gesture but it does not work for this reader.

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[Editor's note:]

As John Stoffman correctly discerned, *CMAJ* wishes to emphasize the content of what we publish and not the qualifications of the authors. The variety of letters after people's names has been growing; while some of these may be as familiar as the MD degree, in other cases it was becoming difficult to determine whether they were in fact academic degrees and what they meant. Most degrees do not describe the subject matter of the degree, only the degree level (undergraduate, masters and doctoral). Our preference is to describe the current position or occupation of the author, not their level of qualification.

Medicare

The information on health expenditures in the Feb. 8, 2000, editorial[1] is dated, although this fact does not necessarily alter the main points made. The national health expenditure database, which is the basis of the Health Canada publication on national health expenditures to which you referred,[2] was transferred from Health Canada to the Canadian Institute for Health Information (CIHI). CIHI has produced 3 annual health expenditure reports since the Health Canada document was released in early 1997. The latest CIHI report was released on Dec. 16, 1999.[3]

According to the latest estimates, Quebec, not Alberta, has the lowest health expenditure per capita among the provinces: $2453 per person in 1999. Alberta has the 5th lowest expenditure, at $2832 per person. Nevertheless, Albertans continued to spend a lower proportion of their provincial gross domestic product on health in 1999 (7.6%) than citizens of any other jurisdiction in Canada.

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The statement in your editorial in the Feb. 8, 2000, issue that "private health care is always more expensive"[1] mixes opinion with fact. The reference you gave[2] provides no statistically valid data to support such a statement. In British Columbia, private surgical clinics offered to provide contract surgical services for medicare patients at 60% of the government-calculated cost in public hospitals. We did not need a study, or a health policy analyst, or a health economist or any other redundant bureaucrat to back up our calculation that we could achieve this and still make a (nasty word) profit. Why *CMAJ*'s editors continue to blindly trust the ability of a state-controlled monopoly to deliver efficient, effective and excellent health care services is mind-boggling to many of us.

The bottom line is very simple. There is nothing morally wrong with spending one's own money on the health of oneself or a loved one. The hogwash being spouted by self-serving lobbyists and unions is being matched by the editors of *CMAJ*.

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Reference

1. Klein's surgical strike at medicare [editorial]. *CMAJ* 2000;162(3):309.
2. Rough seas in US managed care [editor's preface]. *CMAJ* 1999;161(6):669.

[The editor-in-chief responds:]

Perhaps Brian Day, in criticizing our editorial,[1] should reread the referenced paper.[2] Although that piece focused on the debacle of for-profit managed care in the US we could also draw Day's attention to studies specific to the question of hospital ownership. These show, for example, that US medicare spending in 1995 in for-profit markets resulted in $5.9 billion in excess costs when compared with spending in not-for-profit markets.[3] Privately financed care costs considerably more than equivalent publicly financed care.

John Hoey

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