The Kyoto Protocol: In force?

Feb. 16, 2005, marks the entry into force of the Kyoto Protocol and its country-specific targets to reduce emissions of the "greenhouse gases" responsible for global warming. Most scientists agree that the earth's surface air temperature is rising, that this trend has accelerated dramatically since about 1970 (Fig. 1), and that human activity is now its major driver.

By 2100 the global average surface air temperature will be 1.4ºC to 5.8ºC warmer than in the period 1961–1990, even taking into account full implementation of plans to reduce fossil fuel use. In Canada, especially at this time of year, the prospect of our climate warming by a few tenths of a degree per decade hardly seems alarming. But, in the Arctic, such incremental change is sufficient to irreparably disrupt ecosystems and ice reservoirs, with profound implications for traditional lifestyles. The regional effects of climate change will be uneven and unpredictable, but it is clear that the most fragile ecosytems and vulnerable populations will also be the most at risk.

In this issue[1] (see page 501) Sari Kovats and Andrew Haines update an earlier review[2] with a discussion of the emerging health effects of climate change, such as the 2003 heat wave in France, which resulted in more than 14 000 deaths. But, despite what science and common sense tells us, Canada's Kyoto promises have faltered. As our economy has expanded (achieving 40% growth in GDP between 1990 and 2002), so have emissions, which are now roughly 25% higher than in 1990. Canada has committed to achieve, by 2012, a 6% reduction relative to 1990 levels. It seems evident that we will not meet this target. As we write, the government is floating the idea of easing the Kyoto obligations of "large emitters" (the 700 companies that produce 50% of Canada's emissions), even as it launches a chipper "One Tonne Challenge" aimed at persuading individuals to clean up their act (www.climatechange.gc.ca/onetonne/english/index.asp?pid=179).

This latter goal might be achievable. Canada ranks in the top 10 countries in per-capita annual consumption of fossil fuels (16.93 metric tons of CO_2 per person). The European Union does considerably better (eg., 9.52 in Denmark and 6.16 in France).[3] Over 80% of Canada's greenhouse gas emissions in 2002 were in the energy sector (transportation, heating and manufacturing).[4] Green technologies offer some hope, but buy-in from government and consumers has been glacially slow. Solar panels are not sprouting on rooftops. There are more SUVs than hybrids to choose from in car dealer showrooms. Municipalities are still choosing 4-lane commuter roads over light rail.

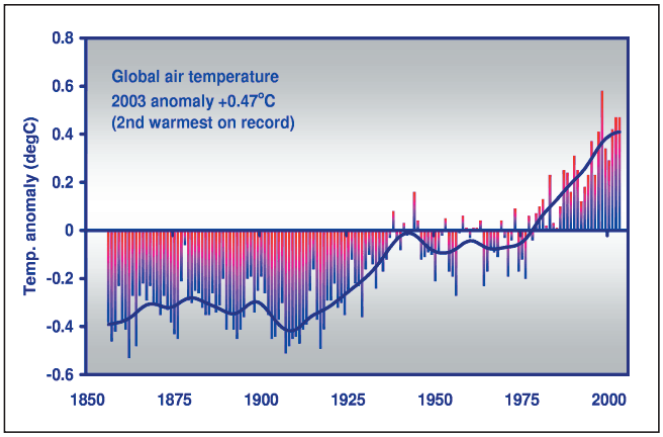

Fig. 1: Global temperature record. Reproduced, with permission, from The Whitney Laboratory for Marine Bioscience, University of Florida.

At least Kyoto has forced participating countries to construct inventories of their energy consumption.[4] Health care delivery, which now represents about 10% of the Canadian economy, will have to address its contribution to global warming and environmental degradation in general. The huge ecological footprint of hospitals has already been quantified,[5] and some institutions are finding ways to minimize their environmental impact. Physicians, many of whom vigorously supported signing on to the Protocol, should take their own "green inventory" and consider what material and behavioural aspects of their practice are due for a retrofit — such as replacing face-to-face visits in clinics and hospitals with real-time audio (and video) communication. At the very least we ought to be assessing the effects of avoidable travel on our patients and the environment. And not to be forgotten are the daily opportunities for physicians to remind patients and the public about the intimate connection between the state of the environment and the state of our health. — *CMAJ*

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DOI:10.1503/cmaj.050083

Le Protocole de Kyoto : en vigueur?

Le 16 février 2005 marque l'entrée en vigueur du Protocole de Kyoto et de ses objectifs nationaux visant à réduire les émissions de gaz «à effet de serre» qui causent le réchauffement de la planète. La plupart des scientifiques reconnaissent que la température de l'air à la surface de la Terre est à la hausse, que cette tendance s'est accélérée de façon spectaculaire depuis 1970 (Fig. 1) environ et que l'activité humaine en est maintenant le principal élément moteur.

En 2100, la température moyenne de l'air à la surface du globe aura augmenté de 1,4° à 5,8° par rapport à la période de 1961 à 1990. Cette projection s'avère même en tenant compte d'une mise en œuvre intégrale des plans visant à réduire la consommation de carburants et de combustibles fossiles. Au Canada, particulièrement en cette période de l'année, la possibilité de réchauffement du climat de quelques dixièmes de degrés par décennie semble à peine alarmante. Dans l'Arctique toutefois, cette augmentation suffit pour perturber irréparablement les écosystèmes et les réservoirs de glace, avec de profondes répercussions sur les habitudes de vie traditionnelles. Le changement climatique aura des effets régionaux inégaux et imprévisibles, mais il est clair que les écosystèmes les plus fragiles et les populations les plus vulnérables seront aussi les plus à risque.

Dans ce numéro[1] (voir page 501), Sari Kovats et Andrew Haines mettent à jour une analyse critique antérieure[2] et discutent des effets émergents du changement climatique sur la santé, notamment la vague de chaleur qui a frappé la France en 2003 et a fait plus de 14 000 victimes. En dépit de ce que nous disent la science et le bon sens, le Canada n'a pas tenu ses promesses de Kyoto. À mesure de l'expansion de notre économie (la croissance du PIB a atteint 40 % entre 1990 et 2002), les émissions ont augmenté elles aussi : elles dépassent maintenant de 25 % le total de 1990. Le Canada s'est engagé à réduire ses émissions de 6 % d'ici à 2012 par rapport au niveau de 1990. Il semble évident que nous n'atteindrons pas cet objectif. Au moment d'aller sous presse, le gouvernement évoquait la possibilité d'atténuer les obligations de Kyoto pour les «émetteurs importants» (les 700 entreprises qui produisent 50 % des émissions du Canada), au moment même où il lance l'enthousiaste «Défi d'une tonne» qui vise à persuader les citoyens d'assainir leurs propres activités (www.climatechange.gc.ca/onetonne/francais/index.asp?pid=179).

Ce dernier but pourrait être atteignable. Le Canada se classe parmi les 10 premiers pays pour la consommation annuelle par habitant de combustibles et de carburants fossiles (16,93 tonnes métriques de CO_2 par personne). L'Union européenne affiche un bilan beaucoup meilleur (p. ex., 9,52 au Danemark et 6,16 en France)[3]. Le secteur de l'énergie (transports, chauffage et fabrication) a produit plus de 80 % des émissions de gaz à effet de serre du Canada en 2002[4]. Les technologies vertes offrent une lueur d'espoir, mais leur adoption par le secteur public et les consommateurs demeure d'une lenteur glaciaire. Les panneaux solaires ne poussent pas comme des champignons sur les toits. Les salles de montre des concessionnaires automobiles offrent plus de VUS que de véhicules hybrides. Les municipalités favorisent toujours les autoroutes à quatre voies plutôt que le rail léger.

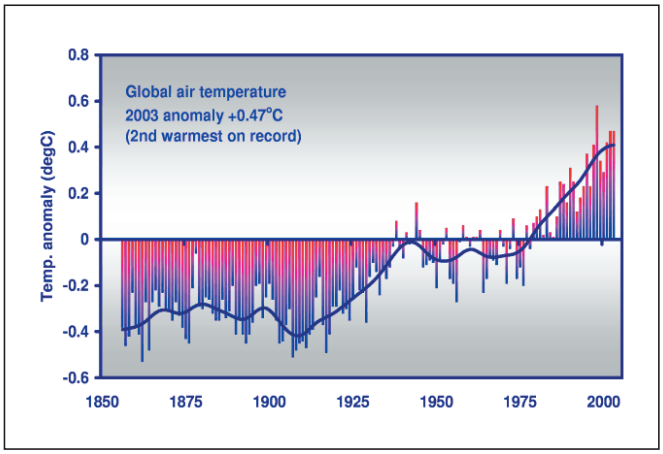

Fig. 1 : Température de l'air à la surface du globe. Reproduit avec la permission du Whitney Laboratory for Marine Bioscience, Université de la Floride.

Le Protocole de Kyoto a au moins forcé les pays participants à répertorier leur consommation d'énergie[4]. Le secteur de la prestation des soins de santé, qui représente maintenant 10 % environ de l'économie canadienne, devra se pencher sur ses contributions au réchauffement de la planète et à la dégradation de l'environnement en général. On a déjà quantifié l'énorme effet écologique des hôpitaux[5], et des établissements trouvent des moyens de réduire leur incidence sur l'environnement. Les médecins, dont beaucoup ont appuyé vigoureusement la signature du Protocole, devraient établir leur propre «inventaire vert» et réfléchir aux aspects matériels et comportementaux de leur pratique qu'il faudrait moderniser — comme les déplacements évitables des patients sur des distances plus ou moins longues. Il ne faut pas oublier les possibilités quotidiennes qui s'offrent aux médecins de rappeler à leurs patients et au public le lien étroit entre l'état de l'environnement et l'état de notre santé. — *JAMC*

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DOI:10.1503/cmaj.050089

Global climate change and health

Canada is experiencing some of the most rapid warming as the temperature of the Earth's land surface slowly rises. As the Kyoto Protocol comes into effect, Kovats and Haines discuss the health implications of global climate change and the need for effective public health interventions for extreme weather events, as well as for research into strategies that will help populations adapt to climate change.
See page 501


Franck Prevel, Associated Press

Le changement du climat mondial et la santé

Le Canada connaît l'un des réchauffements les plus rapides à mesure que les températures de la surface de la Terre grimpent lentement. Au moment où le Protocole de Kyoto entre en vigueur, Kovats et Haines discutent des répercussions pour la santé du changement climatique mondial et du besoin d'interventions efficaces en santé publique contre les événements météorologiques violents, ainsi que des recherches de stratégies qui aideront les populations à s'adapter au changement climatique.
Voir page 501

Sexual risk behaviour among HIV-1 vaccine study recipients

Some HIV-1 vaccine trials have revealed increases in risky sexual behaviour among study subjects, perhaps because participants believe the vaccine being tested is efficacious. Lampinen and colleagues surveyed 291 male participants of a phase III HIV-1 vaccine trial through 18 months of the trial. Using self-reported data from the 6-month period before the trial as a baseline, they established that the rate of unprotected receptive anal intercourse did not change significantly in those 18 months. However, 21% of participants reported having unprotected anal intercourse with a partner whose HIV-1 status was positive or unknown, which puts them at high risk for HIV-1 infection.
See page 479

Comportement sexuel risqué chez des personnes ayant reçu un vaccin à l'étude contre le VIH-1

Des études sur le vaccin contre le VIH-1 ont révélé des augmentations du comportement sexuel risqué chez certains sujets de l'étude, peut-être parce que les participants croient que le vaccin à l'étude est efficace. Lampinen et ses collaborateurs ont sondé 291 sujets de sexe masculin participant à une étude de phase III portant sur un vaccin contre le VIH-1 pendant 18 mois de l'étude et, en utilisant comme niveau de référence des données autodéclarées provenant de la période de six mois précédant l'étude, ils ont établi que le taux des relations anales réceptives non protégées n'a pas changé pour la peine au cours des 18 mois en question. Vingt-et-un pour cent des participants ont toutefois déclaré avoir eu une relation anale non protégée avec un partenaire dont l'infection par le VIH-1 était positive ou inconnue, ce qui en fait un groupe à risque élevé d'infection par le VIH-1.
Voir page 479

References cited in pharmaceutical ads

The primary goal of pharmaceutical advertisements is to convince clinicians to prescribe their product. To determine what kinds of documents are cited in support of claims made in such ads and to assess the availability of the documents to clinicians, Cooper and Schriger examined 438 ads published over 1 year in 10 US medical journals. They found that 29% of the ads did not cite any references. Of the references citing unique source documents, 55% were to journal articles and 19% were to "data on file." Of the original research cited in the ads, 58% was sponsored by or had authors affiliated with the product's manufacturer. Although the references to journal articles were easily obtainable, other published sources were not, and references to unpublished material were seldom available. Improved accessibility to references and monitoring of their validity are required to help clinicians obtain and evaluate the evidence offered in support of claims made in pharmaceutical ads.
See page 487

Références citées dans les annonces des sociétés pharmaceutiques

Les annonces des sociétés pharmaceutiques visent principalement à convaincre les cliniciens de prescrire leur produit. Afin de déterminer le type de

documents que l'on cite pour appuyer les affirmations avancées dans ces annonces et évaluer la disponibilité des documents pour les cliniciens, Cooper et Schriger ont étudié 438 annonces publiées en un an dans 10 journaux médicaux des États-Unis. Ils ont constaté que 29 % des annonces ne citaient aucune référence. Parmi les références où l'on citait des documents d'origine unique, il y avait 55 % d'articles de journaux et 19 % de «données en dossier». Sur les recherches originales citées dans les annonces, 58 % étaient commanditées par le fabricant du produit ou des auteurs de l'étude lui étaient affiliés. Même si les références à des articles de journaux étaient faciles à obtenir, les autres sources publiées ne l'étaient pas et les références à des documents non publiés étaient rarement disponibles. Il faut améliorer l'accessibilité des références et mieux en contrôler la validité pour aider les cliniciens à obtenir et à évaluer les données probantes présentées à l'appui d'affirmations faites dans des annonces de sociétés pharmaceutiques.
Voir page 487

Pertussis

Pertussis is occurring more frequently among children who are too young to be vaccinated and among adolescents and adults. This increase is due mainly to waning immunity among vaccinated individuals, who become susceptible to infection in adolescence and adulthood. Since the clinical presentation in adolescents, adults and vaccinated people may be atypical (e.g., paroxysmal cough of short duration or simply a persistent cough) and because laboratory and microbiologic tests take time, therapy with erythromycin, azithromycin or clarithromycin should be administered on the basis of a clinical diagnosis. Tozzi and colleagues review recent findings and issues in the diagnosis, treatment and prophylaxis of pertussis.
See page 509

Coqueluche

La coqueluche est plus fréquente chez les enfants trop jeunes pour être vaccinés, ainsi que chez les adolescents et les adultes. Cette augmentation est attribuable principalement au fléchissement de l'immunité chez les sujets vaccinés qui deviennent vulnérables à l'infection à l'adolescence et à l'âge adulte. Comme la manifestation clinique chez les adolescents, les adultes et les sujets vaccinés peut être atypique (p. ex., toux paroxystique de brève durée ou simplement toux persistante) et comme les analyses de laboratoire et de microbiologie prennent du temps, il faudrait administrer une thérapie à l'érythromycine, à l'azithromycine ou à la clarithromycine fondée sur un diagnostic clinique. Tozzi et ses collaborateurs passent en revue des constatations récentes et des problèmes de diagnostic, de traitement et de prophylaxie de la coqueluche.
Voir page 509

In Synopsis

In **Analysis**, Balzarini and Van Damme discuss the scientific advances in developing microbicides for intravaginal and intrarectal use in the prevention of HIV infection (**page 461**).

In **Public Health**, Weir advises a systematic investigation of the causes of fever in patients who travel internationally, because malaria may well be the cause (**page 473**).


CDC/Jim Gathany

In **Practice**, Barnabé presents a teaching case report on thyrotoxic periodic paralysis (**page 471**).

Within the **In the Literature section**, Bernstein and Etchells comment on a study that examined the impact of reduced interns' work hours on the rate of medical errors (**page 474**).

In **Clinical Vistas**, Guller and Bach encounter an elderly man with a tympanic abdominal mass that has a rare cause (**page 475**).

Synopsis

Dans Analyses, Balzarini et Van Damme discutent des progrès scientifiques réalisés dans la mise au point de microbicides pour utilisation intravaginale et intrarectale dans la prévention de l'infection par le VIH (**page 461**).

Dans Santé publique, Weir recommande une analyse systématique des causes de la fièvre chez les patients revenant de l'étranger, parce que le paludisme peut très bien en être la cause (**page 473**).

Dans la pratique, Barnabé présente un rapport de cas d'enseignement portant sur une paralysie périodique thyréotoxique (**page 471**).

Dans les écrits, Bernstein et Etchells présentent des commentaires au sujet d'une étude de l'impact de la réduction des heures de travail des internes sur le taux d'erreurs médicales (**page 474**).

Dans Perspective clinique, Guller et Bach rencontrent un homme âgé présentant une masse abdominale tympanique de cause rare (**page 475**).

Ovarian cancer screening

Usha Menon's review of ovarian cancer screening[1] appears to misquote the result of the randomized controlled trial of multimodal screening (with the tumour marker CA125 and ultrasonography) by Jacobs and associates.[2]

In that study the number of deaths from ovarian cancer was 18 among the 10 977 patients in the control group and 9 among the 10 958 patients in the screened group (relative risk of death in the unscreened group 2.0, 95% confidence interval 0.78–5.13); Menon's article seems to state the reverse. Although the difference in number of deaths was not statistically significant, these results represent a possible halving of the death rate by screening, rather than a possible doubling.

Erica L. Eason
Associate Professor
Obstetrics and Gynaecology
University of Ottawa
Ottawa, Ont.

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DOI:10.1503/cmaj.1041644

Usha Menon,[1] in an analysis of ovarian cancer screening, points out that the best evidence for screening comes from a study that found significant longer median survival with screening but no significant difference in the number of deaths from ovarian or fallopian tube cancer.[2] This sounds like a classic example of lead-time bias, in which earlier diagnosis of a disease has no impact on the patient's outcome. In other words, the patient may die of the disease at the same time as she would have if the diagnosis had been made 30 months later. Median survival may appear better, but in fact all we've done is to give the patient a longer cancer experience, without better quality or quantity of life.

If this is the best evidence we have for ovarian cancer screening, then I certainly agree that "Screening is not currently recommended for the general population."

David M. Allen
Sudbury, Ont.

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DOI:10.1503/cmaj.1041601

Treating *C. difficile*

In their review of *Clostridium difficile*-associated diarrhea,[1] Susan Poutanen and Andrew Simor note that concurrent administration of probiotic agents (e.g., *Saccharomyces boulardii* and *Lactobacillus GG*) and antibiotics to prevent recurrence of the problem has yielded mixed results.

There is substantial overlap among antibiotic use, *C. difficile* colonization and subsequent *C. difficile*-induced diarrhea. In fact, 26% to 50% of antibiotic-associated diarrhea can be attributed to *C. difficile*.[2] A meta-analysis[3] of *S. boulardii* and *Lactobacillus GG* co-administered with antibiotics (including the antibiotics regarded as the most common inducers of diarrhea [ampicillin, cephalosporins, clindamycin][2,4]) for treatment of antibiotic-associated diarrhea in a diverse population (881 patients of all ages, including inpatients, outpatients and people from developing countries) provided strong evidence to suggest that probiotic agents prevent antibiotic-associated diarrhea (relative risk 0.40, 95% confidence interval [CI] 0.28–0.57). A larger meta-analysis (1380 patients) of 7 probiotic species administered with a host of antibiotics provided further evidence of the effectiveness of probiotics for the prevention of antibiotic-associated diarrhea (odds ratio 0.37, 95% CI 0.26–0.53).[5]

However, these meta-analyses are limited, in that they provided little information about the species and doses that would yield the most beneficial results and did not identify the patient population(s) that would benefit most. In addition, neither author group performed a meta-analysis for adverse events, nor did they comment on why such an analysis was not done. We might assume that only minor adverse events were reported in the randomized controlled trials reviewed; however, meta-analyses of such trials often overlook important details.[6] Although no adverse events were reported in these meta-analyses, infections resulting from probiotic use (e.g., bacteremia, endocarditis, septicemia, pneumonia and deep abdominal abscesses) have been reported in neonates and severely debilitated and immunocompromised individuals.[7] It is unclear, however, whether exogenous or endogenous *Lactobacilli* were the cause of the few cases of *Lactobacillus bacteremia* that have been reported.[8]

The public health burden of this problem is substantial and the preliminary evidence promising; as such, concurrent use of probiotics with antibiotics in the hospital setting is worth further consideration. However, a research agenda is needed to determine which probiotic species and dosages might provide effective prophylaxis and which hospital population(s) would benefit most.

Bradley C. Johnston
Graduate Student
Sunita Vohra
Director, Complementary and
Alternative Research and Education
(CARE) Program
Department of Pediatrics
University of Alberta
Edmonton, Alta.

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Competing interests: Funding: Bradley Johnston is funded by the University of Alberta Evidence-based Practice Centre and The Hospital for Sick Children Foundation.

DOI:10.1503/cmaj.1041646

In their comprehensive review of *Clostridium difficile*-associated diarrhea (CDAD), Susan Poutanen and Andrew Simor[1] refer to the use of anion-binding resins (colestipol or cholestyramine). It is important to highlight the timing of administration of these agents in relation to other oral therapeutic agents (metronidazole or vancomycin). In addition to binding the toxin and spores of *C. difficile*, the binding agents may also bind orally administered therapeutic agents to various degrees, thereby negating their effect. Ideally, resin binders should be given either an hour before or 4 to 6 hours after administration of the oral antibiotics[2] to avoid this problem. However, in clinical practice, especially in hospitals, I have found that the binders and other agents are often given simultaneously; many of the patients have recurrent disease, are described as being resistant to metronidazole (an otherwise rare situation) and are subsequently given oral vancomycin, which is more costly. I believe that this is a common cause of iatrogenic resistance to oral metronidazole.

There are no studies of this phenomenon (i.e., no evidence in this era of evidenced-based and "evidence-made"[3] medicine), but on the basis of a theoretical understanding of the pathophysiology of CDAD, I often administer 10 to 14 days of oral metronidazole followed by 5 to 7 days of oral cholestyramine (to bind the remaining spores in the gut) and have observed a very low rate of recurrence. It is time to prospectively evaluate this simple strategy of sequential therapy in the management of CDAD in a randomized trial.

Malvinder S. Parmar
Associate Professor, Medicine
Northern Ontario School of Medicine
Laurentian and Lakehead Universities
Sudbury and Thunder Bay, Ont.

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Competing interests: None declared.

DOI:10.1503/cmaj.1041195

[The authors respond to Dr. Parmar:]

We agree with Malvinder Parmar that the role of anion-binding resins in the treatment of CDAD needs to be studied further. Anion-binding resins, such as cholestyramine and colestipol, have been shown to bind *C. difficile* toxins[1] and have consequently been proposed as potentially useful in the treatment of CDAD, as we mentioned in our review.[2] Parmar also suggests that anion-binding resins may also bind *C. difficile* spores, but to the best of our knowledge, this phenomenon has not been described in published reports. Small numbers of mostly anecdotal reports of success and failure with the use of anion-binding resins in the treatment of CDAD have been published (summarized by Ariano and associates[3]), but no large randomized controlled trials have been completed to definitively determine the role of resins. Anion-binding resins have been shown to bind vancomycin[1,4] and theoretically may bind other antibiotics such as metronidazole, although we are not aware of any published data specifically describing this. Given the possibility of antibiotic binding by resins, some authors have suggested not using anion-binding resins in the treatment of CDAD,[5] whereas others recommend using them only if administered at different times from metronidazole or vancomycin.[6] As Parmar suggests, more study is needed to address the optimal indication and timing of anion-binding resins in the treatment of CDAD.

Susan M. Poutanen
Andrew E. Simor
Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, Ont.

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Competing interests: None declared.

DOI:10.1503/cmaj.1041461

Cobalamin deficiency in elderly patients

Emmanuel Andrès and colleagues,[1] in their comprehensive review of diagnosis and treatment of vitamin B_{12} (cobalamin) deficiency, fail to consider 2 elements relevant to the Canadian experience.

First, because Canada's flour supply is fortified with folic acid,[2] plasma homocysteine level (determined primarily by folate status) is much less effective in the diagnostic work-up of suspected cobalamin deficiency.[3] In a large population-based study, we established the

test properties of total plasma homocysteine for the diagnosis of cobalamin deficiency among 692 adults in Ontario, after exclusion of people with renal impairment or folate deficiency (red cell folate less than 215 nmol/L).[2] A homocysteine value of 15 µmol/L or more did not discriminate between cobalamin concentrations below and above 120 pmol/L (positive and negative predictive values 7.4% and 97.2%, respectively), nor did it discriminate "indeterminate" cobalamin levels between 120 and 150 pmol/L (positive and negative predictive values 6.3% and 94.0%, respectively).[2]

Second, the diagnostic algorithm for cobalamin deficiency proposed by Andres and colleagues (Fig. 3 in their article[1]) is unnecessarily complex, especially for seniors, in whom cobalamin malabsorption is commonly found because of age-related atrophic gastritis.[4] Although serum methylmalonic acid (MMA) may have a place in a diagnostic algorithm, this indicator of cobalamin insufficiency is falsely elevated in the presence of modest renal impairment[5] with advancing age. Furthermore, serum MMA is commonly elevated in elderly North Americans,[6] but lowering it through vitamin B_{12} supplementation does not appear to affect blood hemoglobin concentration, neurological disability score or quality of life.[7] Like homocysteine, MMA has not been fully validated as a routine clinical test of cobalamin deficiency,[8] especially in the face of increased folate fortification,[2] and MMA testing is not routinely available in Canadian centres and community laboratories.

We propose a simpler and more direct diagnostic approach in elderly patients (Fig. 1), with 2 options for serum cobalamin concentrations in the "grey zone" of 150 to 200 pmol/L. Option A involves testing for serum holotranscobalamin — the complex formed by cobalamin and its transport protein, transcobalamin — the physiologically active form of vitamin B_{12} that is transported into cells.[9] This inexpensive, simple radioimmunoassay-based test, which will become more readily available in Canada, displayed a sensitivity of 100% and a specificity of 89% for cobalamin deficiency in one study.[9] Option B involves initial treatment with parenteral cobalamin according to the dosing schedule outlined by Andrès and colleagues,[1] with assessment of the clinical response after 3 months. High-dose oral cobalamin (e.g., 1000 µg/day) can be used thereafter, as described by Andrès and colleagues.[1] A therapeutic re-

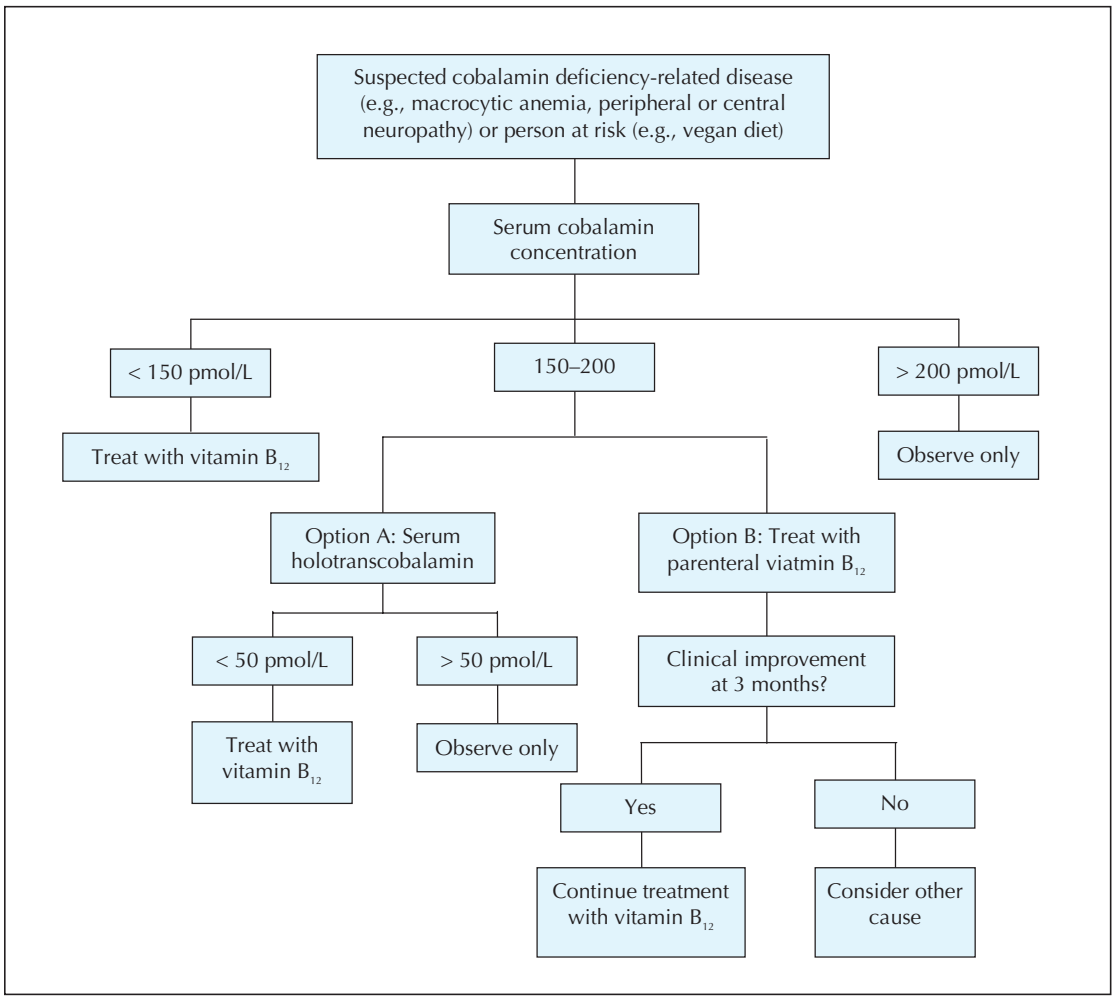

Fig. 1: Diagnostic approach to suspected cobalamin deficiency in elderly patients.

sponse validates not only the diagnosis, but also the treatment, which is otherwise safe and inexpensive.

Joel G. Ray
Assistant Professor
Department of Medicine
St. Michael's Hospital
University of Toronto
Toronto, Ont.
David E.C. Cole
Professor
Department of Pathology
Sunnybrook and Women's College
Health Sciences Centre
University of Toronto
Toronto, Ont.

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Competing interests: None declared.

DOI:10.1503/cmaj.1041365

Emmanuel Andrès and colleagues[1] state that the classic treatment for deficiency of vitamin B_{12} is injections of crystalline vitamin B_{12} and that an oral treatment has "recently" been devised. However, oral treatment of pernicious anemia was described in 1926 by George Minot and William Murphy.[2] Indeed, in 1934, they (along with George Whipple) received the Nobel Prize for this work. Not until 1948 did Karl Folkers and his coworkers at Merck succeed in purifying crystalline vitamin B_{12}.[3]

S. Peter Wetterberg
Consultant Geriatrician
Medi 3 [private hospital]
Aalesund, Norway

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Competing interests: None declared.

DOI:10.1503/cmaj.1041367

In a recent review, Emmanuel Andrès and colleagues[1] recommend parenteral or oral administration of cobalamin as the treatment of choice for food-cobalamin malabsorption syndrome. The authors mention hypochlorhydria as a factor in this problem but do not recommend hydrochloric acid (HCl) and pepsin therapy as a potential treatment.

In a study of 5 patients with hypochlorhydria, all of the patients had decreased urinary excretion of protein-bound cobalamin.[2] After receiving supplemental HCl, pepsin, gastric intrinsic factor or some combination of these, 4 of the 5 patients showed improvement in protein-bound cobalamin absorption. Another study examined the effect of water, cranberry juice (pH 2.5–2.6) or a 0.1N HCl solution (pH 1.2) on the absorption of protein-bound cobalamin in 3 groups of elderly subjects: healthy individuals, subjects pretreated with omeprazole to simulate the hypochlorhydria of atrophic gastritis and patients with diagnosed atrophic gastritis.[3] Administration of diluted HCl increased the absorption of protein-bound cobalamin in all 3 groups, and this difference was statistically significant for both the omeprazole-treated and healthy subjects ($p < 0.001$). The authors noted that this improvement might have been the result of the acid's ability to augment the release of cobalamin from protein.

Maintaining adequate gastric pH ensures a sufficient sterilizing barrier against enteric pathogens, allows for proper absorption of micronutrients, preserves normal intestinal permeability and prevents hypergastrinemia.[4,5] High gastric pH (as occurs in atrophic gastritis) is also associated with the development of gastric malignant tumours;[6] therefore, maintaining adequate gastric pH might be a preventive measure. Supplemental HCl has been shown to reduce (acidify) gastric pH in subjects with simulated hypochlorhydria.[7] The method of administration has been described by several investigators.[5,8-10] Patients usually start with one 5- to 10-grain (325- to 650-mg) capsule of betaine or glutamic acid hydrochloride with each meal; pepsin is sometimes added to these capsules to improve absorption. Patients are instructed to increase the dosage by one 5- to 10-grain capsule with each meal, sometimes working up to 60–80 grains with every meal. Patients are advised against this therapy if they are also receiving nonsteroidal anti-inflammatory medications or corticosteroids, if they have active peptic ulcer disease, if they have abdominal pain, or if they experience abdominal pain or burning with this treatment. Patients are also instructed to use fewer capsules with smaller meals and more capsules at larger meals.

Jonathan E. Prousky
Associate Dean of Clinical Education
Chief Naturopathic Medical Officer
The Canadian College of Naturopathic Medicine
Toronto, Ont.

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Competing interests: Jonathan E. Prousky is a consultant for Swiss Herbal Remedies, Ltd., a company that sells nutritional supplements.

DOI:10.1503/cmaj.1041424

[One of the authors responds:]

We agree with Joel Ray and David Cole regarding the relative practical value of serum total homocysteine and methylmalonic acid in elderly patients with suspected cobalamin deficiency. Although testing for serum holotranscobalamin is not routinely available in many countries, we believe that it may be appropriate in future as a routine clinical test for cobalamin deficiency. However, to date, a consensus on the definition for cobalamin deficiency, especially among elderly patients, has not been achieved.[1] Thus, in our experience, serum total homocysteine is currently a helpful, inexpensive indicator of true (tissue) cobalamin deficiency, as suggested in our article.[2]

We agree with Peter Wetterberg's comments on oral cobalamin. However, the usefulness of oral cobalamin therapy has only recently been documented, starting in 1995, with studies that meet the criteria of evidence-based medicine.[3-6]

We read with great interest Jonathan Prousky's comments, although we have no experience with the therapies he describes. Nevertheless, we believe that this information indirectly supports the concept of food-cobalamin malabsorption.[7]

Emmanuel Andrès
Department of Internal Medicine
University Hospital of Strasbourg
Strasbourg, France

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Competing interests: None declared.

DOI:10.1503/cmaj.1041701

Short ACTH stimulation test for adrenal reserves of cortisol, not adrenal function

The classical description of Addison's disease in a 15-year-old girl[1] is a timely reminder of this well-known but uncommon disorder. In their description of the investigative work-up and discussion, Chantelle Barnard and associates[1] imply that the short adrenocorticotropin hormone (ACTH) stimulation test is diagnostic of primary adrenal insufficiency. This is a common misapprehension.

In the test, an intravenous (or intramuscular) injection of 250 µg of synthetic ACTH (tetracosactrin) results in release of preformed cortisol from adrenal stores, which is measured in the serum 30 (and/or 60) minutes later and compared with the baseline concentration. An abnormal response (a serum cortisol peak below 550 nmol/L or an increment of less than 200 nmol/L from baseline or both) identifies adrenal insufficiency but cannot distinguish Addison's disease (primary adrenal failure) from secondary hypoadrenalism. In pituitary disease (ACTH deficiency), for instance, the result of the test may be abnormal because of reduced stores of cortisol, even though the adrenal glands themselves have normal biosynthetic and secretory func-

Mécanisme de présentation des lettres

Le site amélioré des cyberlettres du *JAMC* est désormais le portail de réception de tous les textes destinés à la chronique Lettres. Pour rédiger une cyberlettre, consultez un article sur le site www.jamc.ca et cliquez ensuite sur le lien «Lettres électroniques : répondre à cet article», dans la boîte en haut à droite de l'article. Toutes les cyberlettres seront étudiées pour une éventuelle publication dans le journal imprimé.

Les lettres répondant à un article publié dans le *JAMC* sont plus susceptibles d'être acceptées pour publication imprimée si elles sont présentées dans les deux mois de la date de publication de l'article. Les lettres acceptées pour publication imprimée sont révisées en fonction du style du *JAMC* et raccourcies au besoin (elles doivent habituellement compter au maximum 250 mots).

tion. In this situation, a prolonged ACTH stimulation test using 1 mg depot tetracosactrin, with serial measurements of serum cortisol concentrations over 24 hours, would allow sufficient time for the otherwise healthy adrenal glands to mount an adequate cortisol response, whereas the test result would be abnormal in Addison's disease (particularly in preclinical disease, in which the result of the shorter test may be normal).

As the authors correctly point out, the hyperpigmentation seen in Addison's disease reflects increased ACTH and melanocyte-stimulating hormone due to dysinhibition of the hypothalamic–pituitary axis, which is in turn a result of low circulating cortisol concentrations. This is a relatively specific sign, and there is therefore little doubt that the hypoadrenalism in the patient described was due to primary adrenal failure. However, an elevated plasma ACTH concentration at baseline reliably distinguishes between primary and secondary causes and would have provided incontrovertible evidence of Addison's disease,[2] besides being far simpler than the prolonged ACTH stimulation test.

R. Deeba Syeda
Devraj Urs Medical College and Research Centre
Kolar, India
Farheena N. Mecci
Dr. Ambedkar Medical College
Bangalore, India
Akheel A. Syed
University of Newcastle
Newcastle-upon-Tyne, UK

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Competing interests: None declared.

DOI:10.1503/cmaj.1041542

[The authors respond:]

We agree with the interpretation of the short ACTH stimulation test described by Deeba Syeda and associates. In the case that we described,[1] a long ACTH stimulation test was unnecessary because of the clinical picture, especially the hyperpigmentation and the markedly increased ACTH level (285 [normally less than 18] pmol/L).

Chantal Barnard
Ronik Kanani
Jeremy N. Friedman
Department of Paediatrics
The Hospital for Sick Children
Toronto, Ont.

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DOI:10.1503/cmaj.1041762

Russia and social "reform"

Paul Webster, in his description of the Russian government's plans "to 'monetize' its social commitments"[1] through reform of a variety of Soviet-era entitlements, fails to cover some important details.

It is true, as stated by a health care analyst from Moscow, that "Russia's system of privileges was never designed to support the poor." But the estimate that "the poorest 10% of the population receive 4% of existing benefits, while the richest 10% receive 20%" is nothing more than speculation. The government used such estimates to prove that the system of natural entitlements must be changed. Shortly after the new law was enacted, when the government started to check how many poor people were eligible for "monetization" of their entitlements, it found that the numbers had been underestimated by up to 30%. Now nobody knows how many people are entitled to monthly subsistence. Of course, this detail is not relevant to the government; the president set the amount without any supporting research.

Economist Mikhail Zurabov, who chairs the Health and Social Development Ministry, is leading the transformation of the most attractive health care institutions to an intermediary propriety state, which would to allow them to be privatized in the short term. Former health minister Yuri Shevchenko, during his years in cabinet, created the huge "national hospital," using federal money to equip it; he then slipped from his ministerial position to that of director of the hospital.

At the other end of the health care spectrum, the new legislation prevents municipal health care services from having access to any monies from the federal or regional budgets; as a result, the wages of staff as well as health care expenditures must come from the limited resources of the municipal bodies. Finally, in the budget for 2005 military spending will increase by up to 30%, but there will be no increase for health care.

The title of Webster's article is absolutely correct: "Reforms mean [that] Russians lose free health care." In January people all across Russia took to the streets to protest against the "monetization" of their entitlements. Members of parliament have called on the government to resign, but in fact, by approving the proposed regulations, they share responsibility for these reforms. The problem of natural entitlements has become the starting point for a huge crisis.

V. Vlassov
Director
Russian Branch of the Nordic Cochrane Centre
Moscow, Russia

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DOI:10.1503/cmaj.1041731

HUMAN RIGHTS

An Afghan doctor's prescription for peace

Human rights officials in Afghanistan have documented thousands of violations in the last 18 months, including illegal detentions, forced evictions, street kidnappings with rape, trafficking, attacks on women not wearing burqas and assaults targeting new girls' schools, says Dr. Sima Samar, chair of the Afghan Independent Human Rights Commission.

"It is not safe — even here in the capital — and human rights violations are constant," she told *CMAJ* during an interview at the AIHRC headquarters in Kabul.

"Violations of women's rights and human rights continue with impunity. Girls' schools are set on fire by fundamentalists. Trafficking of women and children continues. Tactics of intimidation are used to stop people and especially women from exercising their human rights. Prisons hold women and men illegally," she wrote in the commission's 2003–2004 annual report.

Private prisons and militias also operate, contributing to an increasing number of illegal detentions and disappearances, says Samar, who is building a network of commission offices across Afghanistan.

Samar, a surgeon and women's rights activist, was appointed chair of the commission after serving as deputy prime minister and minister for women's affairs in the first 6 months of the Afghan Transitional Authority's first term.

Peacekeepers, including 1000 Canadians housed at Camp Julien outside of Kabul, are essential at this stage of Afghanistan's reconstruction, Samar emphasizes. Despite a new Constitution and Bill of Rights that pledge to abide by international human rights treaties and conventions, and guarantee fair political representation and equal rights for women, those rights are not yet widespread or enforced.

"Rights are not real without security," Samar says. "Increasing poverty — with no real alternatives — makes it easy to have huge tracts of land consigned to opium-poppy cultivation. No one seems able to stand up to the warlords." Afghanistan is the world's number one opium producer.

Samar is concerned about the emphasis on military presence and security to the exclusion of international aid and expertise that establishes gender-inclusive institutions and structures to rebuild civil society. Devoting the majority of limited resources to the military starves efforts to rebuild the justice sector and achieve sustainable peace, she warns.

"I continue to believe that the rehabilitation of our society can only be achieved by integrating and accentuating the role of women in the reconstruction process," she says.

"Rampant corruption and the absence of effective reform mechanisms in government institutions have caused the loss of credibility of our legal and judicial systems in particular," Samar wrote in her report. "In the face of forced marriages and hopelessness about their lives, young women are committing suicide by self-immolation."

Cpl. John Bradley, DND

Most women in Afghanistan continue to wear burqas because it's dangerous not to, says Samar.

In January 2003, Physicians for Human Rights reported that "more than 70% of Afghan women suffered from major depression, nearly two-thirds were suicidal and 16% had already attempted suicide."

"No one should doubt how much the average Afghan wants peace and democracy," Samar says.

Afghanistan ranks in the bottom 5 on the UN Human Development Index and in the top 3 levels of infant mortality and childbirth deaths. It is also home to the largest return of refugees ever recorded (2 million). — *Marilou McPhedran*, Kabul, Afghanistan

Marilou McPhedran is co-director of the International Women's Rights Project at the University of Victoria Centre for Global Studies.

DOI:10.1503/cmaj.050039

ENVIRONMENTAL PROTECTION

Climate change wars stall government plan

The Kyoto Protocol to combat climate change enters into force Feb. 16, leaving Canada with the mammoth challenge of cutting its greenhouse gas emissions by 20%–25% over the next 5 years.

Canada has committed to reducing greenhouse gas emissions to 6% below 1990 levels by 2010 — a reduction of 300 megatonnes per year, according to the Vancouver-based Sage Climate Project. At press time, the federal Climate Change Secretariat did not yet have a plan that accounts for that entire reduction.

Infighting among federal government departments — Natural Resources Canada and Environment Canada, with some weigh-in by Industry Canada — has meant that there is no clear lead agency and no single vision of how to achieve Canada's commitments.

"There's open warfare within the government about what it should be doing," said one source following the file.

An intense industry lobby, led by Alberta and the Canadian Council of Chief Executives, stalled initial efforts to pass a get-tough approach that would have made emission cuts mandatory. The Council argued that implementing the measures would cripple the Canadian economy and give US competitors an even greater advantage, since Washington has refused to sign the accord.

New technology will take care of the climate change problem over time, the Council argues in an April 2004 position paper.

Ottawa has been pursuing a voluntary approach, while rolling out a campaign called "The One-Tonne Challenge," which encourages consumers to cut greenhouse gas emissions by one tonne per household. But that approach, which relies on 20% of Canada's total reductions to come from consumers, versus only 15% from industry, ignores the reality that 700 oil and gas producers, electricity stations, mines and manufacturers produce 50% of Canada's emissions.

The voluntary approach has so far failed, as the *Globe and Mail* revealed in leaked federal documents dated Jan. 5. The document warned that "with current policy and programs, Canada is still going to be significantly off the Kyoto target."

Environment Canada has instead proposed a plan that embraces more regulation and the use of consumer and tax incentives to change behaviour. The plan advocates market-based initiatives such as international carbon trading and investment in projects to credit Canada with reductions when emissions are tallied on a global scale. The plan also relies more heavily on renewable energy.

By contrast, Natural Resources Canada proposes offsetting the emission cuts required of industry with federal investments in energy efficiency and having Canada's forests classified as "carbon sinks" under the international rules, giving Canada credits. — *Laura Eggertson*, CMAJ

DOI:10.1503/cmaj.050070

ETHICS

Media Doctor prognosis for health journalism

A group of Australian academics and clinicians have put medical reporting of new treatments under the microscope with Media Doctor (www.mediadoctor.org.au).

Funded by the Newcastle Institute of Public Health, Media Doctor reviews a selection of current news items about medical treatments, assesses their quality using a standardized rating scale and presents reviews of good and bad examples. Researchers use 10 criteria to rate such attributes as the novelty of the treatment, alternatives mentioned, whether there is evidence of disease mongering, whether the benefits and harms were fairly reported and whether conflicts of interest or costs are mentioned.

Media Doctor expects these independent and objective critiques will improve the accuracy of medical reporting.

One of the sites' founders, Dr. David Henry, a professor of clinical pharmacology at the University of Newcastle, says improved standards of journalism are definitely needed because of the potential for harm an erroneous article can yield and the powerful vested interests in health technologies.

Generally, news coverage of new medical treatments is regarded as poor and is prone to exaggeration, Media Doctor states.

Plans are already under way to improve the site, including providing more detailed information on specific health coverage to senior media staff.

Media Doctor now focuses on the Australian media, but André Picard, a *Globe and Mail* health reporter, thinks Canadians would "absolutely" be interested in a similar service. "I think a Media Doctor, if it is consistent and fair, would be well-read and influential — though perhaps journalists would be reluctant to admit that is the case!"

Researchers in Pakistan, New Zealand and Canada have all expressed interest in replicating the service. Henry says he'd be delighted to see other countries evaluate their health journalism so that international comparisons could be made. — *Alan Cassels*, Victoria

DOI:10.1503/cmaj.1041734

INTERNATIONAL HEALTH

Landmark global tobacco treaty coming into effect

The Canada-inspired global treaty to reduce tobacco sales and use comes into effect Feb. 28.

Canada sponsored the original resolution in 1995 that led to the development of the WHO Framework Convention on Tobacco Control, the world's first international health treaty.

In addition, Canada's tobacco control strategies were a template for many of the measures, said Cynthia Callard, executive director of Physicians for a Smoke-free Canada. "Canada was a big champion of the treaty financially and morally."

The treaty, which is legally binding, bans tobacco advertising and promotion unless constitutional barriers exist and requires warning labels that cover 30% of cigarette packages.

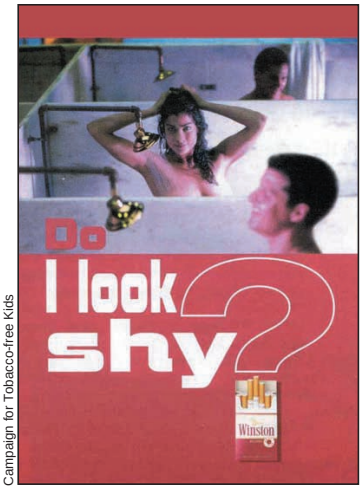
It also provides nations with a roadmap for enacting research-based policies in areas such as secondhand smoke protections, tobacco taxation, tobacco product regulation, combatting cigarette smuggling, public education, and tobacco cessation treatment.

Given that the treaty touches on many legislative areas, including taxation, advertising, education, law and health, it is "quite astounding" that it passed, said Carla Gilders, the director general of Health Canada's International Affairs Directorate.

The treaty was agreed on by WHO's 192 member states in 2003, but wasn't slated to come into effect until 90 days after being ratified by 40 countries. Peru became the 40th on Nov. 30. The US has not yet ratified the treaty despite pressure from lobby groups such as the American Lung Association.

The ratifying countries — 49 as of mid-January — will be part of the Conference of Parties, which will decide how to manage, monitor and finance the treaty, which is binding.

Canada is already in "substantial compliance because much of the treaty was modelled on Canadian legislation," said Gilders. In addition to taking part in the conference, Canada will share its expertise. There is $1 million in the Tobacco Control Strategy fund for international projects.



Campaign for Tobacco-free Kids

What's being sold here? The treaty includes new tobacco advertising guidelines.

Diseases related to tobacco use kill nearly 5 million people worldwide every year. About 84% of smokers live in developing countries, where the tobacco epidemic is still growing. — *Barbara Sibbald*, CMAJ

DOI:10.1503/cmaj.050047

NEW TECHNOLOGY

Private-public partnerships planned for BioMed City

Leading medical microbiologists and biomedical entrepreneurs are teaming up in Winnipeg to create "BioMed City," dedicated to studying and fighting infectious diseases.

The catalyst for BioMed City is the International Centre for Infectious Diseases (ICID), a not-for-profit private agency that will build private–public partnerships to raise money for training, research and commercialization. The federal government has invested $3 million to bring ICID to life.

Winnipeg is "already a Mecca for research in infectious diseases," ICID president and CEO Terry Duguid says. "We want to build on what we have."

Winnipeg's biomedical sector includes the Canadian Public Health Agency and the Canadian Science Centre for Human and Animal Health. These 2 are aligned with the University of Manitoba's department of medical microbiology, where researchers garnered international headlines for identifying a group of HIV-resistant prostitutes in Nairobi. A promising HIV vaccine initiative in partnership with Oxford University is now underway. U of M scientists have also received $23 million from the Gates Foundation to expand an HIV prevention model.

ICID will focus on raising funds for research into new vaccines, biomedical devices, systems of prevention and biosafety. Profits from commercial endeavours will be used to fund additional research.

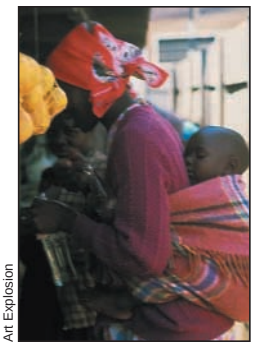
ICID has an all-star board, including Dr. Stephen Moses, U of M researcher; Dr. Frank Plummer, director of the National Microbiology Laboratories; Dr. John Langstaff, president of Winnipeg-based Cangene Corporation; and Dr. Lorne Babiuk, head of the University Saskatchewan's Vaccines for Infectious Diseases Organization.

"Throughout the world, there are groups just concerned with commercialization and groups just concerned with research," said Board Chairman Moses. "We think there is a great value in bringing these groups together." — *Dan Lett*, Winnipeg

DOI:10.1503/cmaj.050024

News @ a glance

HIV rising: The number of women living with HIV has increased in every region of the world over the past 2 years, states a joint UNAIDS and WHO report. The steepest increases are in East Asia (56% increase), followed by Eastern Europe and Central Asia (48% increase). Women now make up nearly half of the 37.2 million adults (15–49) living with HIV worldwide. In sub-Saharan Africa, nearly 60% of adults living with HIV are women — some 13.3 million. Women are more physically susceptible to HIV infection than men (male-to-female transmission during sex is about twice as likely to occur as female–to-male transmission), and many women and girls, particularly in Southern Africa, have to use sex as a commodity in exchange for food and necessities. AIDS Epidemic Update 2004 estimates that 39.4 million people now live with HIV (up from 36.6 million in 2002).


Art Explosion

30 minutes: Several US emergency rooms are being held up to the standards set by pizza delivery businesses. At St. Anne and St. Charles Mercy Hospitals in Toledo, Ohio, for example, anyone who waits longer than 30 minutes receives a gift certificate for a hardware store or passes to a theatre. That might not ease a patient's suffering, but it is meant to underscore the message that the hospital takes its service seriously. Dr. Alan Drummond, past president of the Canadian Association of Emergency Physicians, insists that the approach has merit. "Every institution should recognize that their emergency department is a key part of their marketing strategy," says Drummond, head of emergency at the Great War Memorial Hospital in Perth, Ont. "In our small town, when our community thinks about our hospital, the first thing they think about is the quality of the emergency service provided. That's how they judge you." — *Tim Lougheed*, Ottawa

Tuition woes: The average tuition fees for first year medical students will exceed $10 000 for the first time next September, according to data from the CMA Research Directorate. This academic year, the national average fee is $9814. When Quebec is excluded, the average jumps to $12 792. Fees have tripled since 1995–96. The Canadian Federation of Medical Students is concerned escalating fees are limiting access to medical school. "It will change the demographics of medicine," said CFMS Accessibility Officer Nick Rose. The federation is lobbying the federal government to increase student loans. Many students now graduate with debts of $100 000. The biggest increases now are in Western Canada said Rose. Fees at the University of British Columbia increased a whopping 36% ($10 272 to $14 000) this year. But the highest tuition fees are at the University of Toronto ($16 207). The lowest are at the University of Montreal ($2224).


Comstock

Tsunami warning: India plans to install a deep-sea warning system to provide alerts of possible tsunamis, following the Dec. 26 natural disaster. The country now has 20 deep-sea buoys with sensors. It will add another 20 and deploy 6 to 12 Deep Ocean Assessment and Reporting Systems (DOARS) about 6 km below the sea surface. Essentially pressure sensors mounted on buoys, the DOARS will be able to detect and record changes in seawater movements and transmit signals to a satellite. The project will cost an estimated US$27 million and take 30 months to complete. Tsunamis are rare in the Indian Ocean, and the South Asian nations recently affected did not have a warning system on the lines of the Pacific Tsunami Warning System. India plans a more formal scientific link-up with this system once its own is in place. — *SciDev.net*

1:3 nurses retire: A slight increase in the overall number of nurses in Canada may foster the impression that the shortage is ending. In fact, within a decade or so, a third of Canadian nurses will be getting ready to retire and given that only 1 in 10 nurse is now under age 30 there won't be nearly enough new nurses to replace retirees. The Canadian Nurses Association warns this could have "pretty dire consequences" for patient care. According to 3 new reports from the Canadian Institute of Health Information, the average age of Canadian nurses reached 44.5 years in 2003. In all, 334 006 nurses (RNs, licensed practical nurses and registered psychiatric nurses) were licensed to practise in 2003, an increase of 1.4% from 2002. But only 241 342 of those nurses were employed, of whom only 53.5% worked at full-time jobs, an increase of 1% from the previous year. The Canadian Nurses Association has noted a trend toward hiring nurses on a casual or print-time basis leaving them without job security or genefits. Depsite complaints the situation has improved only slightly. — Compiled by Barbara Sibbald, *CMAJ*

DOI:10.1503/cmaj.050023

ANALYSIS

Intravaginal and intrarectal microbicides to prevent HIV infection

About 40 million people worldwide have HIV infection (UNAIDS 2004 report [www.unaids.org/bangkok2004/report.html]). In 2003 alone, almost 5 million new infections occurred, more than 90% of which were sexually acquired. Nearly 50% of the worlds' HIV-infected people are women, and over 30% of HIV-positive women in some sub-Saharan African countries are teenagers. More than 1000 HIV-infected babies are born each day, often to teenaged mothers. Despite the effectiveness and availability of the condom, the HIV epidemic continues to spread. New prevention strategies are urgently needed. Topical microbicides are being developed as a possible new therapeutic approach to prevent HIV infection. They are formulated as gels, foams, films or vaginal rings designed to be inserted into the vagina or rectum and meet the urgent need for an effective female-controlled method of HIV prevention. More than 60 potential microbicides are being assessed in preclinical and clinical trials.

Improved understanding of the HIV life cycle (binding, fusion, reverse transcription, DNA integration, host-cell activation, transcription, translation, protein assembly, budding and viral release), of the mechanisms for HIV infection and transmission across mucosal epithelium (Fig. 1) and of the tropism of different viral strains opens new possibilities for antiviral interventions. This includes recognition of the role coreceptors play in HIV binding and of the particular role dendritic cells play in transmitting the virus to the lymphatic system. In addition to the high affinity the viral envelope glycoprotein gp120 has for binding to the CD4 protein on the host cell, a coreceptor (e.g., the CCR5 used by macrophage-tropic strains or the CXCR4 used by T-cell-tropic and T-cell-line-adapted strains) is needed for HIV to enter the cell. Dendritic cells are immune cells with thread-like tentacles or dendrites that "capture" antigens and transport them to T cells. Examples of dendritic cells include Langerhans cells found in the skin and mucosal membrane, and follicular dendritic cells found in lymphoid tissue. Dendritic cells carry the CD4 surface marker, and the majority of dendritic cells also carry CXCR4, DC-SIGN and CCR5 that effectively bind HIV through gp120. The bound HIV migrates to lymphatic areas, where T4 lymphocytes can be productively infected.

Microbicides can act in various ways (Fig. 2). Microbicides can be nonspecific, moderately specific or highly (exclusively) specific to HIV (Box 1). The nonspecific and moderately specific agents are often active against a variety of sexually transmitted microorganisms (e.g., chlamydia and herpesvirus) and may have a contraceptive effect. The HIV-specific agents interact directly with one or several steps of the infection or replication cycle of HIV.

Nonspecific microbicides

The nonspecific microbicides consist of buffering agents and of detergents or surfactants that include nonionic, anionic or cationic compounds (Box 1). The detergents destroy the viral envelope by solubilizing membrane proteins. However, this nonspecific mechanism of action may also disrupt the cell

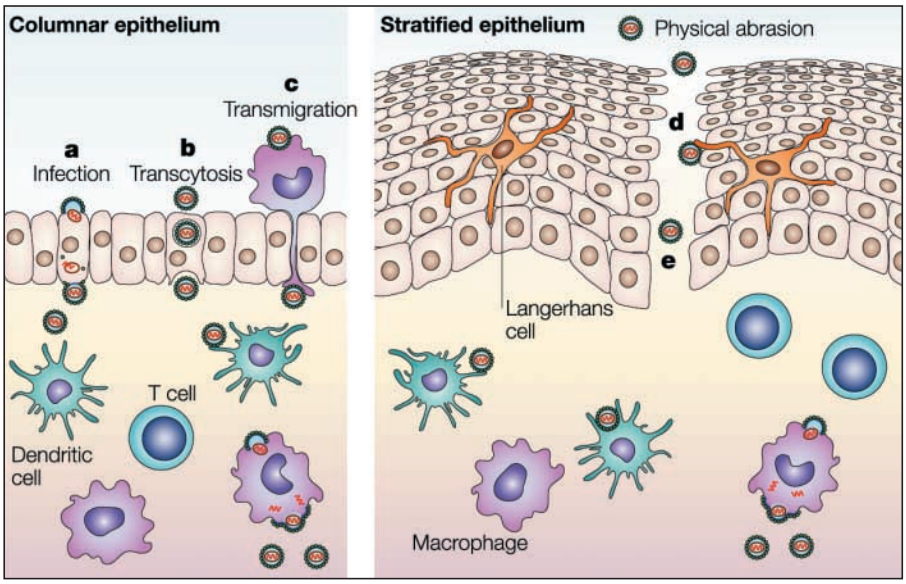


Fig. 1: Potential mechanisms for HIV transmission across mucosal epithelium. (a) Direct infection of epithelial cells; (b) transcytosis through epithelial cells or specialized microfold cells; (c) epithelial transmigration of infected donor cells; (d) uptake by intraepithelial Langerhans cells; (e) circumvention of the epithelial barrier through physical breaches. Successful transfer of the virus across epithelial barriers would result in viral uptake by migratory dendritic cells (by DC-SIGN or other mannose C-type lectin receptors) and subsequent dissemination to T cells in the lymphatic system or localized mucosal infection, leading to recruitment of additional susceptible cells. Reproduced, with permission, from Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nature Rev Microbiol* 2003;1:25-34.

DOI:10.1503/cmaj.1041462

membranes of the vaginal and cervical epithelium and cause erosions and lesions, leading to an increased risk of HIV infection. The therapeutic window of nonspecific microbicides appears to be rather limited. Spermicides, including nonoxynol-9, belong in this category. Nonoxynol-9 is not effective in preventing HIV infection. On the contrary, in a randomized controlled clinical trial involving sex workers, it increased the risk of HIV infection.[1] Currently, a new nonspecific agent, C31G (Savvy), with a higher therapeutic index than nonoxynol-9 is being tested in a phase III HIV prevention trial (Table 1).

The buffering agents (BufferGel and ACIDFORM) also belong to the category of nonspecific products. They act by effecting a local pH change that results in inactivation of the microorganism. A phase IIb trial of BufferGel is planned (Table 1). ACIDFORM is being assessed for long-term safety and prevention of STDs (excluding HIV infection) in combination with the diaphragm.

More specific microbicides

A variety of anionic substances that target the adsorption and fusion process of the virus (Box 1) are under investigation. They bind to the viral envelope through their negative charges and block cell entry. They may be effective not only on HIV but also on other enveloped viruses such as herpesviruses. Although rather efficient in preventing contact between the cell-free virus and its target cell, they are generally less efficient in preventing transmission of the cell-associated virus to uninfected cells. Because of the rather limited general toxicity of these anionic substances, their therapeutic window is higher than that of the detergents or surfactants. Several polyanions have shown an anticoagulant effect in vitro, but this has not been shown in women using these products intravaginally.[2,3] Anionic products are the most advanced of the microbicides in clinical development. One product — Carraguard — is already in a phase III HIV prevention trial (Table 1). This product has no contraceptive effect. Two others (cellulose sulfate and PRO 2000) will soon be tested in phase III trials. A contraceptive phase II trial is underway for cellulose sulfate.

Highly specific microbicides

HIV-specific microbicides should preferentially block the viral replication cycle at a step before integration of the proviral genome into the target cell (Box 1). Several phases of the viral life cycle (virus entry, reverse transcription of the viral RNA genome, proviral DNA integration in the host-cell chromosomes) can be a target for microbicidal intervention.

Soluble CD4, a highly specific antibody against the CXCR4 and CCR5 (co)receptors, and cytokines that represent the natural ligands of the coreceptors CXCR4 or CCR5 have been shown to efficiently inhibit entry of HIV into its target cells. However, their in vitro activity often depends on the virus source and cell type investigated. Because of their peptidic nature and the presence of proteolytic enzymes in vaginal secretions, they may be less attractive as potential microbicides than small molecules that specifically interact with CXCR4, and particularly with CCR5 (Box 1). Natural polypeptides such as mannose and *N*-acetylglucosamine-specific plant lectins (agglutinins stable at acidic pH levels of about 4.5 and temperatures of about 50°C) and the cyanobacterial mannose-specific lectin cyanovirin specifically bind to the sugar moieties present on the envelope gp120 of HIV.[4] These molecules have been shown in cell cultures to efficiently block both infection of cells by free virus particles and virus transmission between virus-infected and uninfected cells. However, the cost of mass production of these proteins may hamper a wide ap-

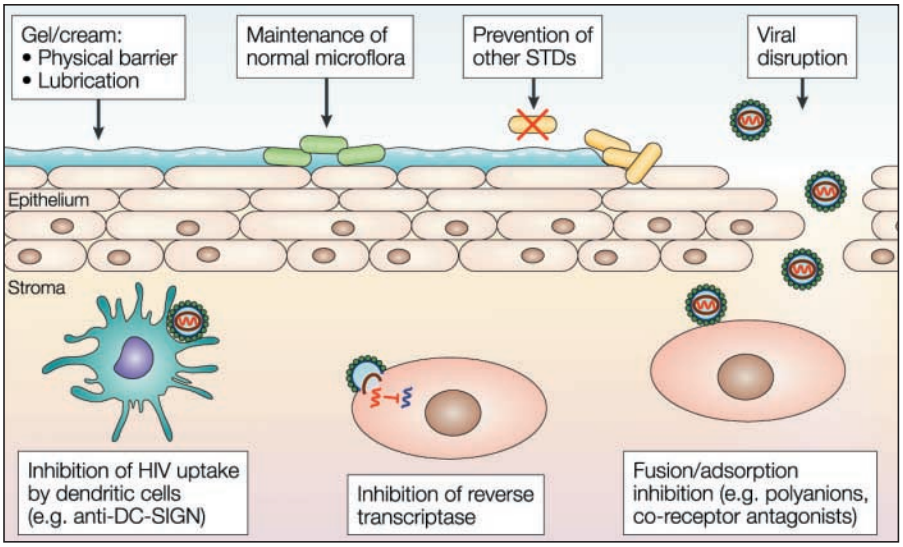


Fig. 2: Potential mechanisms of action for microbicide compounds. Microbicides that act as a lubricant coat the epithelial surface, which might reduce the risk of trauma and provide a physical barrier against viral infection. Prevention (or treatment) of other STDs can reduce the risk of HIV transmission by reducing the risk of epithelial inflammation and ulceration. In the vagina, maintaining the normal flora, and therefore maintaining the vaginal pH at virucidal levels (pH less than 4.5), could also reduce the risk of transmission. Once the virus has crossed the epithelial barrier, potential microbicidal strategies include targeting HIV uptake by dendritic cells, targeting HIV adsorption and fusion, and targeting reverse transcriptase and integration into the host cell genome. Reproduced, with permission, from Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nature Rev Microbiol* 2003;1:25-34.

plication as microbicide drugs. Therefore, attempts are underway to express these proteins by commensal bacteria of the vaginal flora (i.e., lactobacillus) in order to create a local microbicidal environment upon inoculation.

Interestingly, some modified glycopeptide antibiotics related to vancomycin, teicoplanin and eremomycin have recently been shown to prevent both HIV infection and transmission in cell culture, possibly by interacting with the viral envelope gp120. A heterogeneous variety of other substances (Box 1) have been shown in cell culture to prevent virus infection and transmission at nontoxic concentrations, but in vivo activity still needs to be demonstrated. If specific inhibitors of the gp41-driven viral fusion process other than the expensive peptide T-20 (enfuvirtide) become available, they may represent a powerful tool to efficiently prevent HIV infection.

Once the virus has entered the intracellular environment, it can be stopped from productive infection only by inhibiting the virus-encoded reverse transcriptase or integrase enzymes. Several known reverse transcriptase inhibitors (Box 1) are currently the subject of clinical phase I and II trials as potential microbicides. The HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the advantage of a high therapeutic window. The presence of a lipophylic tight-binding NNRTI at the site of virus infection or transmission may result in a virtual direct inactivation of the reverse transcriptase in the virus particle. Because of their lipophylic nature, NNRTIs may easily be incorporated into the drug-exposed target cell membrane, which creates a local protective barrier if the virus tries to enter the cells.

In contrast to NNRTIs, many of the earlier integrase inhibitors have a limited therapeutic window and may not even reach their presumed antiviral target because of their chemical properties. However, the more recently developed integrase inhibitors (Box 1) may be more effective as microbicides.

Systemic absorption and drug resistance

Absorption of microbicides used intravaginally or intrarectally may result in systemic side effects or viral drug resistance or both. The development of viral drug resistance should be avoided as much as possible. Whereas no evidence of systemic absorption was found in safety studies of anionic compounds, such evidence was found after intravaginal application of the reverse transcriptase inhibitors tenofovir, UC-781 and TMC-120. However, it is currently unclear whether such plasma drug levels are associated with a substantial risk of development of drug resistance.

Drug combinations

Because of the complexity of viral entry and spread in the body, a cocktail of several (at least up to 3) drugs may be needed that will intervene at different steps in the virus infection and entry process to optimally prevent transmission. A combination of several drugs may offer the advantage of using lower concentrations of

Box 1: Types of candidate microbicides being developed for intravaginal and intrarectal use as a possible new therapeutic approach to preventing HIV transmission

Nonspecific microbicides

Detergents or surfactants

- Nonionic compounds (e.g., nonoxynol-9, chlorhexidine)
- Anionic compounds (e.g., sodium lauryl sulfate, sodium dodecyl sulfate, monocaprin)
- Cationic compounds (e.g., benzalkonium chloride, C31G, GEDA Plus)

Buffering agents

- BufferGel
- ACIDFORM

More specific microbicides

*Anionic polymers**

- Sulfated polysaccharides (e.g., dextrin sulfate, heparin, cellulose acetate phtalate, cellulose sulfate, carrageenan)
- Sulfonated polymers (e.g., PRO-2000, PAVAS, PVAS)
- Polycarboxylates

Other†

Highly specific anti-HIV microbicides

Entry inhibitors

- Soluble CD4 (e.g., soluble CD4-IgG)
- CXCR4 antagonists (e.g., SFD-1, bicyclams)
- CCR5 antagonists (e.g., RANTES derivatives, LD78β isoform of MIP-1α, SCH-C, TAK779)
- Glycoprotein 120 (gp120)-recognizing agents (e.g., plant lectins and cyanovirin from *Cyanobacterium*; modified glycopeptide antibiotics related to vancomycin, teicoplanin and eremomycin; neutralizing antibodies)
- gp41-interacting agents (i.e., T-20 [enfuvirtide])

Reverse transcriptase inhibitors

- NtRTIs (e.g., [R]-PMPA [tenofovir])
- NNRTIs (e.g., UC-781, TMC-120 [dapivirine])

Integrase inhibitors

- Variety of compounds (i.e., S-1360; C-731,988)

Note: SFD-1 = stromal cell-derived factor 1, MIP-1α = macrophage inflammatory protein-1α, NtRTI = nucleotide reverse transcriptase inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor.
*Anionic polymers act as inhibitors of HIV adsorption or fusion, or both, but are less specific than the substances listed under "highly specific anti-HIV microbicides" in that they may also interact with pathogens other than HIV.
†Includes defensins, protegrin, hypericin, betulinic acid and plant extracts.

Table 1: Clinical trials of microbicide formulations currently underway

Product	Primary research group	Trial countries	Study design
BufferGel and PRO 2000 0.5%	HIV Prevention Trial Networks	India, Malawi, South Africa, Tanzania, United States, Zambia, Zimbabwe	4-arm phase II/IIb
Cellulose sulfate	Global Microbicide Project (GMP-CONRAD)*	Benin, Burkina Faso, India, Kenya, South Africa, Uganda	2-arm phase III
	Family Health International and GMP-CONRAD	Nigeria	2-arm phase III
Carraguard	Population Council	South Africa	2-arm phase III
Pro 2000 0.5% and 2%	UK Microbicides Development Programme*	Cameroon, South Africa, Tanzania, Uganda, Zambia	3-arm phase III
Savvy (C31G)	Family Health International	Nigeria, Ghana	2-arm phase III

*Planned to start in 2005.

each drug, which would offer a reasonable antiviral efficacy but a lower risk of toxic effects. Still, design challenges abound. Not only are the complementary mechanisms of action of the drugs important considerations, but so is the compatibility of different drugs in a single microbicidal formulation.

Conclusion

There is a compelling need to develop and evaluate novel microbicides for intravaginal and intrarectal use that are directed against different targets and steps in HIV infection and transmission. A single microbicidal agent will likely not be sufficient, and instead a combination of several drugs will probably be needed to ensure effective protection. Interestingly, given the tremendous burden of HIV infection on the population, mathematical models have shown that even use of a microbicide that is only moderately effective may have a pronounced impact on public health. Issues of safety and effectiveness aside, additional challenges posed by the prospect of microbicides include avoiding the possibility of decreased condom use, creating a willing market, educating women and men, and providing the product at an affordable price.

Jan Balzarini
Rega Institute for Medical Research
Leuven, Belgium
Lut Van Damme
CONRAD
Arlington, Vt.

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ANALYSIS

Antibiotics that protect the brain

Common antibiotics might do more than just kill bacteria. New research suggests that some antibiotics can protect against the nerve damage associated with diseases such as amyotrophic lateral sclerosis (ALS), dementia, stroke and epilepsy. The beneficial effects of a family of β-lactam antibiotics, which includes antibiotics such as penicillin, was recently discovered by Jeffrey Rothstein and colleagues,[1] who found that these antibiotics could protect against the dysfunctional effects of the neurotransmitter glutamate in mice by activating the expression of a glutamate transporter. This finding suggests a new role for some of the most commonly used pharmaceuticals in the world.

Glutamate's Jekyll-and-Hyde effects

The amino acid glutamate has long been a target in the search for drugs to modify neurologic effects. Such interest is based on the fact that glutamate is a workhorse of the mammalian central nervous system (CNS), functioning primarily as an excitatory neurotransmitter but also contributing to learning and memory.[2] However, when present in excessive amounts or for prolonged periods in the brain, glutamate has a dark side: in such situations, it can destroy neurons and thereby contribute to neurodegenerative diseases.[2]

Glutamate-mediated toxicity is thought to result from the malfunctioning of glutamate's release and reuptake cycle. Normally, glutamate present in the cytoplasm of a neuron is transported into synaptic vesicles, subsequently released into the synaptic cleft to initiate neurotransmission, and then reabsorbed by neurons and surrounding glial cells to terminate its action. The rapid removal of glutamate from the extracellular space prevents neurons from being exposed to its toxic effects, a feat accomplished by proteins called excitatory amino acid transporters (EAATs), whose malfunction can directly result in neurotoxic effects.

Five EAATs are currently known in humans, but EAAT2 appears to be a particularly important glutamate transporter. EEAT2 provides 90% of the total glutamate uptake, and its altered expression in several neurodegenerative diseases suggests an important role in their pathophysiology.[2] For example, the selective loss of EAAT2 expression has been shown to be correlated with the development of ALS and epilepsy.[3]

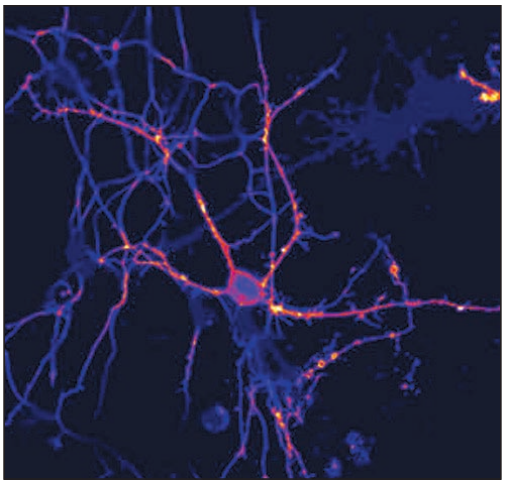
The importance of EAAT2 in balancing glutamate's positive and negative effects makes this protein a prime target in the search for drugs to combat neurodegenerative diseases. Nevertheless, there is as yet no practical pharmaceutical capable of positively modulating EAAT2.[1]

New tricks for old drugs

Rothstein and colleagues' work therefore represents a significant step forward in the search for drugs that modulate EAAT2 expression. They screened 1040 FDA-approved drugs and nutritionals as part of a National Institutes of Health project to search for potential new uses for these compounds. Rothstein and colleagues performed blinded screens that involved adding each drug to rodent spinal cord tissue cultures for 5–7 days and then determining the expression levels of GLT1, the mouse equivalent of human EETA2, in each tissue sample.

Of the 1040 drugs, the structurally related family of β-lactam antibiotics, which include penicillin and cephalosporin antibiotics, were surprisingly effective at increasing the levels of rodent GLT1 protein expression. And in the case of the representative cephalosporin, ceftriaxone, this induction occurred at a concentration found in the CNS during ceftriaxone therapy for meningitis.[4] In contrast, non β-lactam antibiotics such as kanamycin and vancomycin had no effect on GLT1 protein expression. The effect of β-lactam antibiotics also extended to human cells lines, where Rothstein and colleagues revealed that the EAAT2 promoter could be similarly activated.

Rothstein and colleagues went on to look at the effect of ceftriaxone in adult rats. They found that a 5–7 day course of ceftriaxone increased GLT1 expression in the rat brain threefold. This increase correlated with higher levels of glutamate transport in these animals, suggesting that the biochemical activity of GLT1 also increased on ceftriaxone exposure. Similar experiments with penicillin revealed that this antibiotic was also capable of increasing the biochemical activity of GLT1, although to a lesser extent than ceftriaxone, a fact Rothstein and



Two rat hippocampal neurons expressing lipid modified YFP. The lipid modifications cause them to be concentrated 1) at sites of cell:cell contact, presumably synapses and 2) in the growth cones of growing branches. Reprinted with permission by Dr. David Zacharias, The Whitney Laboratory for Marine Bioscience.

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colleagues suggest is due to penicillin's inability to penetrating the brain as effectively as ceftriaxone.

No therapies currently exist to modulate glutamate-mediated injury through glutamate transporters. However, Rothstein and colleagues hypothesized that increasing the levels of glutamate transporters such as EAAT2/GLT1 may help protect neurons from injury. The research group therefore wondered whether β-lactam antibiotics could protect neurons from the negative effects of glutamate. In one set of experiments designed to test this hypothesis, daily injections of ceftriaxone were given to mice engineered to develop symptoms similar to ALS, including muscle weakness and loss of body weight. In each case, ceftriaxone therapy delayed the onset of these symptoms, ultimately extending the lifespan of these mice by 10 days as compared to untreated animals.

Although preliminary, Rothstein and colleagues' results suggest that commonly used β-lactam antibiotics might provide some protection against nerve damage. It is still too early to begin prescribing such antibiotics, since such measures must await a formal clinical trial to ascertain any benefit in human patients. However, such a trial does not appear to be far off. A press release from Johns Hopkins, where Rothstein and colleagues undertook their current study, states that a study of the effect of ceftriaxone treatment in ALS patients is set for the spring (www.hopkinsmedicine.org/Press_releases/2005/01_05_05.html). Thus, it appears that drugs praised for their ability to kill bacteria might still have a few undiscovered tricks up their sleeves. — *David Secko*, Vancouver

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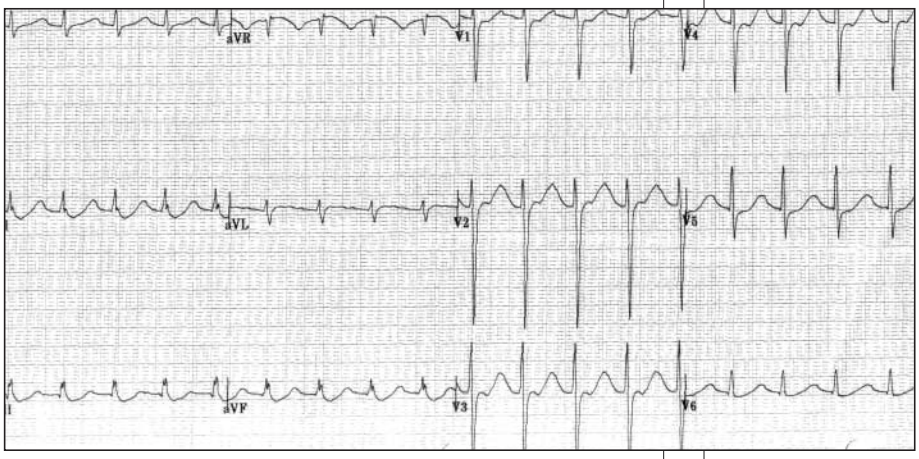
Acute generalized weakness due to thyrotoxic periodic paralysis

THE CASE: A 28-year-old First Nations man was transferred from a northern nursing station to the Health Sciences Centre in Winnipeg for investigation of a 1-day history of generalized weakness that began when he woke in the early morning. He had no fever, myalgia, or gastrointestinal, respiratory or cardiovascular symptoms, and no history of recent illness or known toxic ingestion. He did have a 3-year history of bilateral blindness, for which he had never sought medical attention. His family history was significant only for type 2 diabetes mellitus in his father and several maternal and paternal aunts and uncles.

On examination, he was alert, tachycardic (heart rate 140 beats/min) and afebrile. He had flaccid paralysis of his arms and legs (0/5) and could not lift his head off the bed. His wrist and digit strength were preserved (5/5). Deep tendon reflexes could not be elicited. Sensation to light touch and pinprick were normal. He had normal rectal tone. His visual acuity was decreased because of bilateral cataracts, but the cranial nerves were otherwise intact.

The patient had hypokalemia, with a serum potassium level of 1.6 (normal range 3.5–5.3) mmol/L, and his creatine phosphokinase level was slightly elevated at 328 (normal range 52–175) U/L. Results of other initial laboratory investigations were normal, including complete blood count, and renal and liver function tests.

An electrocardiogram revealed sinus tachycardia, a prolonged QT interval corrected to 664 ms, and ST-segment depressions inferiorly in leads II, III and avF (Fig. 1). A head CT revealed chronic bilateral retinal detachment as the cause of the patient's blindness but no intracranial abnormality to explain his weakness.



Twenty-four hours after symptom onset the patient still had hypokalemia (serum potassium level 1.9 mmol/L), despite receiving a total of 200 mEq of potassium orally and 160 mEq parenterally. His distal lower limb strength had improved to 5/5, with some return of strength in his shoulders and hips (2/5). He was still unable to lift his head off the bed. Mild hyperreflexia was now present in his lower limbs.

Dramatically, 2 hours later, the patient was walking independently. His serum potassium level was normal (5.0 mmol/L), as was an electrocardiogram. Potassium replacement therapy was discontinued.

The results of thyroid function testing revealed thyrotoxicosis, with a thyroid stimulating hormone level of < 0.01 (normal range 0.4–4.2) mU/L, an elevated free thyroxine level of 57 (normal range 9.7–25.7) pmol/L and a free triiodothyronine level of 18 (normal range 3.7–6.9) pmol/L. The patient agreed to treatment with propranolol followed by the addition of tapazole, but he declined radioactive iodine. At 10-month follow-up no paralysis had recurred.

Thyrotoxic periodic paralysis (TPP) is a disorder characterized by thyrotoxicosis, hypokalemia and predominantly proximal lower limb paralysis. Despite the female predominance of hyperthyroidism, TPP occurs most frequently in males in a ratio of 20:1, and 90% of patients are of Asian descent.[1]

Prodromal symptoms may consist of muscle stiffness or cramping. Sensation, as well as bulbar and respiratory muscle strength, remains intact. Reflexes may be decreased or absent.

Attacks may be precipitated by a high carbohydrate meal (secondary to insulin secretion) or physical exertion. In one series, 84% of attacks occurred between 1 and 6 am.[2] Episodes are acute in onset and last 1–96 hours. As in this patient, symptoms and signs of hyperthyroidism may be subtle at initial presentation.

Electrocardiographic findings such as ST-segment depression with T-wave flattening and the presence of U waves are

DOI:10.1503/cmaj.1041042

typical of hypokalemia. Findings supportive of a diagnosis of TPP are sinus tachycardia, elevated QRS voltage and first-degree AV block (sensitivity 97%, specificity 65%).[3]

The exact pathophysiology of TPP is unknown. Thyroid hormone itself has a direct effect in stimulating the sodium–potassium–adenosinetriphophatase (Na–K–ATPase) pump. Pump sensitivity to adrenergic stimulation may be higher in patients with TPP than in those with hyperthyroidism alone, resulting in intracellular potassium shift and subsequent hypokalemia. Some human leukocyte antigen subtypes (DRw8, A2BW22, AW19B17, B5, BW46) and genetic mutations (KCNE3) have been associated with TPP.[4]

Potassium replacement therapy is the mainstay of treatment for TPP. It should be administered carefully because of the risk of rebound hyperkalemia and resulting cardiac complications. Recent literature has advocated instead for the use of β-blockers to reverse the adrenergic overstimulation of the Na–K–ATPase pump by elevated thyroid hormone levels. Evidence suggests that propranolol monotherapy reduces the duration of the TPP event and is associated with a lower risk of rebound hyperkalemia than potassium replacement therapy.[5] Although β-blockers may be used in the acute setting, definitive management requires correction of the hyperthyroid state.

The differential diagnosis of acute weakness is summarized in Box 1. Broad categories to consider are electrolyte abnormalities, muscular disorders and central nervous system disorders at spinal cord, synapse and peripheral nerve levels. Specific causes of hypokalemic paralysis are summarized in Box 2.

In summary, TPP should be suspected in patients presenting with acute proximal lower limb weakness. Management should include necessary resuscitative efforts, followed by β-blocker therapy and careful administration of potassium replacement therapy. Further attacks may be avoided by treatment of the hyperthyroid state.

Cheryl Barnabé
Resident
Department of Internal Medicine
University of Manitoba
Winnipeg, Man.

Box 1: Differential diagnosis of acute weakness[1,6]

Electrolyte disturbances
- Hypo- or hyperkalemia
- Hypercalcemia
- Hypo- or hypernatremia
- Hypophosphatemia
- Hypo- or hypermagnesemia

Muscle disorders
- Channelopathies: periodic paralyses
- Metabolic defects of muscle (e.g., mitochondrial defects, impaired carbohydrate or fatty acid utilization)
- Myopathies: inflammatory, polymyositis, dermatomyositis, alcoholic myopathy, acute viral infection, parasitic polymyositis, Lyme disease, Legionnaire's disease

Neuromuscular junction disorders
- Myasthenia gravis
- Eaton–Lambert syndrome
- Organophosphate poisoning
- Botulism

Central nervous system disorders
- Transient ischemic attack (brainstem)
- Transient global cerebral ischemia
- Multiple sclerosis

Polyneuropathies
- Guillain–Barré syndrome
- Infections: poliomyelitis, West Nile virus
- Toxins
- Transverse myelitis

Box 2: Causes of hypokalemic paralysis[1,5]

Transcellular potassium shift
- Thyrotoxic periodic paralysis
- Familial hypokalemic periodic paralysis (autosomal dominant inheritance)
- Barium poisoning
- Insulin excess

Potassium deficit

Renal potassium loss
- Renal tubular acidosis
  Type 1: hereditary, toluene exposure, Sjögren's syndrome
  Type 2: Fanconi's syndrome
- Hyperaldosteronism
  Primary (Conn's syndrome)
  Secondary: licorice ingestion
- Diuretics

Gastrointestinal potassium loss
- Celiac disease
- Infectious enteritis
- Short-bowel syndrome

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Malaria update

Background and epidemiology: In November 2004 the Public Health Agency of Canada released a travel health advisory warning of the risk of malaria in the Dominican Republic after receiving notice of 3 laboratory-confirmed cases of *Plasmodium falciform* malaria in Canadian travellers who had visited the country within the previous month. *P. falciform* is a mosquito-borne parasite that, through successive stages of its life cycle, invades the liver and then erythrocytes of infected humans. The infection can be fatal if it progresses to severe anemia or cerebral malaria (through the adhesion of infected erythrocytes to cerebral capillaries).

Malaria used to be endemic in Canada. During the building of the Rideau Canal in Ottawa in the 1820s, more than 500 workers and countless other settlers succumbed to infection from the temperate species *P. vivax*. Today, thanks to environmental and infection control interventions and changing local ecologies, the threat of malaria in Canada has been reduced to an international travel-related illness. This is not the case for much of the rest of the world, where malaria continues to threaten nearly 40% of the global population, accounting for 3–5 million deaths and 300–500 million new cases annually. In recent years global resources have been mobilized to fight malaria in the very poor countries of the world, mostly in Africa and Asia, through initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Malaria Vaccine Initiative.

Clinical management: The 3 recent cases of malaria in Canadian travellers returning from the Dominican Republic serve as a strong reminder for Canadian physicians to take a systematic, comprehensive approach to the investigation of fever in the international traveller, such as that outlined by the Committee to Advise on Tropical Medicine and Travel (www.phac-aspc.gc.ca/publicat/ccdr-rmtc/97vol23/23sup/acs1.html). The "gold standard" for diagnosis of malaria is the thick and thin peripheral blood smear, stained with Giemsa stain. The rapid malarial test provides a simple alternative, with overall sensitivity and specificity levels of about 90%, which fall dramatically with low-level parasitemia.[1] Treatment of malaria may be oral or parenteral and depends on the infecting *Plasmodium* species, the geographic area of acquisition and the severity of infection.[1]

Prevention: Environmental measures to reduce mosquito breeding sites, personal protective measures to reduce the risk of mosquito bites and chemoprophylaxis appropriate for the geographic area of potential exposure remain the mainstays of prevention.[1] Malaria vaccine development has seen a surge of activity in the last decade or so, owing largely to the mobilization of global funds and the advances made in the field of genetic engineering and biotechnology.[2] The 3 immediate goals of vaccine research are the induction of strong, strain-transcending, durable immune responses; the identification of protective antigens for immunity at specific stages of the parasite's life cycle (pre-erythrocytic, erythrocytic and sexual); and the successful combination of candidate immunogens.[3] Several candidate antigens that induce immune responses in the pre-erythrocytic stage (e.g., circumsporozoite protein and the thrombospodin-related adhesive protein) and the erythrocytic stage (e.g., merozoite surface protein) have been identified, and vaccine trials involving humans and primates are underway. However, beyond the identification of immunogenic antigens, further considerations

CDC/Jim Gathany

challenge vaccine development. They pertain to technical issues, such as determining the form and delivery of the vaccine (e.g., synthetic peptide, recombinant, DNA plasmid) and understanding and effecting T-cell protection, and to logistical issues such as combining vaccine development efforts, licensing vaccines for use in very young children, acquiring informed consent in communities with low levels of literacy, and predicting and controlling costs.

Optimists in the field of malaria vaccine development suggest that, with sustained funding and dedicated cooperation, an available effective vaccine formulation is about 10 years away.[3]

Erica Weir
CMAJ

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DOI:10.1503/cmaj.045270

IN THE LITERATURE

Does reducing interns' work hours reduce the rate of medical errors?

Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med* 2004;351: 1838-48.

Background: Although multiple studies have shown that sleep deprivation affects physicians' abilities to perform various tasks, the impact of sleep deprivation on patient care remains controversial.[1,2] This is the first randomized trial to examine the impact of reduced physician work hours on medical error.

Design: This prospective, randomized single-centre intervention trial assigned interns to either a "traditional" on-call schedule every third night with extended work shifts of up to 28 hours or an "intervention" schedule that eliminated 24-hour shifts and decreased the number of scheduled hours per week. Rotations were of 4 weeks' duration in either the coronary care unit or the medical intensive care unit. The primary outcome was serious errors associated with interns. Trained physician observers were used as the primary method for detecting errors. Voluntary staff reporting, chart review and a computerized event-detection monitor were supplementary methods. All detected errors were verified and classified by blinded physician reviewers. Secondary end points included all serious errors, errors that were caught ("intercepted") by other staff and preventable adverse events.

Results: Interns worked about 79 hours per week during the traditional schedule and 63 hours per week during the intervention schedule. The rate of serious medical errors made by interns was 36% higher during the traditional schedule than during the intervention schedule (136 v. 100 per 1000 patient-days, $p < 0.001$). The rate of nonintercepted serious errors was also higher during the traditional schedule (44.8 v. 28.6 per 1000 patient-days, $p = 0.02$), as was the rate of all serious errors (193.2 v. 158.4 per 100 patient-days, $p < 0.001$). No difference in the rates of preventable adverse events was detected (38.6 for the traditional schedule v. 38.5 for the intervention schedule per 1000 patient-days).

Commentary: An accompanying study suggested that the observed reduction in medical errors is explained by more hours of sleep and fewer attentional failures among interns on the intervention schedule.[3] Although a blinded study physician reviewed all potential errors and events, a potential weakness of the study was the lack of blinding of the interns, staff and other observers. However, such blinding would be virtually impossible to achieve. The reported reduction in serious errors is intriguing, but the real goal is to avoid harm to patients. This study was not designed to detect an effect on preventable adverse events, so the impact of reduced work hours on patient safety remains to be defined. It is also important to note that the study group created a system for careful sign-over of patients to minimize errors associated with cross-coverage by multiple physicians.

How would this intervention play out in other settings? More experienced physicians may be less susceptible to serious errors when fatigued. Error rates would likely be lower outside of intensive care unit settings, so the impact of reduced work hours would be less. Moreover, many hospitals lack the sophisticated methods to detect errors that were used in this study, so reductions in error would not be immediately apparent in typical clinical settings.

Practice implications: The study results are not surprising to any clinician who has received sign-over from a fatigued colleague after a night on call. Still, the rigorous methods and promising results of this study should stimulate additional attention on physician fatigue and sleep deprivation. Residency training programs, particularly those with rotations in intensive and coronary care units, should note the uncomfortably high rate of nonintercepted serious errors. At a minimum, multicentre trials of reduced physician work hours should be undertaken in teaching and nonteaching hospitals. Further, physicians should document their shift lengths and total hours worked per week, so that the latent hazard of physician fatigue becomes more visible to hospitals and governments. The intervention in this study was accomplished by adding an extra intern to the call pool. Medical schools, hospitals and governments will need to plan for additional physician resources to achieve similar results.

Michael Bernstein
Division of General Internal Medicine
Edward E. Etchells
Division of General Internal Medicine, Patient Safety Service
Sunnybrook and Women's College Health Sciences Centre
Toronto, Ont.

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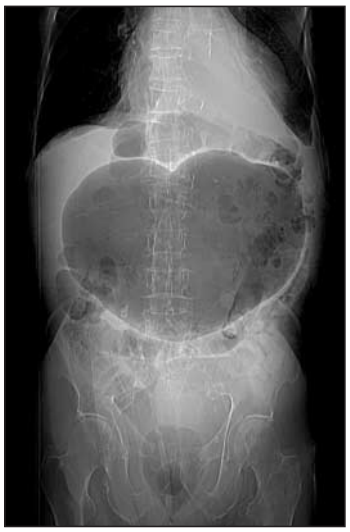
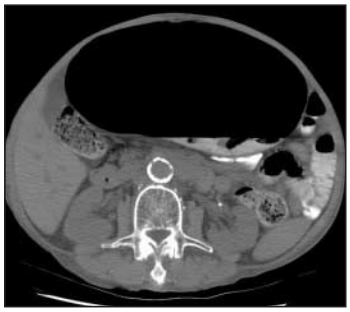
DOI:10.1503/cmaj.050042

An 87-year-old man with a tympanic abdominal mass

DOI:10.1503/cmaj.1040799

An 87-year-old man presented with a 3-day history of progressive, diffuse abdominal pain. He denied nausea, vomiting, fever or chills. He had no history of rectal bleeding, diarrhea or constipation, but he had noticed increased flatulence, which helped relieve the pain. His vital signs were normal. He had a distended, diffusely tender abdomen with a large left upper quadrant mass that was tympanic to percussion. A digital rectal examination was normal, but his stool was positive for occult blood. His leukocyte count was normal, but his hemoglobin level was low at 82 (normally 110–150) g/L, which was consistent with a 2-year history of anemia, for which the patient had refused investigation. Plain radiographs demonstrated a large radiolucent structure (11 cm × 22 cm) in the upper abdomen with no signs of obstruction (Fig. 1).





The patient was admitted to hospital for further investigation and was managed conservatively with bowel rest, intravenous fluids, pain management and antibiotics for suspicion of diverticulitis. A CT scan revealed that the structure was continuous with the sigmoid colon (Fig. 2), which was confirmed when contrast material administered through the rectum entered the smooth-walled structure. The mass was diagnosed as a giant sigmoid diverticulum. The patient's pain ceased after the passage of a large amount of flatus the next day. After no further rectal bleeding the patient was discharged home, having refused further management.

Giant colonic diverticulum is rare, with fewer than 100 cases reported in the literature. It affects men and women equally, occurs most commonly in patients 60–80 years of age and affects the sigmoid colon in over 90% of cases.[1] Patients may be asymptomatic or have nonspecific symptoms, such as fever, nausea, vomiting, diarrhea, constipation, or abdominal pain or distension, or they may present with complications such as perforation (followed by pneumoperitoneum), diverticulitis, abscess formation, gastrointestinal hemorrhage or bowel obstruction.[2,3] In addition, giant diverticula carry a 2% risk of adenocarcinoma of the involved colon at the time of presentation.[3]

The mechanism by which ordinary diverticula become giant diverticula is not fully understood. One theory is that colonic inflammation narrows the outlet and creates a "ball-valve" mechanism that allows air to enter but not escape the diverticulum, which results in its progressive dilatation. Other theories suggest that gas-producing microorganisms cause the diverticulum expansion, or that a small colonic perforation causes pseudocyst formation, followed by the "ball-valve" mechanism.[1,2]

Abdominal radiographs will show a large round or elliptical lucency with smooth margins[2] that may contain an air–fluid level.[1] A barium enema results in the opacification of 60% of diverticula, and if the contrast penetrates into the diverticulum then the borders should be smooth. Irregular borders should raise the suspicion of chronic inflammatory or neoplastic changes.[4] CT scans will show a large gas-filled cavity with smooth margins that is continuous with the colon.[5]

Treatment includes conservative management such as pain control and colonic decompression as needed. Surgical intervention such as diverticulectomy or colectomy may be required if abdominal pain becomes intractable or profuse bleeding occurs. Because of the risk of recurrence and adenocarcinoma, surgical resection is felt by some to be the preferred management in all cases.[3]

Dmitry Guller
Faculty of Medicine and Dentistry
David Bach
Department of Diagnostic Radiology and Nuclear Medicine
University of Western Ontario
London, Ont.

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Sexual risk behaviour of Canadian participants in the first efficacy trial of a preventive HIV-1 vaccine

Thomas M. Lampinen, Keith Chan, Robert S. Remis, Maraki Fikre Merid, Melanie Rusch, Jean Vincelette, Ken Logue, Vladimir Popovic, Michel Alary, Martin T. Schechter, Robert S. Hogg

Abstract

Background: Phase I and phase II HIV-1 vaccine trials have revealed increases in risky sexual activity among study subjects during the trials, perhaps because the subjects believe that the vaccine being tested is efficacious; subjects may thus suffer harm from their participation. We evaluated the sexual behaviour of Canadian men who have sex with men (MSM) who participated in the phase III Vax004 trial of an HIV-1 vaccine.

Methods: Using self-reports of sexual behaviours during the 6 months before trial entry as a baseline, we determined changes in reported sexual behaviour after 6, 12 and 18 months of participation in the trial.

Results: Of 291 HIV-seronegative MSM enrolled from July to October 1999, 260 (89%) completed 18 months of follow-up, 19 (7%) experienced seroconversion, and 12 (4%) did not complete follow-up. Unprotected receptive anal intercourse during the previous 6 months with partners whose HIV-1 serostatus was positive or unknown was reported by 21% of men at enrolment and by 27% at any point during 18 months of follow-up. No increase in this behaviour from baseline was reported by participants, including among men who were motivated to enrol because of expected protection from HIV-1 infection, men who believed they had received the vaccine, men who believed that the vaccine had greater than 50% efficacy, or men who believed that they had received the vaccine and that vaccine efficacy was greater than 50%.

Interpretation: MSM can be successfully enrolled in HIV-1 vaccine efficacy trials without evident increases in those sexual behaviours most associated with HIV-1 risk.

CMAJ 2005;172(4):479-83

Development of preventive HIV-1 vaccines requires clinical trials that effectively recruit, enrol and retain high-risk subjects, including men who have sex with men (MSM). Since candidate vaccines may prove to have little or no efficacy, these trials must also strive to minimize harms associated with participation. A major concern has been that trial participants might believe vaccination affords some protection and therefore increase their sexual risk-taking.[1,2] This concern derives in part from increases in unprotected anal intercourse observed during phase I and phase II vaccine trials. For example, self-reports of unprotected insertive anal intercourse during the previous 6 months increased among 44 gay men enrolled in San Francisco trials, from 9% at enrolment to 20% at the 12-month assessment; however, the HIV status of sexual partners was not assessed.[1] The world's first phase III trial to evaluate a candidate preventive HIV-1 vaccine was recently completed in North America and Europe.[2] A consortium sponsored by the Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC) was formed to assess participation, retention and change in sexual risk behaviour at trial sites in this country. We report here the Canadian experience in this trial through 18 months of follow-up and assess trends in high-risk sexual behaviour reported by participants.

Methods

MSM were recruited by print advertisements and outreach in Montreal, Toronto, Vancouver and other sites in North America and Europe to participate in the Vax004 trial, a randomized, placebo-controlled evaluation of a bivalent recombinant gp120 HIV-1 subtype B vaccine (AIDSVAX B/B, Vaxgen Inc., Brisbane, Calif.).[2] HIV-seronegative MSM from 18 to 60 years of age who reported anal intercourse during the previous 12 months and who were not involved in a continuous monogamous relationship with an HIV-negative partner during the same period were eligible to participate. Men were ineligible if they felt unable to complete 3 years of follow-up or reported previous injection drug use, HIV-1 vaccination, receipt of another vaccine or immunoglobulin during the 2 weeks before enrolment or receipt of a live-attenuated vaccine during the 4 weeks before enrolment.

Following screening, eligible participants were asked to return for baseline and then semiannual follow-up visits for 36 months. At each visit, vaccination, medical evaluations and structured risk assessment interviews were performed, and risk reduction counselling was provided. The risk assessments elicited self-reports of sexual behaviour according to the HIV-1 status of partners (seronegative, seropositive or status unknown). Behavioural assessments were discontinued if HIV-1 seroconversion, the primary trial end point, occurred.

The baseline questionnaire included questions about whether enrolment in the trial had been motivated by a belief that vaccination would provide protection against HIV-1 (grouped in the present analysis as any level of agreement v. other) and about perceived vaccine efficacy (grouped in the present analysis as efficacy > 50% v. efficacy ≤ 50% or don't know). The 12-month follow-up questionnaire asked participants if they believed they had received vaccine or placebo or didn't know (grouped as vaccine v. other). Ethical review boards at each site approved the

DOI:10.1503/cmaj.1031785

trial protocol, and participants provided written informed consent; the consent form specified the 2:1 ratio of assignment to vaccine or placebo.

The present study represents secondary analyses using trial data that were requested by CANVAC collaborators and provided by the trial sponsor. Groups were compared using χ^2 and Fisher's exact tests for categorical variables and Wilcoxon rank-sum and Kruskall–Wallis statistics for continuous variables. The percentage of men reporting unprotected anal intercourse by 18 months' follow-up (defined as any unprotected encounter during the period between study visits) was estimated using life table methods, and groups were compared using log-rank tests; in these analyses, data for men who experienced seroconversion and those who dropped out or were withdrawn prematurely from the trial were censored following their last risk assessment. We compared participants whose data was censored with those who completed follow-up. Because this comparison would be confounded by trial site (associated with both censorship and high-risk behaviours), we matched each participant whose data were censored with 4 randomly selected participants who had completed 18 months of follow-up at the same site.

The primary behavioural end point was unprotected receptive anal intercourse with a partner whose HIV-1 serostatus was positive or unknown. However, incomplete assessment of the behaviour of high-risk participants (because of seroconversion or dropping out) could lead to selection of a progressively lower-risk group, thereby producing the spurious impression of a decline in overall risk behaviour during follow-up. To guard against this bias, in these analyses we made the following conservative ("worst case") assumption for every follow-up assessment that was missing: we assumed that these participants would have reported engaging in unprotected receptive anal intercourse with partners of positive or unknown serostatus at these times. Change in sexual risk behaviour was assessed using paired (McNemar's) tests that compared participants' behaviour before enrolment with that reported at the 6-, 12- and 18-month follow-up visits.

Results

From July to October 1999, 291 MSM enrolled in the Vax004 trial at 3 Canadian sites (105 in Vancouver, 99 in Montreal and 87 in Toronto). The median age of participants was 37 years, and most had received some college education (Table 1). Significant differences were observed across sites with respect to participants' level of education, reasons for joining the study and recent recreational drug use; as well, site-specific differences were observed with respect to recent diagnosis of STDs and percentage of men reporting sexual relations during the 6 months before enrolment with HIV-positive, HIV-negative and status-unknown partners. Among men who had an HIV-positive or status-unknown partner, the percentage engaging in unprotected receptive anal intercourse with each type of partner was not materially different across sites (site-specific data available from the authors upon request).

During 18 months of follow-up, data for 11% of the men were censored because of seroconversion (n = 19) or because of withdrawal from the trial or loss to follow-up (n = 12). The number of men for whom data were censored before their 6-, 12- and 18-month follow-up visits were 6, 19 and 6, respectively. The percentage of men for whom data were censored at each site differed significantly (Mon-

Table 1: Characteristics of Canadian Vax004 trial participants at enrolment

Characteristic	Group; no. (%) of participants*			
	All *n = 291*	With censored data *n = 31*	Matched controls *n = 124*	*p* value†
Median age (IQR), yr	37 (31–43)	35 (31–41)	37.5 (32–43)	0.16
Postsecondary education	208 (71)	23 (74)	92 (74)	> 0.99
Motive for joining study				
Some HIV-1 protection	129 (44)	16 (52)	62 (50)	0.87
Believed vaccine efficacy > 50%	68 (23)	4 (13)	32 (26)	0.13
Drug use‡				
Marijuana	140 (48)	17 (55)	61 (40)	0.57
Volatile nitrite inhalants ("poppers")	126 (43)	16 (52)	61 (40)	0.81
Crack cocaine	7 (2)	1 (3)	3 (2)	> 0.99
Amphetamines	37 (13)	10 (32)	14 (11)	0.01
Tranquilizers	30 (10)	6 (19)	17 (14)	0.41
Hallucinogens	65 (22)	11 (35)	33 (27)	0.33
Cocaine (snorted)	42 (14)	6 (19)	18 (15)	0.58
Viagra	37 (13)	6 (19)	21 (17)	0.75

Note: IQR = interquartile range.
*Except as otherwise indicated.
†For comparison of subjects with censored data and matched controls.
‡During the 6 months before enrolment.

treal 2/99 [2%], Vancouver 12/105 [11%] and Toronto 17/87 [20%], $p < 0.001$). Compared with the matched controls (who remained HIV-1 seronegative), MSM for whom data were censored were more likely to report recreational use of amphetamines (Table 1), as well as unprotected sex with HIV-positive and status-unknown partners during the 6 months before their enrolment and greater numbers of HIV-positive partners (Table 2).

At enrolment, 61 (21%) of the 291 men reported having engaged in unprotected receptive anal intercourse during the previous 6 months with partners whose HIV-1 status was positive or unknown. The prevalence of this behaviour at the 6-, 12- and 18-month follow-up visits was 20%, 20% and 18%, respectively, using the most conservative assumption (that men with censored or missing data had engaged in risky behaviour); the matched-pair odds ratios indicated no significant change in participants' behaviour from baseline to any of these time points (Table 3). Furthermore, we did not observe any change in this behaviour among subgroups of participants who did and did not report a motivation to enter the trial for protection from HIV-1 infection, a belief that they had received the vaccine, a belief that vaccine efficacy was greater than 50%, or a belief that they had received vaccine and that vaccine efficacy was greater than 50% (data not shown).

The cumulative percentage of men reporting unprotected receptive anal intercourse with an HIV-positive or status-unknown partner at any point during 18 months of follow-up was 27%. The cumulative probability of engaging in this behaviour at any point during 18 months of follow-up was not significantly greater among men who reported being motivated to enrol in the trial for protection from HIV-1 infection, those who believed they had received vaccine, those who believed that vaccine efficacy was greater than 50%, or

Table 2: Sexual behaviour of Canadian Vax004 trial participants during the 6 months before enrolment, as reported at enrolment

Sexual behaviour	Group; no. (%) of participants* All *n = 291*	With censored data *n = 31*	Matched controls *n = 124*	*p* value†
No. with male partner				
HIV-1 positive	124 (43)	20 (65)	60 (48)	0.11
HIV-1 negative	127 (44)	14 (45)	53 (43)	0.81
HIV-1 status unknown	233 (80)	26 (84)	93 (75)	0.30
Median no. of male partners (IQR)				
Total	7 (4–20)	10 (4–30)	7.5 (3–15)	0.20
HIV-1 positive	1 (1–2)‡	1 (0–2)	0 (0–1)	0.01
HIV-1 negative	2 (1–4)‡	0 (0–3)	0 (0–2)	0.69
HIV-1 status unknown	7 (4–20)‡	7 (2–20)	7 (2–20)	0.35
HIV-1 positive partner				
Unprotected oral	32 (26)‡	9 (29)	13 (10)	0.02
Unprotected anal receptive	19 (15)‡	6 (19)	7 (6)	0.02
Unprotected anal insertive	43 (35)‡	10 (32)	21 (17)	0.06
HIV-1 negative partner				
Unprotected oral	62 (49)‡	6 (19)	25 (20)	0.92
Unprotected anal receptive	43 (34)‡	6 (19)	18 (15)	0.58
Unprotected anal insertive	52 (41)‡	5 (16)	22 (18)	0.82
HIV-1 status unknown partner				
Unprotected oral	109 (47)‡	18 (58)	42 (34)	0.02
Unprotected anal receptive	45 (19)‡	9 (29)	17 (14)	0.06
Unprotected anal insertive	71 (30)‡	12 (39)	33 (27)	0.18
HIV-1 positive or status unknown partner				
Unprotected anal receptive	60 (23)‡	12 (39)	24 (19)	0.02
Unprotected anal insertive	95 (36)‡	17 (55)	44 (35)	0.05
Any unprotected anal sex	116 (44)‡	19 (61)	52 (42)	0.05

* Except as otherwise indicated.
†For comparison of subjects with censored data and matched controls.
‡Among men having such partners.

those who believed that they had received the vaccine and that vaccine efficacy was greater than 50% (Table 4). The cumulative percentage of men who reported unprotected receptive anal intercourse with any partner at any point during follow-up was 40%; 13% of men reportedly engaged in this behaviour with HIV-negative partners only, 14% with HIV-positive or status-unknown partners only, and 13% with both HIV-negative and HIV-positive or status-unknown partners. With regard to the latter group, we did not assess the temporal ordering of such encounters.

Table 3: Prevalence of unprotected receptive anal intercourse with an HIV-positive or status-unknown partner* at enrolment and during follow-up in the Vax004 trial

Time of assessment	No. (%) of subjects *n = 291*	OR† (95% CI)	*p* value
Enrolment	61 (21)	1.0	
6 mo‡	58 (20)	0.9 (0.5–1.4)	0.81
12 mo§	57 (20)	0.9 (0.5–1.4)	0.71
18 mo¶	52 (18)	0.8 (0.4–1.2)	0.34

Note: OR = odds ratio, CI = confidence interval.
*Using the most conservative assumption that subjects with censored or missing data engaged in this behaviour.
†Matched-pair OR indicating the likelihood of high-risk behaviour at follow-up, compared with enrolment.
‡Includes 6 censored and 2 missing observations.
§Includes 25 censored and 1 missing observation.
¶Includes 31 censored and 1 missing observation.

Interpretation

Among Canadian MSM enrolled in the Vax004 trial, we observed no significant change in high-risk unprotected receptive anal intercourse between enrolment and the 6-, 12- and 18-month follow-up assessments. This result has special importance, given the announcement by the trial sponsors that the AIDSVAX vaccine did not provide protection from HIV-1 infection.[3]

The percentage of trial participants reporting any unprotected receptive anal intercourse is consistent with that reported in contemporary studies of MSM in these cities.[4–6] However, the Vax004 trial questionnaire also assessed the HIV-1 status of partners with whom such intercourse occurred. Importantly, 21% of the 291 trial participants (including 15% [16/105] of those in Vancouver) reported that during the 6 months before enrolment they had engaged in unprotected receptive anal intercourse with a partner whose HIV-1 status was positive or unknown. For comparison, we recently reported that only 14% of 282 young MSM in a cohort study in Vancouver engaged in this behaviour during the previous 12 months[7] but that most HIV-1 seroconversions occurred in such men. Thus, despite intensive counselling, Canadian participants in the Vax004 trial appeared to be at relatively high risk for HIV-1 infection. If subsequent analyses confirm that seroconversion during the trial occurred mainly among men who reported unprotected receptive anal intercourse with partners

Table 4: Life table estimates of the probability of reporting unprotected receptive anal intercourse with a partner whose HIV-1 serostatus was positive or unknown (URAI) at any point during the 18 months following enrolment in the Vax004 vaccine trial, by participants' motivation and beliefs

Motivation or belief	No. (%) of subjects *n = 291*	Probability of URAI during 18-mo follow-up	*p* value
Participant enrolled for protection from HIV-1 infection*			0.48
Yes	129 (44)	0.29	
No	162 (56)	0.25	
Participant believed that he had received vaccine†			0.45
Yes	50 (19)	0.30	
No	215 (91)	0.25	
Participant believed that vaccine efficacy was > 50%*			0.84
Yes	68 (23)	0.27	
No	223 (77)	0.26	
Participant believed that he had received vaccine† and that vaccine efficacy was > 50%			0.52
Yes	19 (7)	0.32	
No	246 (93)	0.25	

*Assessed at time of enrolment.
†Participant's belief that he had received vaccine or placebo or didn't know (grouped as vaccine v. other) was assessed at the 12-month follow-up visit; 26 observations were missing.

whose HIV-1 serostatus was positive or unknown, the findings will have important implications for targeting preventive interventions to MSM and for selecting high-risk participants for future vaccine efficacy trials.

There are several limitations to the present study. First, assessment of whether trial participation per se was associated with behavioural change is not possible, since the Vax004 trial lacked a comparison group of MSM who received neither vaccine nor placebo. Nevertheless, it is reassuring that, despite conservative assumptions in our analysis, we found no evidence of an increase in the sexual risk behaviour of trial participants; during the same calendar period, substantial increases in risk behaviours among MSM in North America and Europe were reported.[8] Second, self-reports of sexual behaviours are subject to social desirability effects that may produce underestimates of risk. Third, if participants with censored data are more likely than those completing follow-up to begin unprotected anal intercourse, the cumulative percentages we report may be underestimates by as much as several percentage points. Finally, trial participants may not be representative of other MSM, and caution should be used in generalizing our results. Indeed, if high-risk MSM tend to enrol in vaccine trials,[1,9,10] regression to the mean could explain reductions in sexual risk behaviours that might be reported from vaccine trials lacking a comparison group that receives neither vaccine nor placebo.

The largest number of incident HIV-1 infections and AIDS diagnoses reported in Canada continues to be among MSM.[11] Recent clinically motivated shifts toward delayed or interrupted prescribing of antiretroviral therapy[12–14] are expected to yield a net increase in the infectiousness of HIV-positive sexual partners. This increase may, in turn, portend increases in HIV-1 seroincidence among MSM.[15] Our results demonstrate that high-risk MSM in Canada can be successfully recruited, enrolled and retained in HIV-1 vaccine efficacy trials, and they underscore the importance of continued counselling and sexual risk measurements during such studies.[12]

This article has been peer reviewed.

From the British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC (Lampinen, Chan, Rusch, Schechter, Hogg); the Department of Health Care and Epidemiology, University of British Columbia, Vancouver, BC (Lampinen, Rusch, Schechter, Hogg); the Department of Public Health Science, University of Toronto, Toronto, Ont. (Remis, Merid); Hôpital Saint-Luc du Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Que. (Vincelette); University Health Network, Toronto General Hospital, Toronto, Ont. (Logue); Vaxgen Inc., Brisbane, Calif. (Popovic); and the Population Health Research Unit, Centre hospitalier affilié universitaire de Québec and Université Laval, Québec, Que. (Alary). Robert Remis is coordinator of CANVAC Project 1.5 (Behavioural and Epidemiological Aspects of HIV Vaccine Trials), and Robert Remis, Jean Vincelette and Michel Alary are coinvestigators with the project.

Competing interests: Vladimir Popovic was, at the time this study was performed, an employee of Vaxgen Inc. None declared for all other authors.

Contributors: Thomas Lampinen designed the study with assistance from Robert Remis, Martin Schechter and Robert Hogg. Data were collected and managed by Robert Remis, Jean Vincelette, Ken Logue, Vladimir Popovic, Michel Alary, Robert Hogg and Maraki Fikre Merid and analyzed by Thomas Lampinen, Keith Chan and Melanie Rusch. Thomas Lampinen wrote the report. All authors contributed to the revision of various drafts and approved the final version of the submitted manuscript.

Acknowledgements: We are indebted to the 291 Canadian men enrolled in the Vax004 trial. We thank Vaxgen Inc. for providing the trial data. For clinical and logistic support with the study, we thank Anne-Marie Bourgault, Joseph De Wet, Christiane Gaudreau, Peter Granger, Marianne Harris, Val Montessori, Carol Murphy, Michael V. O'Shaughnessy, Peter Phillips, Mark Tyndall, Robert Voigt, Phil Sestak, Brian Willoughby and Brian Woodfall, as well as Eric Demers, Liz Ferris, Lesley Gallagher, Roger Le Clerc, Nancy McLean, P. Pellerin (deceased) and Jean Roy. Funding for this study was provided by the Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC Project 1.5, Behavioural and Epidemiological Aspects of HIV Vaccine Trials). Thomas Lampinen, Robert Hogg and Melanie Rusch are supported by the Michael Smith Foundation for Health Research.

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Correspondence to: *Dr. Thomas M. Lampinen, BC Centre for Excellence in HIV/AIDS, 608–1081 Burrard St., Vancouver BC V6Z 1Y6; fax 604 806-9044; tlampinen@cfenet.ubc.ca*

The availability of references and the sponsorship of original research cited in pharmaceutical advertisements

Richelle J. Cooper, David L. Schriger

Abstract

Background: The primary goal of pharmaceutical advertisements is to convince physicians to prescribe the manufacturer's product. We sought to determine what materials are cited in support of claims in pharmaceutical ads and medical research articles, and whether health care professionals seeking to verify the claims could obtain these references.

Methods: We reviewed 438 unique ads from the 1999 issues of 10 American medical journals, and a random sample of 400 references in medical research articles selected from the same journals. We classified references as journal article, data on file, meeting abstract or presentation, book or monograph, marketing report, prescribing information, government document or Internet site. We attempted to confirm or obtain each reference through library and Internet searches or by direct request from the manufacturer. The main outcome we sought to determine was the availability of the reference to a clinician. We also ascertained the source of funding for original research cited in the ads and the research articles.

Results: In the 438 ads with medical claims, 126 contained no references and 312 contained 721 unique references. Of these ad references, 55% (396/721) cited journal articles and 19% (135/721) cited data on file. In contrast, in the sample of research article references, 88% (351/400) cited journal articles and 8% (33/400) cited books. Overall, 84% of the citations from the ads were available: 98% of journal articles, 86% of books, 71% of meeting abstracts or presentations and 20% of data-on-file references. In all, 99% of the sample of research article references were available. We determined that 58% of the original research cited in the pharmaceutical ads was sponsored by or had an author affiliated with the product's manufacturer, as compared with 8% of the articles cited in the research articles.

Interpretation: Many pharmaceutical ads contain no references for medical claims. Although references to journal articles were usually obtainable, other published sources were not as easily acquired. The majority of unpublished data-on-file references were not available, and the majority of original research cited to substantiate claims in the pharmaceutical ads was funded by or had authors affiliated with the product's manufacturer.

CMAJ 2005;172(4):487-91

DOI:10.1503/cmaj.1031940

The primary goal of pharmaceutical advertisements is to convince clinicians to prescribe their product. These ads often cite external documents in support of their claims, but studies have shown that these claims may be misleading, distort the reporting of scientific data or fail to provide enough information to accurately interpret the data they present.[1–6] The transparency of pharmaceutical ads is important for 2 reasons. First, there is evidence that physician prescribing is influenced by pharmaceutical ads.[7–9] Second, the pharmaceutical industry views ads as one way in which they can educate physicians.[10,11] Given the potential for misrepresentation, health care professionals should be able to examine the cited references to determine whether the manufacturer's claims are justified.

In 2002, pharmaceutical companies submitted over 34 000 ads to the US Federal Drug Administration (FDA) (Thomas Abrams, Director, Division of Drug Marketing, Advertising, and Communications of the FDA, Rockville, Md.: personal communication, 2003). Most ads made several claims about the drug's efficacy or effectiveness. The sheer volume makes it difficult for the FDA to adequately check the validity of many of the ads.[12] The absence of tight government oversight makes it particularly important that individual clinicians and groups (e.g., hospital pharmacy and therapeutics committees) can obtain cited documents to determine whether a claim is adequately substantiated. We performed this study to describe the kinds of documents cited in support of claims made in pharmaceutical ads, and to assess the availability of these documents to health care practitioners. We also examined whether original research cited by the pharmaceutical ads was sponsored or performed by the product's manufacturer. To provide a standard for comparison, we repeated these investigations for randomly selected references in research articles published in the same journals in which we studied the ads.

Methods

We retrospectively examined all references in the 438 unique pharmaceutical ads contained in the 1999 issues of 10 medical journals (*American Journal of Psychiatry*, *Annals of Emergency Medicine*, *Annals of Internal Medicine*, *Annals of Surgery*, *Hospital Practice*, *Journal of the American Medical Association*, *New England Journal of Medicine*, *Neurology*, *Obstetrics and Gynecology* and *Pediatrics*). This convenience sample of journals was chosen to reflect a range of general and specialty care and, therefore, ads for a range of pharmaceutical products. A database of the ads was initially created to examine the quantity and quality of graphic data displays in pharmaceutical ads.[5] All of the journals are peer-reviewed except *Hospital Practice*, a journal that is free to house staff in the United States.

Two of 3 trained reviewers independently reviewed each ad and identified the number of unique references cited. We defined

a reference as material cited in support of the information in the ad. The reviewers classified each reference as: journal article, generic data on file (a reference to an unspecified, unpublished company document), specific data on file (e.g., "Drug Company packet WP 1234"), meeting abstract or presentation, book or monograph, marketing report (material cited in support of claims such as "prescribed over 2 million times in 1999"), prescribing information (e.g., *Physicians' Desk Reference* [*PDR*] or package insert), government document (e.g., the US Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report* [*MMWR*]) or Internet site. The *PDR* is an annual publication that provides information on drug usage, pharmacology and pharmacokinetics, FDA-approved indications, warnings and drug interactions for over 4000 drugs.[13]

For the purpose of comparison, we randomly selected 1 issue of each of the study journals from 1999, randomly reduced the references to a maximum of 40 per research article, then randomly selected a total of 40 references from each journal. These 400 references were categorized in the same way as the references in the pharmaceutical ads. In addition, we examined a random sample of 100 of the journal references citing original research and all of the pharmaceutical ad references to original research to determine whether the research was sponsored by or had authors affiliated with a pharmaceutical company.

We considered a reference "available" if we could obtain a copy of the cited material. All journal citations found in the National Library of Medicine's MEDLINE/PubMed were considered available (www.ncbi.nlm.nih.gov/entrez/query.fcgi). For other journal citations, abstracts, meeting presentations and books, we attempted to locate and obtain the document through searches of other databases (e.g., WorldCat) and in the California Digital Library (a colibrary of the University of California, www.cdlib.org), which includes a national network of libraries that permit interlibrary loans. Searches were conducted using single and multiple terms (e.g., individual author names, journal issue, title and page numbers) to ensure that typographical errors in the citation did not interfere with verification of the reference. We kept a record of cases in which errors were found.

We used an Internet search engine (www.google.com) to confirm the existence of documents not available through our library search. This included searching titles, authors and, for abstracts and presentations, the meeting's host organization. If no link to meeting proceedings could be found, we asked the host organization to provide a copy of the document.

We determined whether the journal articles cited were from journals in the National Library of Medicine's (NLM's) list of journals indexed for MEDLINE,[14] whether the article appeared in a journal supplement, and the type of article (original research, review article, letter or editorial) cited. When we located a cited journal article that presented original research, we determined the source of funding and whether any authors were affiliated with the manufacturer of the product being studied.

We checked government documents by searching the Web site of the appropriate agency (e.g., www.cdc.gov, www.NIH.gov), and verified Internet references by accessing the listed URLs.

We verified the existence of marketing reports (e.g., Source Prescription Audit, IMS National Prescription Audit, Medi-Span) but did not attempt to obtain these documents, since we did not believe they would be of interest to clinicians.

We wrote directly to the manufacturer to request copies of data-on-file references. For specific data-on-file references, we requested each cited document by number. For generic data-on-file references our request included details about the citation and the journal (name, volume and date) in which the ad appeared. For manufacturers with 1 or 2 references to generic data on file across all of their ads in the database, we requested all material. For manufacturers with more than 2 references to generic data on file, we requested 2 randomly selected documents. All letters included email and US postal addresses to which the documents could be sent. A separate letter was sent for each reference. We used a variety of aliases and addresses so that no company received more than 1 letter request from a specific individual or address. If we did not receive a response within 6–8 weeks, a repeat request was mailed. We attributed responses postmarked within 5 days of our second mailing to the initial mailing. We classified each response as "decline" ("information proprietary" or "not available"), "unpublished study data" or "journal reprint." We did not categorize package inserts or referrals to the company's Web page as available, since they were not the data-on-file references we requested.

We did not set out to test specific hypotheses, but rather to describe the availability of the references cited in pharmaceutical ads and the sponsorship of original research cited in the references.

Results

Of the 438 ads in the database 126 (29%) offered no references in support of their claims. In the remaining 312 ads, there were a total of 1072 references, with 721 citing a unique source document. The 312 ads listed a median of 2 references (range 1–25). The 10 randomly selected journal issues (1 issue of each journal) contained 184 research articles with a total of 5233 references, of which we randomly selected 40 references per journal, as described in Methods.

The most commonly cited sources in the pharmaceutical ads were journal articles (55%) and data on file (19%). In the sample of research article references, the most commonly cited sources were journal articles (88%) and books (8%). Among the confirmed references (i.e., those to journal articles, books, abstracts and government documents), we found errors (e.g., wrong author, title, journal, page number, year) in 6% (30/476) of the drug ad references and 4% (14/397) of the research article references.

A total of 84% (494/590) of the citations in the pharmaceutical ads and 99% (397/400) of the citations in the research papers were available (Table 1). A majority (98% [390/396]) of the pharmaceutical ad references to journal articles were available; 90% (352/390) were from journals in the NLM's list of journals indexed for MEDLINE, and 12% of the available references were published in journal supplements. Of the research article references, 99% (348/351) of the journal articles were available; 99% (345/348) were from journals in the list of journals indexed for MEDLINE, and 4% (14/351) of the available references were published in supplements. The majority of the journal references in both samples were to original research or review articles (Appendix 1).

Of the 294 pharmaceutical ad references citing original research, 58% indicated that the research was sponsored by or had authors affiliated with the product's manufacturer,

19% stated funding by a government or charitable organization, and the remainder (23%) had no statement regarding funding or specifically reported no funding. In contrast, in the sample of 100 original research papers cited in the journal articles, 8% were sponsored by or had authors affiliated with the product's manufacturer, 44% were funded by a government or charitable organization, and 48% had either no statement regarding funding or specifically reported no funding.

Approximately half (54% [167/312]) of the pharmaceutical ads had at least 1 data-on-file reference, for a total of 135 unique references. Forty-two (52%) of the 80 companies in the drug ad database cited to data-on-file references in at least 1 ad. The pharmaceutical companies replied to 37 (42%) of our 88 requests for data-on-file, but 19 (51%) of the responses were letters stating that the data on file would not be provided because it was proprietary (17) or because of company policy (2) (Table 2). Thus, only 20% (18/88) of our requests produced a document. In 3 of these cases, the company indicated that additional material had been withheld because of its proprietary nature. None of our letters was returned as undeliverable.

We obtained 71% of the meeting abstracts and presentations from the pharmaceutical ad references, including 17 of the 19 references to published abstracts of meetings and 10 of the 19 references to meetings. Six of the 11 unavailable references were from confirmed meetings but the program details were unavailable. Of the remaining 5, in 2 instances we confirmed the meeting and the author or presentation but could not obtain the abstract, in 2 cases we

Table 1: Classification and availability of references cited in pharmaceutical ads and research articles

	No. (%) of references in pharmaceutical ads *n = 721*		No. (%) of references in research articles *n = 400*	
Reference type	Unique number	References available	Unique number	References available
Journal article	396 (55)	390/396 (98)	351 (88)	348/351 (99)
Generic data on file (general statement)	103 (14)	12/56 (21)†	0	–
Specific data on file (explicit document no.)	32 (4)	6/32 (19)	0	–
Meeting abstract or presentation	38 (5)	27/38 (71)	6 (2)	6/6 (100)
Book or monograph	36 (5)	31/36 (86)	33 (8)	33/33 (100)
Marketing report	38 (5)	NA	0	–
Prescribing information	46 (6)	NA	0	–
Government document	28 (4)	28/28 (100)	5 (1)	5/5 (100)
Other*	4 (1)	0/4 (0)	5 (1)	5/5 (100)
Total	721 (100)	494/590 (84)	400 (100)	397/400 (99)

Note: NA = not applicable.
*Includes Internet document, conversation, software, thesis.
†The availability of general data on file is based on a random sample, stratified by pharmaceutical manufacturer, and included requests for 56 separate documents (details of sample in text).

Table 2: Responses to requests for data-on-file references in pharmaceutical ads

	Type of reference requested; no. (%) of requests	
Variable	General data on file *n = 56*	Specific data on file *n = 32*
No response	36 (64)	15 (47)
Response to initial request	16 (29)	12 (37)
Response after repeat request	4 (7)	5 (16)
Type of response		
Decline (information is proprietary or unavailable)	8 (14)	11 (34)
Unpublished data	7 (12)	3 (9)
Journal reprint	2 (4)	1 (3)
Unpublished data and journal reprint	3 (5)	2 (6)
Data-on-file references that produced information	12 (21)	6 (19)

Note: The median response time was 53 (range 21–147) days overall, with declines taking 38 (21–109) days and receipt of documents taking 70 (28–147) days. Nine of the 11 responses declining requests for specific data-on-file references were sent by email (median response time 25 [21–48] days); all other communication was by mail. We failed to send 1 repeat request letter in the generic data-on-file group.

could not confirm the meeting or abstract, and in 1 case we found meeting proceedings that did not include the cited reference. Five (14%) of the 36 books and monographs cited in the ads were unavailable. In contrast 100% of the abstracts and books cited in the sample of 400 research articles were available (Table 1).

All 28 unique references to government documents in the pharmaceutical ads were confirmed. We checked the 3 Internet references cited in the pharmaceutical ads in November 2002 and found that the sites were operational (e.g., www.NIH.gov), but the specific pages cited were unavailable.

Interpretation

One-third of the pharmaceutical ads did not provide any references in support of their claims. Although the references to articles in journals indexed for MEDLINE were easily obtainable, other published sources were not as easily acquired, and references to unpublished material were seldom available. We confirmed 98% of the references to journal articles, as compared with 83% reported in a study of drug promotional brochures.[3] This difference may be due in part to our use of multiple library sources and the interlibrary borrowing privileges of a large university.

In contrast with the research articles, the pharmaceutical ads cited a large number of unpublished documents. Nineteen percent of the ad references were to data on file, which is consistent with Mindell and Kemp's finding of 20% in ads in *BMJ*.[15] Despite follow-up mailings, only 20% of our requests for data-on-file references yielded information from the pharmaceutical companies. This is consistent with the results of Hafeez and Mirza, who found a 26% response rate for mailed requests for product information.[16] Although companies in the United States must comply with FDA requests for proprietary documents,[17] the companies have no legal obligation to make these documents available to clinicians (Thomas Abrams, Director, Division of Drug Marketing, Advertising, and Communications of the FDA, Rockville, Md.: personal communication, 2003). In Canada, the Pharmaceutical Advertising Advisory Board's (PAAB) Code of Advertising Acceptance requires that data-on-file references be available to the PAAB's commissioner and a summary copy of these data be provided to health care professionals who request it.[18] However, it is not known how often physicians seek this information. The World Health Organization (WHO) has stated that "Scientific data in the public domain should be made available to prescribers and any other person entitled to receive it, on request, as appropriate to their requirements."[19] Our findings demonstrate that the WHO policy is not being followed.

We also found that 58% of the original research cited in pharmaceutical ads was sponsored by or had authors affiliated with that same pharmaceutical company, as compared with 8% of the references to original research in the research articles. Although it is not surprising that a manufacturer would cite research that it had sponsored, previous research indicates that conclusions of trials sponsored by pharmaceutical companies may be misleading or incompletely reported.[20–26] Recent calls for improved transparency of pharmaceutical industry-sponsored research may improve the quality of trial reporting and publication.[27]

There are a number of limitations to our findings. We examined only the availability of references cited in support of claims. We did not attempt to verify whether each claim made in the ad was supported by a specific citation. In addition, we did not examine the cited documents to determine whether they adequately substantiated the claims made in the ads. Previous research indicates that journal articles cited to substantiate statements in pharmaceutical ads failed to do so in 19%–44% of claims.[1-3,6,15] We did not assess the quality of the journal articles, because others have already demonstrated methodological flaws in articles cited in pharmaceutical ads;[15,28] however, we did find that 12% of the articles in our sample were published in supplements, which may be of lesser quality than articles published in the parent journal.[29,30] Our access to the extensive libraries and interlibrary loan requests may not be representative of a typical clinician's access, and our repeated efforts to obtain documents may be greater than those of a practising clinician. Finally, some unconfirmed references may have been due to errors in the citation listing in the ad. We tried to circumvent these problems by using multiple terms when searching.

In contrast to the citations in published research articles, clinicians will be unable to obtain the evidence offered in support of a substantial number of claims in pharmaceutical ads and will therefore be unable to assess the validity of these claims. Improved accessibility to and monitoring of the validity of references in pharmaceutical ads is required to allow clinicians to practise evidence-based prescribing and help policy-makers adequately assess the utility of the pharmaceutical products in question.

This article has been peer reviewed.

From the UCLA Emergency Center, UCLA School of Medicine, Los Angeles, Calif. (Cooper and Schriger)

Competing interests: None declared.

Contributors: Richelle Cooper contributed to the conception and design of the manuscript, along with acquisition, management, analysis and interpretation of data. She drafted the manuscript and contributed critical revision for intellectual content. David Schriger contributed to the conception, design and critical revision of the manuscript along with acquisition, analysis and interpretation of the data. Both authors approved the final version of the paper.

Acknowledgements: We thank Michael S. Wilkes for his contributions to the conceptualization of the study, Vladislav J. Mikulich for his help in data collection and management and Jun T. Huang for his help with data collection.

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***Correspondence to**: Dr. Richelle J. Cooper, UCLA Emergency Medicine Center, 300–924 Westwood Blvd, Los Angeles CA 90024, USA; fax 310 794-0599; richelle@ucla.edu*

Appendix: Types of journal articles cited in pharmaceutical ads and research articles published in the same journals

Type of article	Pharmaceutical ads; no. (%) of articles *n = 396*	Research articles; no. (%) of articles *n = 351*
Original research	294 (74)	250 (71)
Review	65 (16)	70 (20)
Meta-analysis	5 (1)	4 (1)
Guideline or position statement	18 (5)	3 (1)
Editorial or comment	6 (2)	9 (3)
Case report	2 (0.5)	9 (3)
Letter	0	2 (0.6)
Unconfirmed (unavailable) citation	6 (2)	4 (1)

Case report

Cerebral cholesterol granuloma in homozygous familial hypercholesterolemia

Gordon A. Francis, Royce L. Johnson, J. Max Findlay, Jian Wang, Robert A. Hegele

Abstract

Familial hypercholesterolemia (FH) is characterized by the accumulation of excess cholesterol in tissues including the artery wall and tendons. We describe a patient with homozygous FH who presented with asymptomatic cholesterol granuloma of the brain. The patient's plasma low-density lipoprotein cholesterol level was remarkably responsive to combination hypolipidemic therapy with statin plus ezetimibe. This case illustrates another potential complication of whole-body cholesterol excess and underscores the differences in phenotype and in response to therapy among patients with FH.

CMAJ 2005;172(4):495-7

A 45-year-old Chinese-Canadian woman presented with chemosis of several years' duration. As a teenager the patient had noticed corneal arcus and thickening of her Achilles tendons. At age 20 she was found to have a fasting total cholesterol level of 18.0 (normal < 5.2) mmol/L and a low-density lipoprotein (LDL) cholesterol level of 15.4 (normal < 3.4) mmol/L. On the basis of these findings and a family history of hypercholesterolemia in both parents and premature coronary artery disease in her father, homozygous familial hypercholesterolemia (FH) was diagnosed. The initial treatment was with bile acid-binding resins, followed by the addition of hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, when she was 29. She has been intolerant of fibrates and niacin, both of which caused rashes. At age 30, angina pectoris necessitated coronary artery bypass grafting, and she has since remained free of cardiovascular symptoms. At age 40, carotid ultrasound imaging, conducted after carotid bruits were detected, revealed more than 95% and 50%–79% stenoses of the left and right carotid arteries respectively. She began taking 325 mg of ASA daily and has remained free of neurologic symptoms. Her total cholesterol level and LDL cholesterol level fell to 10.1 and 8.2 mmol/L respectively after she began taking 80 mg of atorvastatin and 4 g of colestipol daily, and her Achilles tendon xanthomas also shrank over time. Her lipoprotein (a) level was elevated at 0.44 (normal < 0.3) g/L. Her sitosterol level was 2.4 (normal ≤ 5.0) µg/mL, and her homocysteine level was 8.0 (normal < 12.1) µmol/L); her ApoE genotype (ε3/ε3) was also normal. The patient's high-density lipoprotein cholesterol level was 0.8 (normal > 0.9) mmol/L on no lipid therapy and has ranged between 0.6 and 1.1 mmol/L with atorvastatin and colestipol therapy; her triglyceride level was 2.7 (normal < 2.3) mmol/L at baseline and has ranged from 1.4 to 3.6 mmol/L with therapy.

A genomic DNA sequence analysis showed that she was homozygous for proline-to-leucine substitution at residue 644 of the LDL receptor known as FH-Zambia[1] or FH-Gujerat,[2] which has not been reported in Canada.[3] This mutation is associated with slowed maturation and attenuated cell-surface expression of LDL receptors[4] but does not abolish receptor function. Partial LDL receptor function appears to explain the patient's responsiveness to therapy, which was better than expected for most patients with homozygous FH. The addition of 10 mg daily of ezetimibe to the atorvastatin and colestipol therapy lowered the patient's LDL cholesterol level to 6.9 mmol/L. When colestipol was discontinued, this level decreased further to 5.9 mmol/L, which suggests an enhanced response to combination statin–ezetimibe therapy in the absence of bile acid-binding resin. Fig. 1 shows the sites of action of medications taken by the patient. We are considering LDL apheresis to further decrease LDL levels.

Ophthalmologic examination revealed bilateral chemosis and conjunctival redness with no ocular hypertension or congested retinal vasculature. The patient was clinically and biochemically euthyroid, with no thyroid antibodies. Although the chemosis was felt to have resulted from chronic use of vasoconstricting eye whiteners, a head MRI scan was performed to rule out thyroid ophthalmopathy. It revealed an incidental large calcified mass involving the skull and meninges of the left temporal-occipital area (Fig. 2). Craniotomy for the resection of a presumed meningioma revealed a large, encapsulated, avascular mass emanating from the petrous bone that was filled with necrotic tan-to-yellowish paste-like material. Microscopy of the lesion's capsule showed cholesterol clefts with granulomatous tissue including lipid-containing macrophages, multinucleated giant cells, chronic inflammation and fibrosis, with the contents showing shards of cholesterol and foci

DOI:10.1503/cmaj.1041152

of calcification, consistent with a cholesterol granuloma. The patient had no perioperative complications or neurologic sequelae. A head CT scan performed 18 months after the operation showed no residual or recurrent mass, which is typical following resection of these tumours if the petrous bone is properly pneumatized.[6] The chemosis persists, but we feel that, rather than being related to the tumour, it is a consequence of rebound vasodilatation sec-

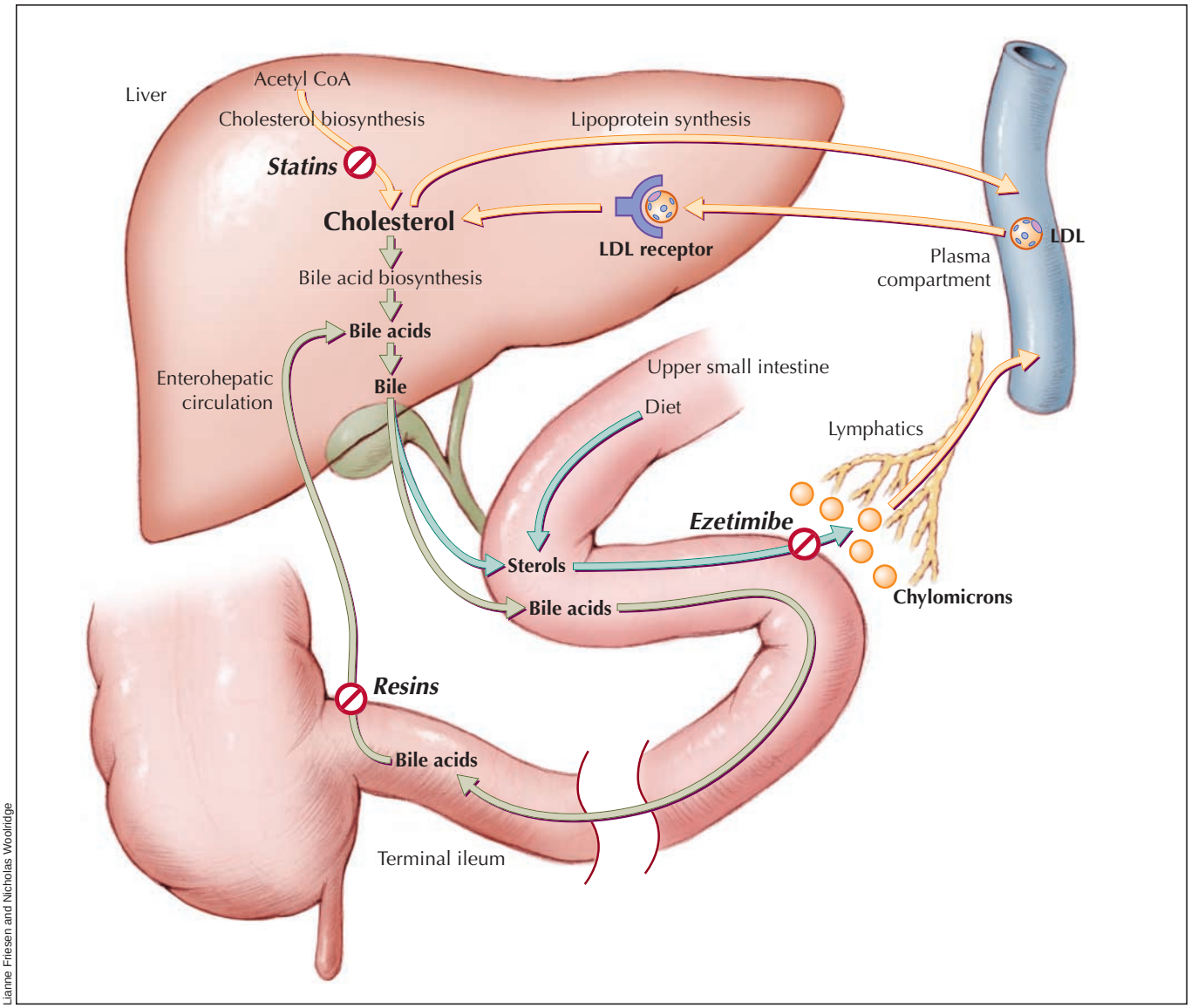

Fig. 1: Sites of action of medications taken by the patient. The liver is central to cholesterol metabolism. Hepatic cholesterol can be synthesized from acetyl coenzyme A (CoA) in a multistep enzymatic process, whose rate-limiting enzyme (3-hydroxy-3-methylglutaryl CoA reductase) is inhibited by statins such as atorvastatin. Hepatic cholesterol is used in part to synthesize bile acids that are destined, with sterols, for secretion in bile. The luminal sterol pool in the upper portion of the small intestine comes from both dietary and biliary sterols. Intestinal luminal sterols are transported into enterocytes and repackaged into chylomicrons for secretion into lymph and, ultimately, plasma. Ezetimibe likely inhibits sterol absorption by interfering with the sterol transporter Niemann–Pick C1 Like 1 protein.[5] Bile acids advance through the intestinal lumen and facilitate intestinal cholesterol absorption. Unbound bile acids are normally recycled through the terminal ileum into the enterohepatic circulation. Bile acid-binding resins, such as colestipol, prevent this recycling and force more hepatic cholesterol into bile acid synthesis. To compensate for the depletion of hepatic cholesterol stores induced by all of these drugs, the liver increases expression of cell-surface low-density lipoprotein (LDL) receptors to extract more cholesterol from the plasma by receptor-mediated endocytosis. Although both copies of the LDL-receptor gene were defective in this patient –causing very high baseline plasma LDL cholesterol –each had some residual activity, and she was able to respond to treatment. See the animated figure at www.cmaj.ca/cgi/content/full/172/4/495/DC1.

ondary to chronic use of eye whiteners, even though the patient has stopped using them.

Most cerebral cholesterol granulomata have not been associated with genetic hypercholesterolemia,[7,8] with only 1 previous case linked to homozygous FH.[9] These lesions arise silently and are thought to occur as a foreign body reaction to cholesterol crystals deposited in or adjacent to the mastoid air cells following blockage of the air cell system, in which negative pressure and hypoxia lead to local tissue and blood cell necrosis.[7] Cholesterol granulomata occur in about 1 per 2–3 million population each year.[8,10] They frequently cause neurosensory hearing loss or cranial nerve palsies or both,[7,8] but our patient had neither. She also had no history of known antecedents to cholesterol granulomata, including cholesteatoma, otitis media or cerebral bleeding.[7] It seems surprising that cholesterol granulomata have not been more commonly reported in cases of homozygous FH, a condition with whole-body cholesterol excess.[1] The absence of neurologic symptoms despite the large intracranial mass was likely a result of the very slow growth of the granuloma. The constellation of an asymptomatic cerebral cholesterol granuloma, comparatively late-onset cardiovascular disease and relatively good response to hypolipidemic therapy underscores the phenotypic heterogeneity among patients with homozygous FH. Cerebral cholesterol granulomata should be added to the list of potential complications of FH.

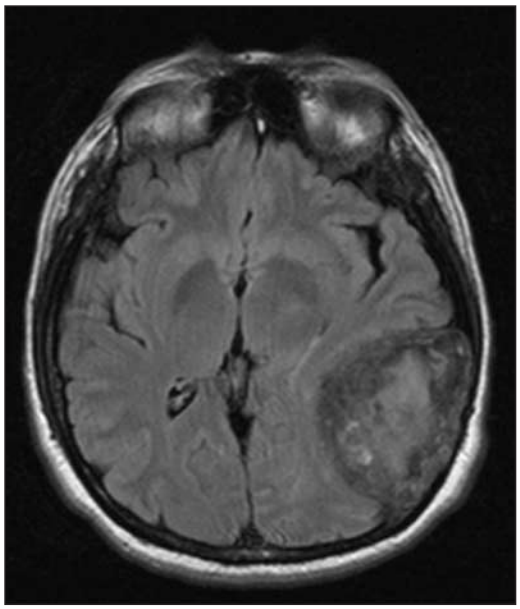

Fig. 2: MRI of a large intracranial cholesterol granuloma complicating homozygous familial hypercholesterolemia.

This article has been peer reviewed.

From the Departments of Medicine and Biochemistry (Francis), Ophthalmology (Johnson) and Neurosurgery (Findlay), University of Alberta, Edmonton, Alta., and the Blackburn Cardiovascular Genetics Laboratory, Robarts Research Institute (Wang, Hegele), London, Ont.

Competing interests: Royce Johnson, Max Findlay and Jian Wang have no conflicts of interest to report. Gordon Francis and Robert Hegele have received consultancy fees and speakers honoraria from Pfizer, Merck Frosst/Schering and AstraZeneca.

Contributors: Gordon Francis, Royce Johnson and Max Findlay provided medical care to the patient, and Jian Wang and Robert Hegele performed the genomic DNA sequence analysis. Gordon Francis and Robert Hegele wrote most of the article. All authors contributed to the revision of the article and approved the final version.

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Correspondence to: *Dr. Gordon A. Francis, Cardiovascular Risk Reduction Clinic, 328 HMRC, University of Alberta, Edmonton AB T6G 2S2; gordon.francis@ualberta.ca*

Global climate change and health: recent findings and future steps

R. Sari Kovats, Andrew Haines

More than 7 years after the Kyoto Protocol was adopted at a United Nations conference on climate change, this international and legally binding agreement to reduce greenhouse gas emissions worldwide comes into force on Feb. 16, having finally been ratified by a sufficient number of nations. Although the commitments are small, the Kyoto Protocol represents an important political step in translating the rhetoric about the need for sustainable development into action.

The evidence that the climate is changing and that these changes can be attributed to human activities has become stronger in recent years.[1] The land surface of Earth has warmed by about 0.6°C since the late 19th century, and Canada has experienced some of the most rapid warming. The range of current projections, which predict an increase in the global average surface temperature of 1.4°C to 5.8°C by the year 2100 (relative to the 1961–1990 average), takes into account scenarios in which fossil fuel use remains intensive, and those in which reliance on renewable energy sources is increased.[1]

Scientific understanding of the potential effects of climate change on ecosystems and human health has progressed since this journal published a review of the subject in 2000,[2] although there are still many uncertainties. Epidemiologic studies have further quantified relationships between weather and climate parameters and disease outcomes. There were early claims that a change in climate might already be causing changes in the geographic range and seasonality of some diseases, particularly those transmitted by mosquito vectors. However, there is as yet no convincing evidence that this is happening.[3] Robust studies require more than 20 years of good-quality epidemiologic data, with complete information on confounders (e.g., antimalarial drug resistance and population movement), and therefore the opportunities to study the impact of observed climate change on disease patterns are limited.

The effects of climate change go beyond the potential gradual spread of disease. Extreme events such as floods, droughts and heat waves are likely to increase under global warming and will challenge our ability to manage health risks and test the resilience of our infrastructures in many areas, including health service delivery. In 2003, Europe experienced summer temperatures that were unprecedented in the instrumental record. In France, over 14 000 more deaths were reported during the August heat wave than were typical for that time of year, and the total for Europe was in the region of 20 000. In Paris, the number of deaths increased by 140% over usual figures, and the mortality rate after the heat wave was not lower than usual; this indicates that the deaths that occurred during the heat wave were not simply a displacement of expected deaths for that year and that a substantial loss of life-years occurred in that population.[4] The European heat wave clearly demonstrates that, even in wealthy countries, populations may be susceptible to extreme temperatures and we cannot assume that physiologic adaptation will be sufficient to avert the health effects of rising temperatures. Climate scientists have declared it "very likely" that human influence on the climate has at least doubled the risk of heat waves such as this.[5]

A prerequisite for the prevention of adverse health effects of extreme events is public knowledge about the nature of the risk. Although public awareness increases after a natural disaster, it is often short lived. There is a clear need to develop and evaluate effective public health interventions for extreme weather events, such as heat health warning systems to reduce the impact of heat waves. However, the implication of the French heat wave was that not only public health officers but also the entire infrastructure was unprepared for such extreme temperatures. It will take many decades to adapt housing to maintain comfortable indoor temperatures in the face of prolonged extreme outdoor temperatures, especially in ways that will not increase energy consumption.

The effects of dramatic weather events on human health are clear, but we must look beyond the easily quantified and extrapolated effects of climate change. In particular, qualitative research can help us develop strategies to adapt to a changing climate. Climate change is projected to have a significant impact on the distribution of sea ice and on ecosystems in the Arctic Circle. Inuit in Nunavik and Labrador have reported significant changes in their environment in the past 20–30 years that have affected their ability to travel at certain times of the year, to find and hunt certain types of food, and to gain access to potable water.[6]

The modest climate change that occurred between the mid 1970s and the year 2000 is estimated to have caused the annual loss of over 150 000 lives and 5 500 000 disability-adjusted life-years.[7] If we do not alter the human activities that are driving greenhouse gas emissions, the health burdens of climate change are likely to approximately double by 2020, mostly because of increased rates of diarrheal disease and malnutrition in low-income countries.

DOI:10.1503/cmaj.050020

There have been recent efforts to link policies to adapt to climate change with those for international development.[8] Improving the capacity of populations to adapt to climate change should also reduce the burden of disease related to climate variability, including the El Niño phenomenon,[9] and should therefore yield benefits in the near term as well as in the more distant future. The commitments made by governments in signing the Kyoto Protocol are not sufficient to tackle climate change; however, they form a basis for future, more far-reaching, agreements to promote increases in energy efficiency and the use of renewable energy technologies. Such approaches also have the potential to benefit health in the near term by reducing deaths resulting from air pollution.[10] There will always be uncertainty about the magnitude of the adverse effects of climate change, and the burden of those effects will most probably fall predominantly on populations who have contributed little to greenhouse gas emissions, but these considerations should not prevent nations that have benefited most from access to low-cost fossil fuels from leading the way toward reduced dependence on them.

Sari Kovats is a Lecturer in the Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK, and a member of Working Group II of the Intergovernmental Panel on Climate Change. Andrew Haines is Director and Professor of Public Health and Primary Care, London School of Hygiene and Tropical Medicine, London, UK, and a reviewer for the Intergovernmental Panel on Climate Change.

Competing interests: None declared.

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Correspondence to: *R. Sari Kovats, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, Keppel St., London UK WC1E 7HT; sari.kovats@tshtm.ac.uk*

Enhanced weekend service: an affordable means to increased hospital procedure volume

Chaim M. Bell, Donald A. Redelmeier

Decreasing waiting times for medical procedures and diagnostic tests has become a major focus for health policy in Canada. Although some commentators have called for increased infrastructure to handle the demand, building and equipping new hospitals comes with enormous costs and delays, which raises the question of whether our current levels of efficiency can be improved. Because many hospitals do not operate at full capacity every day, we wondered how many more procedures could be completed if services were increased on weekends.

We examined 6 procedures that reflect diverse technologies and are regularly used in acute medical care: esophageal gastroduodenoscopy, echocardiography, coronary angiography, pulmonary ventilation-perfusion scanning, MRI and fibreoptic bronchoscopy.[1] These procedures require specialized equipment and, in our clinical experience, entail substantial delays for inpatients. To obtain realistic projections of the demand for each procedure based on past practice patterns, we identified consecutive patients admitted to all Ontario acute-care hospitals through an emergency department from Apr. 1, 1988, to Mar. 31, 1997, to determine how many underwent 1 of the 6 procedures as their most significant procedure when in hospital.[2]

The administrative database analysis revealed a total of 3 789 917 emergency hospital admissions to all acute-care hospitals during the 10-year interval; among these, 126 759 patients had 1 of the 6 selected procedures (Table 1). We found that 120 855 (95%) procedures were performed on a weekday and 5904 (5%) on a weekend. For every procedure, the observed weekday to weekend proportion differed substantially from the theoretical 71% to 29% split.

Given the large decrease in the volume of procedures performed on weekends compared with weekdays, we examined 3 scenarios to explore the effect of using weekend days to increase productivity. These scenarios were as follows: (1) all 7 days running at the same capacity as the best weekday; (2) weekend days unchanged and all 5 weekdays running at the same capacity as the average weekday capacity; (3) weekend days running at 50% of the average weekday capacity (Table 2). As expected, the first scenario generated a large increase in the potential volume of procedures. We also observed that, even if weekend days operated at only 50% of best weekday capacity, a large increase in the absolute number of procedures could be realized (most notably for echocardiography, with 700 additional procedures).

Focusing on echocardiography alone at the 110 hospitals in the cohort, we identified the 2 hospitals that demonstrated the most and the least skewed distribution of weekday to weekend services (99% of procedures performed on weekdays vs. 1% on weekends, and 85% on weekdays v. 15% on weekends, respectively). The hospital with the most skewed distribution, which performed a total of 7950 echocardiograms, would increase the total by 508 procedures per year under the first scenario. The hospital with the least skewed distribution performed a total of 2037 echocardiograms over the 10-year period and would increase the total by 150 procedures per year under the first scenario. In both hospitals, all scenarios led to potential increases in output ranging from 3% to 74%.

Interpretation

Anecdotal evidence suggests that increasing weekend hospital capacity is feasible, safe and practical.[3,4] Our work demonstrates that even conservative growth in weekend service can achieve an increase in procedure volume of about 15%. More significant effects can be attained in specific and targeted situations, depending on the individual hospital's circumstances. To our knowledge, such models of increasing weekend activity to increase the productivity of a health care system have not been examined previously.

Most earlier studies of waiting times and queues have focused on outpatient delays for high-technology procedures. Other initiatives have targeted rate-limiting departments to realize savings in fixed "hoteling" costs (which may outweigh any marginal direct procedural costs).[3] Reports have also described some success with initiatives for weekend cardiology procedures, augmented surgery and physiotherapy programs, and after-hours radiologic and nuclear medicine investigations.[3–6] These initiatives aim to reduce hos-

Table 1: Day of performance for 6 procedures regularly used in acute medical care

Procedure	Total *n = 126 759*	Weekday, no.	Weekend, no. (% of total)*
Esophageal gastroduodenoscopy	45 167	41 565	3602 (8.0)
Echocardiogram	40 965	39 972	993 (2.4)
Coronary angiogram	21 690	21 356	334 (1.5)
Ventilation perfusion scan	10 639	10 207	432 (4.1)
MRI of any structure	4325	4027	298 (6.9)
Fibreoptic bronchoscopy	3973	3728	245 (6.2)

DOI:10.1503/cmaj.1041063

Table 2: Projected yearly increases in procedure volume resulting from enhanced weekend service

Procedure	Scenario; no. of additional procedures performed (% increase)		
	All 7 days at same capacity as best weekday	Weekend days unchanged; weekdays at best capacity	Weekend days at 50% of average weekday capacity; weekdays unchanged
Esophageal gastroduodenoscopy	2016 (45)	510 (11)	471 (10)
Echocardiogram	2172 (53)	480 (12)	700 (17)
Coronary angiogram	1200 (55)	271 (13)	394 (18)
Ventilation perfusion scan	877 (83)	366 (34)	161 (15)
MRI of any structure	193 (45)	44 (10)	51 (12)
Fibreoptic bronchoscopy	177 (45)	37 (9)	50 (13)
All	6635 (52)	1708 (14)	1827 (14)

pital length of stay but still preserve (or enhance) the delivery of services. Further, they sometimes provide faster results and have the potential to alter clinical decisions.[5]

Human resource issues in health care are substantial, yet creative scheduling in echocardiography (and other services) employing free-market mechanisms may be a means of increasing weekend staffing.[3] Other obstacles to consider include service time for equipment, the quality of life of clinicians, the handling of on-call responsibilities and the goals of unions. Weekends are also typified by a lack of availability of administrators, supervisors and support staff. Moreover, our analysis focused on admitted patients only; hence, additional weekend capacity could also be considered to shorten outpatient queues and satisfy the preferences of some patients and their families.

Given that the administrative data we used may contain coding errors, our projections are preliminary. However, the proportions of procedures performed on weekends were similar to those described elsewhere.[7] Also, the basic assumptions of extrapolation we used in our simulations might not fully reflect real-world potential, local cultures and complex system factors (e.g., elective queues). For example, our analysis did not account for holidays, which may dilute the observed weekday/weekend comparisons and alter some of the estimates of productivity. Our analysis does not account for nursing salaries and premiums for other salary costs beyond conventional full-time staffing. However, even with increased wages for weekend work, some health care institutions have found it economical to increase the amount of care provided on weekends.[3,4] Further, we included only those patients who were admitted to hospital through emergency departments; patients admitted electively and those requiring the same procedures as outpatients only add to the skewed delivery of care, as they rarely obtain procedures on weekends. Finally, we did not incorporate into our analysis complex salary structures reflecting particular marketplace conditions.

Waiting for information and procedures can jeopardize sound decision-making, delay important clinical care and affect patient outcomes.[2,5] Thus wasted time is an important component of the differences between weekday and weekday processes of care, and interventions to reduce wasted time issue might have implications for quality of care. In the quest for more timely medical care, staffing efficiencies may provide a more feasible solution for some hospitals than capital expansion. Constructing new staffing schedules is likely to cost less and to create fewer delays and disruptions than constructing new buildings.

This article has been peer reviewed.

From the Departments of Medicine and of Health Policy, Management and Evaluation, University of Toronto, and the Institute for Clinical Evaluative Sciences (Bell, Redelmeier); Department of Medicine, St. Michael's Hospital (Bell); and the Department of Medicine, Patient Safety Service, and Clinical Epidemiology Unit of Sunnybrook and Women's College Health Sciences Centre, Toronto, Ont. (Redelmeier)

Competing interests: None declared.

Contributors: Both authors contributed substantially to the conception and design of the project. Chaim Bell conducted the analysis and both authors interpreted the data. Both authors participated in writing the manuscript and approved the submitted version.

Acknowledgements: Chaim Bell is funded by Clinician Scientist Awards from the Canadian Institutes of Health Research and the University of Toronto Department of Medicine. Donald Redelmeier was funded by a Canada Research Chair in Medical Decision Sciences. We thank Alex Kopp for help with computer programming. We are also grateful to Ross Baker, Allan Detsky, Ed Etchells, Claudio Martin, Art Slutsky and Jack Tu for comments on drafts of this manuscript.

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Correspondence to: *Dr. Chaim M. Bell, St. Michael's Hospital, 30 Bond St., Toronto ON M5B 1W8; fax 416 864-5485; bellc@smh.toronto.on.ca*

Diagnosis and management of pertussis

Alberto E. Tozzi, Lucia Pastore Celentano, Marta Luisa Ciofi degli Atti, Stefania Salmaso

Abstract

PERTUSSIS IS INCREASING IN FREQUENCY among children too young to be vaccinated and among adolescents and adults. This increase is due mainly to waning immunity among vaccinated individuals, who become susceptible during adolescence and adulthood and maintain the circulation of *Bordetella pertussis*. Infants are at highest risk of severe illness requiring hospital admission, complications and death. The clinical presentation in adolescents, adults and vaccinated individuals may be atypical, with paroxysmal cough of short duration or simply a persistent cough. Culture and polymerase chain reaction may be used to identify *B. pertussis* infection, but their sensitivity is high only in the early phase of the disease. Serologic tests are not standardized for the diagnosis of pertussis, and their clinical application is limited. Erythromycin is still considered in some countries to be the "gold standard" for therapy and prophylaxis; however, azithromycin and clarithromycin seem equally efficacious and are associated with fewer side effects.

CMAJ 2005;172(4):509-15

The increase worldwide in vaccination coverage against pertussis has substantially reduced the morbidity and mortality associated with this disease. However, because of variability in age-specific vaccine coverage rates and waning immunity, the epidemiologic pattern of pertussis in developed countries has radically changed. Managing pertussis in a setting with high rates of vaccination uptake requires knowledge of the clinical picture of pertussis according to the vaccination status and age of the patient, the most sensitive and timely laboratory tests for diagnosis, and the safest and most efficacious methods of treatment and prophylaxis. In this article we review recent findings and issues in the diagnosis, treatment and prophylaxis of pertussis. (An outline of our strategy for the literature search is available in Appendix 1.)

Epidemiology and pathogenesis

In the 1990s *Bordetella pertussis* caused an estimated 20 to 40 million cases of pertussis worldwide and 200 000 to 400 000 deaths each year.[1] Although improved vaccination coverage has decreased the incidence of pertussis dramatically over the last decade, many developed countries have recently experienced a resurgence of the disease among infants too young to be vaccinated and among adolescents and adults.[2–6] Outbreaks have been reported even in populations with high vaccination coverage, primarily because of waning immunity, which results in a large number of susceptible adolescents and adults.[7] Indeed, neither natural infection nor primary immunization induces permanent immunity.[8] Because of its variable presentation among patients with different degrees of susceptibility, pertussis is likely largely underdiagnosed among young infants and among adults unless an outbreak occurs.

B. pertussis is transmitted person to person by close contact with aerosolized droplets. The incubation period may vary between 6 and 21 days but is typically 6–10 days. Bacteria invade and damage the epithelium of the airway and the alveoli through the combined action of several virulence factors that interfere with normal ciliary movement (Fig. 1), namely fimbriae, pertactin, pertussis toxin, filamentous hemagglutinin, adenylate cyclase, tracheal cytotoxin, dermonecrotic toxin, lipopolysaccharide, tracheal colonization factor, serum resistance factor and type III secretion.[9] Symptoms of pertussis may persist long after clearance of the infecting organism has occurred.[10]

Clinical presentation

After the incubation period, pertussis begins with a catarrhal phase. This phase lasts 1–2 weeks, during which patients are most contagious, and it is clinically indistinguishable from a mild upper respiratory tract infection. As the catarrhal stage progresses, the cough increases in frequency and severity. The subsequent paroxysmal phase, which lasts 3–6 weeks, is characterized by spells of coughing with the characteristic whoop, vomiting, cyanosis and apnea. The symptoms gradually decrease in severity during the convalescent phase, which can last up to several months (Table 1).

The clinical course may be influenced by various factors, including age, sex and immunization status of the patient (Table 2, Table 3). Observations made on the determinants of the clinical presentation of 788 laboratory-confirmed cases of pertussis in children during a trial in Italy of acellular pertussis vaccines found that the clinical course of pertussis was independent of age and sex until the age of 3; after this age, the duration of spasmodic cough was 7 days longer among girls than among boys and decreased with age, and the duration of cough increased.[11] Many children under 6 months of age do not develop paroxysmal cough or the characteristic inspiratory whoop. Recurrent episodes of apnea, cyanosis and bradycardia can dominate the clinical

DOI:10.1503/cmaj.1040766

picture in infants, and a prolonged and complicated course is often observed.[13,14] Although adolescents and adults usually experience the 3 typical stages of pertussis, some may have only a protracted cough.[2,15] Smoking or asthma may increase the duration of paroxysmal cough and the number of nights with disturbed sleep.[15] Pertussis is less severe in vaccinated individuals.[11,12,16] One study involving vaccinated people 5–30 years of age showed that the 3 typical stages of pertussis were absent, the clinical course was characterized by cough lasting a median of 3 weeks, and only 6% of the patients with pertussis had the classic whoop.[16]

Complications

The most frequent complication observed in children is pneumonia, which occurs in 6% of cases.[17] Other complications include sinusitis, otitis media, viral and bacterial superinfections, nutritional deficiencies resulting from repeated vomiting and neurologic complications, which are due mostly to hypoxia during coughing spells and apnea.[8,17] In 1990 it was estimated that 50 000 children worldwide experienced long-term neurologic complications of pertussis,[18] and in the late 1990s it was reported that 0.9 per 100 000 pertussis cases were complicated by encephalopathy.[19] The risk of complications is higher among infants and adults than among older children and adolescents. In a prospective case series in Germany, the rate of complications among infants less than 6 months of age was 24%, as compared with 5% among older children.[17] In the first 2 months of life, pneumonia, seizures and encephalopathy have been reported in 25%, 3% and 1% of cases, respectively.[20] Cardiac arrhythmias and episodes of intractable hypoglycemia have also been reported.[14] After childhood, the risk of complications increases with age.[15,17] Pneumonia has been observed in 2% of patients less than 30 years of age, as compared with 5%–9% of older patients. Syncope, urinary incontinence, back pain, rib fracture and hernia have been also described.[8,15]

Severe paroxysm, post-tussive cyanosis, whooping, post-tussive vomiting, apnea, pneumonia and seizures are the most frequent reasons patients are admitted to hospital, regardless of age.[21–23] Infants, especially those who have not been vaccinated or have been incompletely vaccinated, are the most likely to require hospital care.[6,21–30] Birth before 37 weeks' gestation and low birth weight have been inconsistently indicated as independent risk factors for hospital admission.[21,23]

Death from pertussis is inversely related to age, with almost 90% of reported deaths occurring in unvaccinated

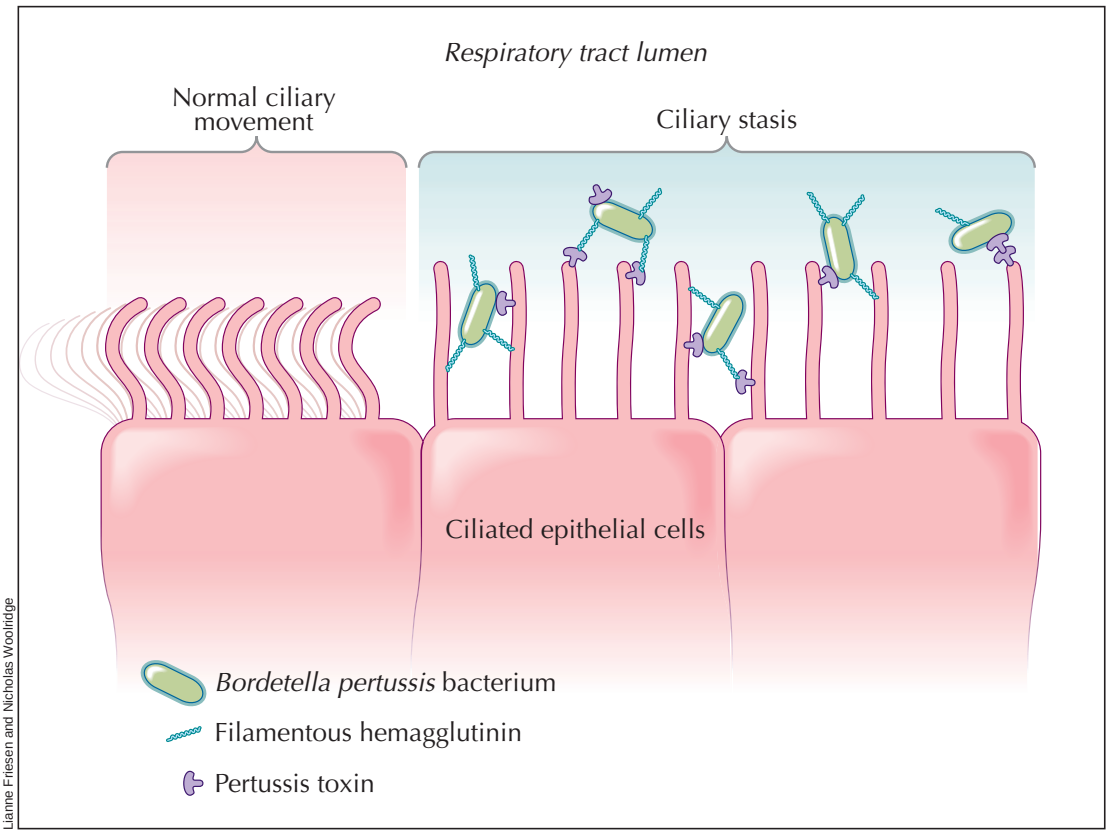

Fig. 1: Synergy between pertussis toxin and filamentous hemagglutinin in binding to ciliated respiratory epithelial cells. *Bordetella pertussis* attach strongly to the ciliated cells with the combined action of other adhesins (e.g., fimbriae and pertactin). Pertussis toxin has the ability to enter the bloodstream and plays an important role in the induction of clinical immunity.

infants less than 1 year old, who have a case-fatality rate of 0.6%.[20,31,32] High levels of leukocytosis and lymphocytosis may predict a fatal outcome in children admitted to hospital.[32–35] An association between pertussis and sudden unexpected death in infants has been observed.[36] Therefore, pertussis should be ruled out in cases of sudden infant death syndrome.

Diagnosis

A mild increase in the leukocyte count and marked lymphocytosis are classic markers of pertussis and have been shown to be useful indicators of the disease if observed with typical symptoms or positive microbiological assay results.[37] Traditional laboratory methods for diagnosis include identification of *B. pertussis* through culture of nasopharyngeal secretions and serologic testing for evidence of seroconversion of specific antibodies in the convalescent phase of the disease compared with the acute phase. High rates of vaccination coverage, the occurrence of cases with mild symptoms, recurrence of natural exposure and the increased age at which pertussis develops influence the sensitivity and specificity of the laboratory methods (Table 4), and no single assay is considered to be the "gold standard" in common practice.

For culture, nasopharyngeal secretions are collected through swabbing or aspiration. Culture takes several days to be completed and includes an enrichment step and the use of selective media in order to prevent growth of competing organisms of the upper respiratory tract.[9] Although the positive predictive value is 100%, the sensitivity of culture is highest in the early stage of infection, before the natural clearance of bacteria, in severe cases, in unvaccinated patients and in infants (Table 1).[46–48] The likelihood of a positive result may be negatively affected by antibiotic treatment.

Polymerase chain reaction (PCR) methods enhance the probability of identification of *B. pertussis*, since positive results may be obtained even when the organism is no longer culturable. In a recent study in France involving 217 adults with persistent cough, 70 had laboratory-confirmed pertussis (confirmed by culture, PCR or serologic testing); of these cases, only 1 was confirmed by means of culture, as compared with 36 by PCR.[40] PCR assays require the availability of adequate specimens as well as particular laboratory experience, since the risk of false-positive results is high.[49] Sensitivity and specificity of PCR depend on the primers used, and various combined techniques have been reported to enhance the performance of this method.[50,51] However, the sensitivity of PCR decreases with the duration of symptoms, since the method is based on the detection of the microorganism.

Serologic testing is based on the identification of a significant variation in IgG or IgA titres against the most rel-

Table 2: Observed influence of factors on duration of cough and spasmodic cough in children with pertussis[11]

Factor	Effect on duration of cough	Effect on duration of spasmodic cough
Immunized with an acellular pertussis vaccine	↓	↓
Culture positive pertussis	↑	↑
Received antibiotic treatment*	↑	↑
Female sex	↔	↔†
Age	↑	↓‡
Background incidence	↔	↔

Note: ↓ = decrease, ↑ = increase, ↔ = no effect.
*Antibiotic use thought to be a marker of disease severity.
†Female sex was associated with a longer duration of spasmodic cough only in children over 33 months of age.
‡Age was inversely related to duration of spasmodic cough only in children over 33 months of age.

Table 1: Typical course of pertussis — evolution of symptoms, relative sensitivity of diagnostic methods and effect of antibiotic therapy, by phase of pertussis

Variable	Catarrhal phase (1–2 wk)	Paroxismal phase (3–6 wk)	Convalescent phase (> 6 wk)
Symptom			
Cough	++	+++	++
Paroxysmal cough	–/+	+++	–/+
Whooping cough	–	+++	–/+
Vomiting	–	+++	–/+
Cyanosis	–	+++	–
Apnea	–	+++	–
Test sensitivity			
Culture	++	–/+	–
PCR	++	++	–
Serology	–/+	++	++
Effect of antibiotic therapy			
Symptoms alleviated	++	–/+	–

Note: + present, – absent, –/+ equivocal.

evant virulence factors of *B. pertussis* between the acute and the convalescent phases of the disease. The antigens most often targeted by such testing are pertussis toxin, filamentous hemagglutinin and pertactin. However, the ability to show seroconversion may be affected by the previous immunological priming of the patient (owing to vaccination or previous infection) and by when serum samples are collected. If the acute sample is taken after the specific humoral response has already been elicited, seroconversion may be difficult to detect. In one study, although a vigorous antibody response to adenylate cyclase toxin was elicited by natural infection in previously unvaccinated patients, the response was very limited in patients who had been vaccinated.[52] Therefore, diagnosis by means of serologic testing may be difficult in vaccinated or adult patients.

Identification of a cutoff value for detecting acute infection from a single serum sample has been attempted by studying the kinetics of the humoral response.[53–55] Only humoral responses to pertussis toxin have been shown to be consistent among vaccinated and unvaccinated patients. Responses to filamentous hemagglutinin have had a lower specificity than responses to pertussis toxin, possibly because of cross-reactions with antigens of different origins. Responses to pertactin have had a lower sensitivity than those to the other 2 antigens. Wide use of serum IgG anti-pertussis toxin antibody levels as a diagnostic indicator, however, is limited. The decay of IgG anti-pertussis toxin antibody levels is more rapid than that of IgG levels in response to filamentous hemagglutinin, pertactin or fimbriae,[53,54] and the antibody response to pertussis toxin has been found to vary considerably, both in magnitude and in duration, between individuals.[55] Only a small subset of patients may have a humoral response of sufficient magnitude and duration for diagnosis.[55] Nevertheless, a serum IgG anti-pertussis toxin antibody level above 100–125 EU/mL has been considered a reasonable threshold for a positive test result.[8] The variability of results, the usefulness of this method only late in the clinical course of the disease and the lack of standardized commercial test kits make serologic testing difficult to use in common practice with reproducible results. A combination of various methods should be used instead, matching culture or PCR results with serologic test results.[8]

Table 3: Summary of selected studies that describe and illustrate variability in the clinical presentation of pertussis

Study	Location of study	Patient age group	Vaccinated	Duration of cough, wk	% of cases with spasmodic cough	% of cases with vomiting	% of cases with apnea
Tozzi et al, 2003[11]	Italy	6 mo–6 yr	No	7–9*	83–98	76–86†	73–84†
			Yes	4–6*	65–91	54–71†	35–47†
Preziosi et al, 2003[12]	Senegal	6 mo–8 yr	No	14*	NR	74	NR
Senzilet et al, 2001[2]	Canada	≥ 12 yr	No	8‡	NR	45	14

Note: NR = not reported.
*Median.
†Children aged 6–33 mo only.
‡Mean.

Table 4: Sensitivity of diagnostic tests for pertussis in various studies involving adults*

Study	Duration of cough, d	Sensitivity, %		
		Culture	PCR	Serologic testing (antigens)
Mink et al, 1992[38]	≥ 6	0	NA	100 (IgG/A-PT, IgG/A-FHA)
Rosenthal et al, 1995[39]	> 6	10	NA	100 (IgG/A-PT, IgG/A-FHA)
Gilberg et al, 2002[40]	> 6	1	51	57 (IgG-PT)
Schmitt-Grohé et al, 1995[41]	≥ 7	8	13	92 (IgG/A-PT, IgG/A-FHA, IgG/A-PRN, IgG/A-FIM2, agglutinins)
Senzilet et al, 2001[2]	> 7	2	3	95 (IgG/A-PT, IgG/A-FHA, IgG/A-PRN, IgG/A-FIM2)
Strebel et al, 2001[42]	> 7	30	37	89 (IgG/A-PT)
Wright et al, 1995[43]	≥ 14	0	NA	100 (IgG-PT, IgG-FHA)
Birkebaek et al, 1999[44]	> 14	11	32	97 (IgG-PT)
Wirsing von Konig et al, 1995[45]	> 21	1	NA	100 (IgG/A-PT, IgG/A-FHA, IgG/A-PRN)

Note: PCR = polymerase chain reaction, NA = not available, IgG/A = IgG or IgA, PT = pertussis toxin, FHA = filamentous hemagglutinin, PRN = pertactin, FIM = fimbriae.
*Adapted from reference 8.

Treatment

Since a timely laboratory confirmation of pertussis diagnosis is problematic, administering an antibiotic on the basis of a clinical diagnosis should be considered. Antibiotics eradicate *B. pertussis* from the airway but limit the severity of disease only if started in the catarrhal phase (Table 1).[56,57] The standard treatment of pertussis has been a full dose of erythromycin for 14 days.[58] Evidence suggests that a shorter, 7-day course is equally effective.[59] More recently many national agencies have tended to encourage the use of other macrolides for therapy.[60] New macrolides exhibit high and sustained intracellular penetration and therefore may be particularly effective against organisms such as *B. pertussis*, although they are more expensive than erythromycin.[61] Azithromycin, 10 mg/kg on the first day followed by a daily dose of 5 mg/kg (maximum dose 1000 mg on day 1 and 500 mg on days 2 to 5), has been shown to be effective in eradicating *B. pertussis* in 97% of cases after 2–3 days and in 100% after 14–21 days.[62] In a study involving 37 patients aged 2–18 months who were given azithromycin for 3–5 days, 94% had negative cultures for pertussis 7 days after the initiation of therapy and 100% had negative cultures 14 days after the initiation of therapy.[63] A comparison of erythromycin with azithromycin in a pediatric population showed that the drugs were equally effective in eradicating *B. pertussis* (100% efficacy) 1 week after the end of treatment.[57] Clarithromycin has been shown to be efficacious in treating patients with pertussis as well.[64]

Resistance to erythromycin seems exceptional, but sensitivity to this and other macrolides is rarely performed during laboratory diagnosis.[65] In case of intolerance to macrolides or resistance, use of trimethoprim–sulfamethoxazole (8 and 40 mg/kg per day, respectively, in divided doses) is indicated.[58]

The frequent gastrointestinal side effects observed in patients treated with erythromycin may reduce compliance.[57] Moreover, the administration of erythromycin in infants may be associated with pyloric stenosis in up to 3.5% of cases.[66] Gastrointestinal symptoms such as nausea, vomiting or diarrhea are observed in up to 41% of patients given erythromycin[57] and in up to 19% of those given azithromycin.[57,62] Azithromycin has also been associated with a slight and transient elevation of liver enzyme levels in up to 20% of patients.[63]

Attention must be paid to potential drug interactions. Erythromycin can increase serum concentrations of theophylline, carbamazepine, warfarin, cyclosporine and terfenadine when administered concurrently. Clarithromycin interacts with theophylline, carbamazepine and terfenadine. The effect of these drugs administrated concurrently with azithromycin has not been studied.[61]

Use of dexbrompheniramine plus pseudoephedrine for 1 week, or ipratropium (0.06%) nasal spray for 1 week, has been proposed for the treatment of cough. Alternatively, inhaled ipratropium therapy (four 18-μg puffs 4 times daily using a metered-dose inhaler with spacer) for 1–3 weeks, systemic corticosteroid therapy tapered over 2–3 weeks, or antitussives acting on the cough centre in the brain have been used.[67] However, a recent systematic review that examined the efficacy of antihistamines, diphenhydramine, corticosteroids and salbutamol concluded that the effectiveness of these therapies in treating cough in pertussis is uncertain and that their use is not justified.[68]

Treatment of severe cases is mostly supportive. In some cases intravenous pertussis immune globulin therapy has been shown to decrease whooping, to improve oxygen saturation and to stop bradicardic episodes.[69,70] Recently, leukopheresis and exchange transfusion have been proposed to reduce the leukocyte mass in cases with very high leukocyte counts.[71] Extracorporeal membrane oxygenation is widely used in the management of severe pertussis, but it has had limited success, and pertussis severe enough to require its use is in itself a predictor of a poor outcome.[32,34]

Table 5: Recommendations of the US Centers for Disease Control and Prevention for antibiotic prophylaxis in close contacts of patients with pertussis, regardless of vaccination status, to prevent health care-associated pneumonia[72]

Drug	Dose	Duration of prophylaxis, d	Indication	Contraindications
Erythromycin	Children: 40–50 mg/kg daily Aduls: 500 mg 4 times daily if erythromycin estolate; 333 mg 3 times daily if delayed-release tablets	14	First-choice therapy	Intolerance to macrolides; age ≤ 2 wk
Azithromycin	10–12 mg/kg daily	5–7	Patients with intolerance to erythromycin or infants aged ≤ 2 wk	Intolerance to macrolides
	10 mg/kg on day 1; 5 mg/kg daily on days 2–5	5		
Clarithromycin	Children: 15–20 mg/kg daily in divided doses Adults: 500 mg twice daily	10–14	Patients with intolerance to erythromycin or infants aged ≤ 2 wk	Intolerance to macrolides
Trimethoprim–sulfamethoxazole (TMP–SXT)	Children: TMP 8 mg/kg and SXT 40 mg/kg daily in divided doses Adults: one double-strength tablet twice daily	14	Hypersensitivity or intolerance to macrolides	Pregnancy at term; nursing; age < 2 mo

Prevention of secondary cases

Prevention of secondary cases is of upmost importance in health care settings and in households with infants. An accelerated schedule for vaccinating children less than 7 years old who have not completed their primary vaccinations is recommended, and the first dose of vaccine can be administered as early as 6 weeks of age.[72] Close contacts should also receive antibiotic prophylaxis (Table 5). The US Centers for Disease Control and Prevention (CDC) still recommends erythromycin as the drug of choice in these cases except in infants 2 weeks of age or younger. The treatment should extend over 14 days for the prevention of health care-associated pneumonia.[72] Patients intolerant to erythromycin or infants too young to be given the drug should be treated with azithromycin or clarithromycin. Those who do not tolerate macrolides should receive trimethoprim–sulfamethoxazole.[72] Patients are considered not to be contagious after 5 days of antimicrobial treatment, or 21 days after the onset of cough if unable to take antibiotics.

Despite evidence that antibiotic prophylaxis has been successful in controlling outbreaks of pertussis, the effectiveness of erythromycin therapy in preventing individual secondary cases of pertussis has been considered modest.[73,74] Erythromycin prophylaxis is more efficacious if initiated within 21 days (preferably 14 days) of onset of paroxysmal cough in the index case.[74,75]

Conclusion

Long after the discovery of effective antibiotic treatments and the implementation of universal vaccination strategies, pertussis remains a disease associated with an important burden even in developed countries. Since the clinical presentation of pertussis has changed because of vaccination, the disease likely is largely underdiagnosed. The development of sensitive and standardized diagnostic methods is essential. Treatment and prophylaxis with macrolides other than erythromycin will likely ensure better compliance.

This article has been peer reviewed.

From the Epidemiology Unit, Bambino Gesù Hospital (Tozzi), and the National Epidemiology Centre, Istituto Superiore di Sanità (Pastore Celentano, Ciofi degli Atti, Salmaso), Rome, Italy.

Competing interests: None declared.

Contributors: Alberto Tozzi designed the structure of the paper, performed the literature search and assembly of data, and drafted and revised the manuscript. All of the authors contributed equally to the preparation, analysis and synthesis of the available data and approved the final version to be published.

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Correspondence to: *Dr. Alberto E. Tozzi, Epidemiology Unit, Bambino Gesù Hospital, Piazza S. Onofrio, 4, 00165 Rome, Italy; fax 39 06-68592583; alberto.tozzi@opbg.net*

Appendix 1: Search strategy

We searched MEDLINE for relevant articles published from 1995 to 2004 using the following strategy:

- "whooping cough" [MeSH] + "epidemiology" [MeSH] + "human" [MeSH]
- "whooping cough" [MeSH] + "etiology" [MeSH] + "human" [MeSH]
- "whooping cough" [MeSH] + "signs and symptoms" [MeSH] + "human" [MeSH]
- "whooping cough" [MeSH] + "laboratory techniques and procedures" [MeSH] + "human" [MeSH]
- "whooping cough" [MeSH] + "therapy" [MeSH] + "human" [MeSH]

We also searched the Cochrane Library database using the term "whooping cough"

We found a total of 575 articles in the MEDLINE search and 3 in the Cochrane Library search. Articles without an available abstract were not considered. After reading the abstracts, we excluded articles that dealt with pertussis immunization only.

A total of 153 articles were thoroughly reviewed. Relevant references cited in these articles were retrieved and reviewed, even if they were published outside of the time frame of the main search.

The Left Atrium

Migraine chronicle

Claire's head
Catherine Bush
Toronto: McClelland & Stewart; 2004
336 pp $32.99 (cloth) 0-7710-1752-9

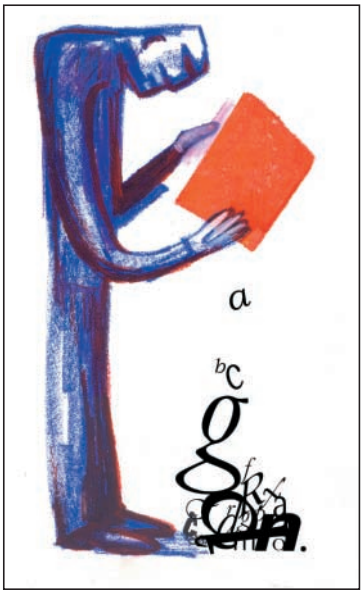
Catherine Bush is a young writer of some prominence, her two earlier novels having gained an appreciative reception (shortlistings for the City of Toronto Book Award, mention as a *New York Times* Notable Book, plus others). *Claire's Head*, her third novel, offered Bush an opportunity to consolidate that reputation by writing more than a merely good book; this was her moment to write a *great* book, one that is mature, thoughtful, surprising, intricate, sympathetic, and … well, great.

Structurally speaking, Bush has definitely succeeded. The story of Claire Barber and the pursuit of her missing sister Rachel around the globe is well paced, and the characters are believable and compelling. The greatest success in this novel, though, is Bush's ability to make migraine, an affliction suffered by both Claire and Rachel, into a virtual character. It is clear that Bush has done her homework on the nature of migraines; her fictional treatment is medically sound without being overbearing. It is also the stuff of good storytelling, for her protagonists' migraines are portrayed as capricious and debilitating, an implacable force. Migraines have personality in this book; they dominate the lives of Claire and Rachel, who cannot be understood as characters with the migraine element taken out. Almost every decision these sisters make is made in some way with an eye to the potential for a migraine attack. Bush describes Claire's migraine-sense:

> And how was it possible not to think of them, not consider their possibility, not be aware of each subtle fluctuation of sensation within her head, her body? It was like an awareness of the weather, the internal weather of her nervous system.

The reader cannot help but sympathize with Claire, given headacheologues like this one:

> Claire had migraines long before her parents' death. She'd had migraines since childhood. She'd suffered from them even before Rachel had. She could not remember anything as decisive as a first headache, rather she had a growing awareness of their being part of her life's landscape. They were not as frequent during her childhood, however. And when they came — when they shook her, then she was capsized into them — the headaches always took her by surprise. She had no sense, then, of warning signals. Nor was she able to attribute the migraines to any obvious cause, if they were in fact caused by anything outside her body and its complicated neurochemistry, her faulty nervous system with its particular sensitivity to pain … the pain simply appeared. It was. She became it. One side of her head was seized, one side of her body. It took her over, like a fit. Even without a headache, she'd feel suddenly at sea and vomit …



Fred Sebastian

Despite such strengths, I have misgivings. As can be seen from even this brief excerpt, such is not the stuff of an *auteur*, a stylist willing to recast the language through feats of fantastic metaphor and sinuous syntax. Bush's prose does not dazzle. Rather, it slowly accumulates and adumbrates, doing a fairly standard job in the process, though whole swaths read as rather flat and plain. The boring quotient to this book eventually becomes too formidable, its serial blandness making me wish at times for a prose Ferrari to whip across the page, for Bush's pedestrianism to suddenly get swept up in hot exposition. My wishes were answered with space-wasting character chat, with lacklustre, inert paragraphs that serve only to move the plot along. At a basic level this novel could be deemed a failure, for it fails at the level of the sentence. The sentence is not a beautiful instrument in Bush's hands, and consequently greatness has not been grasped. It is true that in *Claire's Head* the migraine has been captured competently; there are compelling relationships; things happen. All markers of a developing novelist. But the next crucial stage in the evolution of Bush as artist is to take hold of the potential of the sentence, to give over to the sentence the power and emphasis she places on plot and dialogue. Then devices like migraines will be incidental, characters superfluous, plot an afterthought. We will be convinced in all of these things because we trust the author's sentences.

Shane Neilson
Family Physician
Guelph, Ont.

DOI:10.1503/cmaj.055244

Aspirin take two

Aspirin: the story of a wonder drug
Diarmuid Jeffreys
London: Bloomsbury Publishing; 2004
335 pp. $27.95 (paper) ISBN 0 7475 7443

I once met a man whose child had inadvertently entertained the parish priest by asking him to provide more details to the story of "Gladly the cross-eyed bear." Similarly, I recall as a child being confused by television commercials that extolled the virtues of a medication with a "bear cross on every tablet." The medication in question was Aspirin of course, its trademark the famous "Bayer cross," one company's ultimately successful attempt to brand its product in a world where fierce competition for market share among arguable equals continues to complicate, confuse and threaten.

In *Aspirin: the Story of a Wonder Drug*, a new book by British journalist and television producer Diarmuid Jeffreys, the discovery of acetylsalicylic acid, or ASA, and its subsequent branding is wonderfully laid out. Unlike the rather dry, chalky medication whose history it traces, this account is highly palatable; Jeffreys introduces an eclectic menu of characters (some less savoury than others) and clearly traces the complex story of how ASA became "one of those rare commodities whose very existence seems to have influenced history, its invention provoking decisions and events that might not have otherwise occurred."

Jeffreys outlines in great detail the connection between Farbenfabriken Bayer, a company ultimately descended from a mid-nineteenth century partnership between dye merchants Friedrich Bayer and Johann Weskott, and the subsequently notorious Interessengemeinschaft der Deutschen Teefarbenfabriken (Community of Interests of the German Tar-dye Factories), or IG Farben. He pulls no punches when he states that the cartel that was IG Farben was "one of the buttresses of the most grotesque and brutal dictatorship [sic] the world has ever seen," that of Hitler's Third Reich. "The line from Aspirin," Jeffreys writes, "leads all the way on up to Auschwitz."

Another highly interesting and thought-provoking theme is the popularization of ASA around the globe and the numerous fortunes that were made and lost along the way. Various and sundry legal machinations, patent contests and under-the-table shenanigans are related in simple prose that is not, for all that, bereft of colour. Jeffreys writes well and provides a useful index as well as an extensive bibliography. Moreover, he manages to provide sufficient scientific and legal detail to adequately inform but not intimidate a general readership. Although one could quibble with his perhaps careless use of the expression "heart failure" in one or two places, this is of less significance than the fact that he provides accurate information (within limits) regarding ASA's use as an antiplatelet agent and the benefits that seem to accrue to regular users. Notions of primary versus secondary prevention are not addressed, although Jeffreys reminds his readers that "Aspirin is not a cure-all … [and that] it is worth repeating that it can have side effects."


Fred Sebastian

Duly and interestingly noted is the fact that, in spite of a growing number of small studies reporting the efficacy of ASA in fighting a broad range of cancers, not to mention AIDS, simple economics precludes the likelihood of any large-scale research. As Jeffreys notes:

> [A]spirin is eighty or more years out of patent. It is also extremely inexpensive … . Its producers will always fund a few trials out of altruism but there's no real financial incentive for them to do more because the profit margins on the product are so small and anyone can make it.

Jeffreys gives relatively short shrift to the late twentieth-century coalescing of numerous pharmaceutical companies into the multinational giants that dominate the industry today. Also lacking — for obvious reasons — in the brief segments devoted to selective COX-2 inhibitors, are references to the ongoing "revelations" prominent in the news today. Nevertheless, these are minor criticisms; the book is less an esposé of the pharmaceutical and medical industries than a history of a medication that in today's regulated climate might not have made it to market.

Physicians and laypersons alike need always and everywhere to be wary of "wonder drugs." This especially is true in these post-Vioxx days, when arguably well-informed patients are more and more skeptical of the benefits promised by the various medications they are prescribed so frequently. Indeed, it appears that patients are not only skeptical about the putative returns of taking their medications; they are increasingly and justifiably suspicious of the physicians who prescribe them.

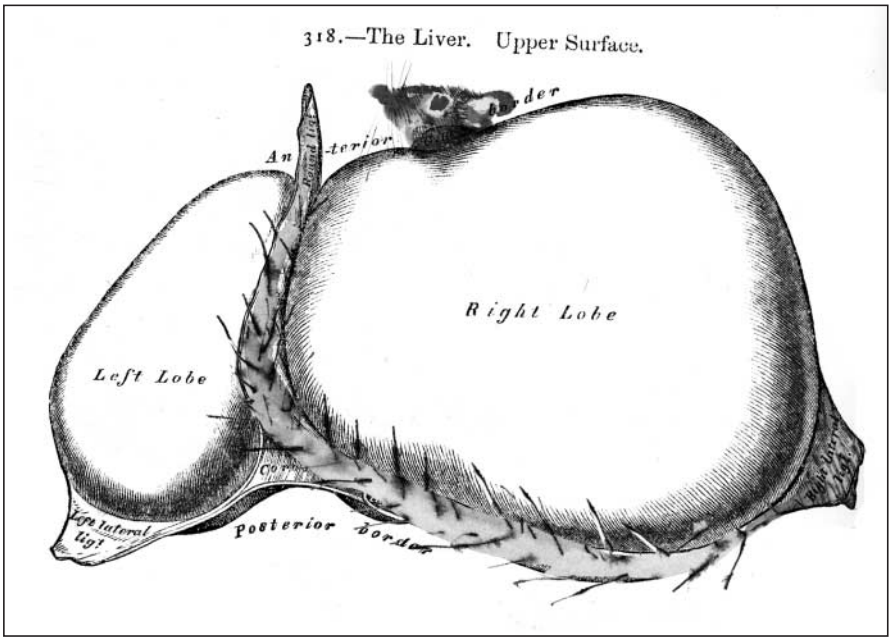
In spite and perhaps because of this, Jeffreys' history of Aspirin well repays the easy hours required to read it. In these halcyon days of "evidence-based medicine," we do well to remember that the jury is always out. The simple passage of time dictates that tomorrow inevitably will bring new evidence (or at least bring new evidence to light). And perhaps we ought all to keep in mind the words of an eighteenth-century satirist quoted thusly by Jeffreys: "Cur'd yesterday of my disease, I died last night of my Physician."

Ted St. Godard
PGY1
Family Medical Centre
University of Manitoba
Winnipeg, Man.

DOI:10.1503/cmaj.050009

Room for a view

Of scrubs and rats



Fred Sebastian

The nurses had warned me before I went to see her.

"Mme St-Laurent? Oh, such a tough patient for such a nice-looking young doctor."

"Mme St-Laurent? Be careful — she'll steal things from your pocket if you're not looking."

"Mme St-Laurent? Better wear some armour."

No matter: I was keen, I was fresh, and I was open-minded. As per my preclinical training, I was going to treat each of my patients with dignity, respect and tolerance. Thus determined, I entered Mme St-Laurent's room with a smile on my face and a bright yellow Snoopy tie on my chest.

"Oh great, another medical student. What do you want, Scrubs?" she sneered.

I asked her a few novice questions, some of which she ignored, and others she met with curt replies. "Have I been in the hospital before? Look it up in the chart. ... Who do I live with? That's none of your business. You really are snoopy." Then, turning to two nurses chatting in the hallway, Mme St-Laurent shrieked, "Go find another corner to do your business!" and muttered "whores" under her breath.

Welcome to ward medicine, indeed.

I stammered and ended the interaction weakly. Hiding in the empty nursing station, I looked more thoroughly through her chart. She had a history of physical abuse and drug dependence and was estranged from her family. Were these the sources of her hostility?

The next time I saw her I was again all smiles. "Ugh, you're back. Why do you torment me like this?" But I clung to my pleasant-demeanour policy. I explained everything I was going to ask, everything I was going to do. I tried to empathize and take my time. Her humour became less accusatory and more self-deprecating. I touched her shoulder, squeezed her hand and looked her in the eye. "If you keep smiling like this I'm going to start a nasty rumour that you're actually a very kind woman," I jokingly warned.

She laughed and replied, "You know, I do kinda like you. That's why I don't throw bedpans at you." She motioned to a curved dent in the wall facing her bed. "That was for a nurse who was *really* annoying me."

I stood silent for a moment, feeling both flabbergasted and thankful.

"Well then, I'm glad I'm on your good side, Mme St-Laurent."

As if to further demonstrate her protective arsenal she added, "And I don't fart at you, either!"

Having completed my exam, and not knowing the correct reply to threats of flatulence, I left the room in a bit of a haze. As a young nurse entered the room to take bloods, I could distinctly hear Mme St-Laurent passing wind.

Mme St-Laurent had lived hard. In social rounds we wondered if she had been a prostitute, if the "ex-husband" she talked about was actually a pimp.

One day a new attending staff physician arrived and chose Mme St-Laurent for bedside learning on examation of the liver. (Her span was 17 cm, the result of hepatitis C infection.) I was intrigued to see how my superiors would interact with her.

As our flurry of white coats stormed into her room, Mme St-Laurent fell disgustedly back into her bed. Then she noticed my pale presence among the group. The attending greeted her. "Mme St-Laurent. We'd like to examine you today."

Completely ignoring him, Mme St-Laurent rose to a seated position, frowned, and yelled to me, "So you've brought your curious friends with you, heh, Rat?"

From the disapproving looks on their faces I knew the other members of the team were wondering how I could have forged such a poor alliance with any patient.

Saying nothing in defence of myself, I took solace in Mme St-Laurent's contracted sphincter and the bed pan resting peacefully on the floor.

Eric Cadesky
PGY-1, Family Medicine
McGill University
Montréal, Que.

DOI:10.1503/cmaj.045275

Room for a view

The stone circle

The Tao is a whole. —Fritjof Capra

I was enjoying a beautiful sunset at my home in the Himalayas when my local caretaker broke the silence. He wanted me to take a look at his ailing father.

I fetched my stethoscope and we set off down the narrow slopes to the old man's hut. As we drew near, I became aware of the stench of disease pervading the fresh mountain air. My caretaker's father had been losing weight steadily, coughing up blood-tinged sputum. His body was warm to the touch. His lungs sounded coarse. He was probably suffering from tuberculosis, which was not uncommon in the region. He needed urgent treatment, but the nearest hospital was 100 kilometres away. His family gathered round. They wanted to know the cost of hospital care. I estimated it to be a few thousand rupees, less than a hundred American dollars. The old man refused to go. His granddaughter's wedding was only a few weeks away, and the family needed all the money they had saved to pay for it.

We finally respected his decision. But he insisted on paying me for my visit. He offered me a black stone shaped in the form of a deity, which he had recovered from a climb in the mountains several years before. It had brought him good luck. He hoped it would aid me in my efforts to be a good doctor. Reluctantly, I took the stone and put it in my pocket. His sunken eyes appeared deeper than the surrounding valleys as I left his hut. The sun that had hidden behind these slopes appeared to be only a shadow of the true sun.

A few weeks later I was on my regular shift in the emergency room in a small community hospital in upstate New York. One of my regular patients was wheeled into the emergency room for the third time that month. He had been found lying drunk on the road by the paramedics. He told them that he had been just lying there after a few drinks. We went through our routine of long and fruitless investigations: CT scans, blood tests and urine screens. As expected, they turned out to be normal, aside from the elevated blood alcohol level. We sent him home, urging him not to drink again. In the back of my mind a thought niggled: How much had it cost to do all those tests?

Several months later my patient came to the emergency department again. Not having seen him for some time, I was a bit apprehensive about his condition, but he told me that after the last episode he had decided to stop drinking. He thanked me for my efforts and explained that he had come to return the stone that had fallen out of my pocket during his last visit.

I had completely forgotten about the stone and hadn't noticed it was missing. I was ashamed to realize that I had also forgotten all about the old man who gave it to me. That day I called home, only to find out that he had died the day before his granddaughter's wedding and that as a consequence the family had postponed the wedding for a year.

On the surface it seemed that my visit to the old man's hut and his decision to forgo treatment had been fruitless. But somehow I felt that the old man's death had meaning. Although I had failed to help him, his resilient spirit had inspired me. Perhaps his example had strengthened me as a doctor. Did his stone fall into the hands of a patient half a world a way merely by chance? I do not know. I do not believe in miracles, but I know he somehow played a role in the life of my patient in America. Hidden from the surface was the truth that my patients from miles across the globe and I held a common thread of life and hope that bound us together.

Sonal Singh
Department of Medicine
Unity Health System
Rochester, NY

DOI:10.1503/cmaj.045006

Deaf patient

You can't make small talk with a pen.
A physician who talks too much,
a twentysomething patient with slender hands
and a diagnostic clipboard.

In an overflowing morning
we alternate scratching through the history.
Laborious, luxurious.
In the wait while she writes
the quiet is lovely and full:
    the roll of the wheels on my stool,
    air blowing through the ducts,
    the rush of wet tires on Bayswater.
Tangible as my scribbled
'Pain? Fever? Nausea?'

The pelvic is pure procedure,
a silent demonstration on a model
that blinks, breathes.
I mute the clang of the speculum,
the rustle of packaged swabs.
No words, no audience, and I am no disturber of the peace.

Slanting up the margins
the writing, visit, calm, stretch on,
for side effects look sinister, omissions are obvious in print.
When pens are down, heads up, she signs thank-you;
with black hair, dark eyes, white teeth
she is bright and magnified.

Martina Scholtens
Family Physician
Vancouver, BC

DOI:10.1503/cmaj.050041

Deaths

Nécrologie

Notice – CMAJ welcomes obituaries submitted within 60 days of a death. These should be no longer than 200 words, and colourful writing is encouraged. Send to Kyle Rooks, kyle.rooks@cma.ca; fax 613 565-5471.

Dr. Marc Baltzan, a pioneer in kidney transplantation in Canada and a leader for the profession, died Jan. 1, 2005. He was 75.

He was the first president of the Saskatchewan Medical Association (1967) and later became president of the CMA (1982–3). During his tenure as CMA president, he locked horns with federal health minister Monique Bégin over the creation of the Canada Health Act. He wrote that hospitals are being underfunded and the proposed act "completely ignores this situation and even attempts to sweep it under an ideological rug: equality will be achieved by equality of denial" (*CMAJ* 1983;128:736).

A graduate of McGill University (1953), Dr. Baltzan specialized in nephrology at Royal University and St. Paul's hospitals in Saskatoon. He was also the chair of the University of Saskatchewan's Department of Medicine.

Dr. Baltzan received the Order of Canada in 1995 and the Saskatchewan Order of Merit in 1999. Roy Romanow told the *Globe & Mail* that Dr. Baltzan was "one of Canada's outstanding Canadians" and "a caregiver in the most beautiful and most expansive meaning of that word."

He is survived by his wife, Nahid Ahmad, 4 children and 5 grandchildren.

Abdelmessih, Adib Makar, Regina; Cairo University (Egypt), 1952; staff, Regina Medical Centre. Died July 13, 2004, aged 79; survived by his wife, Fawzia, son Samir and daughters Nadia, Salina and Leila. "In Adib's last years, his passions became his God, his family and a genuine concern for his patients and friends."

Andrukaitis, Édouard V., Saint-Laurent, Que.; Université de Montréal, 1943; neurology; FRCPC; staff, Hopital Bellechasse. Died Aug. 13, 2004, aged 88; survived by his wife, Josephine Nowojczyk, and daughter, Bonnie.

Angus, Donald M., Napanee, Ont.; University of Otago (NZ), 1959; internal medicine; ChB, FRCPC; staff, Richmond Medical Centre. Died July 11, 2004, aged 69.

Bakierska, Agnieszka, Verdun, Que.; Université de Montréal, 2002. Died July 10, 2004, aged 27; survived by her parents, Maria and Stanislaw, and sister Anna.

Bethel, Frances J., Ottawa; University of Toronto, 1940. Died Feb 21, 2004, aged 88.

Bie, William F., Nanoose Bay, BC; McGill University, 1939; obstetrics and gynecology; MBE, MD CM; senior staff, Vancouver General Hospital, and associate professor, University of British Columbia. Died Aug. 12, 2004, aged 89; survived by his wife, Jean, and daughters Sherry and Beverley.

Brady, Patrick B., North York, Ont.; University of Toronto, 1968; family medicine. Died July 6, 2004, aged 61; survived by his wife, Lynn, and children Patrick and Martha.

Brown, Edwin L., St. Thomas, Ont.; University of Western Ontario, 1940; family medicine; chief of staff, Memorial and St. Thomas–Elgin General hospitals. Died Aug. 13, 2004, aged 89; survived by his wife, Valetta Squance, and his children C.J., Linda and Janet.

Campolongo, Joseph T., Guelph, Ont.; University of Toronto, 1949; active staff, St. Joseph's & Guelph General hospitals. Died July 11, 2004, aged 78.

Causing, Sergio S., Edmonton; University of Santo Tomas (Philippines), 1953. Died Aug. 1, 2004, aged 79.

Clark, George C., Cambridge, Ont.; Queen's University, 1949; anesthesia; FRCPC; staff, Cambridge Memorial Hospital. Died Aug. 9, 2004, aged 86; survived by his wife, Mary, and daughters Maggie and Linn. "George will be remembered for his love of music and painting as much for his sense of justice and passion for life."

Coburn, Frank E., Saskatoon; University of Toronto, 1939; psychiatry; former professor and student-health psychiatrist, University of Saskatchewan, and former president, Saskatchewan NDP. Died Apr. 19, 2004, aged 91. Survived by his 2 children. His daughter, Judi, wrote: "He died as he would have liked, discussing with his son the latest Saskatchewan budget, with the TV channel turned to hockey, regretting that both the Leafs and the Senators couldn't win, and falling gently asleep."

Delage, Maurice, Québec; Université Laval, 1942; physiatry. Died July 29, 2004, aged 89.

Dysart, Robert M., Moncton, NB; McGill University, 1947; general surgery and internal medicine; FACS, FRCSC, FRCPC; staff, Moncton and Dr. Georges-L. Dumont hospitals. Died Aug. 13, 2004, aged 80.

Fiedler, Maciej J., Lindsay, Ont.; Akademia Medyczna (Poland), 1980; family medicine; staff, Ross Memorial Hospital. Died July 19, 2004, aged 49; survived by his wife and three daughters. Dr. Peter Petrosoniak, a former colleague, stated: "He was very much liked by his patients, and just a really nice person."

Forman, Joan M. Vale, Toronto; University of Toronto, 1949; internal medicine; FRCPC; associate chief of medicine, Women's College Hospital and associate professor of medicine, University of Toronto. Died Aug. 10, 2004, aged 77; survived by her children Janet and Peggy.

DOI:10.1503/cmaj.050097

Friedman, Morris H.W., Edmonton; University of Alberta, 1954; general surgery. Died Aug. 2, 2004, aged 73.

Haber, Julius, Toronto; University of Toronto, 1945. Died Aug. 4, 2004, aged 91.

Hastings, John Elgin F., East York, Ont.; University of Toronto, 1951; public health; DPH, FRCPC; former associate dean, division of community health, University of Toronto and president, Canadian Public Health Association. Died suddenly of a heart attack, Aug. 11, 2004, aged 76; survived by his wife, Ulrike, and children Sascha, Thomas, Andrew and Martin.

Hooge, Peter D., Kelowna, BC; University of Manitoba, 1941; staff, Kelowna General Hospital. Died June 14, 2004, aged 93.

Howell-Jones, Hugh, Calgary; University of London (UK), 1945; anesthesia. Died July 25, 2004, aged 84.

Jacques, Robert A., Victoria; University of Manitoba, 1942; family medicine. Died July 15, 2004, aged 90. "He was a lifelong learner; he healed; he sang; he loved and was loved."

Jefferson, John C., Fredericton, NB; Dalhousie University, 1965; diagnostic radiology; chief of radiology, Oromocto Public Hospital. Died Aug. 4, 2004, aged 64; survived by his wife, Elisabeth, and 4 children.

Kaufman, Paul M., Toronto; University of Toronto, 1944; diagnostic radiology; DMR, FRCPC; staff, St. Clair-Dufferin Medical Centre. Died May 20, 2004, aged 83.

Kohari, Joseph, North York, Ont.; Semmelweis Orvostudomanyi Egyetem (Hungary), 1937; family medicine and general surgery; FRCS(Ed.), FRCSC. Died Aug. 9, 2004, aged 91; survived by his wife, Martha, and daughter Anne-Sophie. He was also a researcher, author, artist, volunteer and founder of the United Hungarian Fund.

Kubinski, Halina M., Delta, BC; Université libre de Bruxelles (Belgium); internal medicine. Died Aug. 8, 2004, aged 79.

Lafrenière, Robert E., Ste. Anne, Man.; Université Laval, 1956; family medicine. Died July 18, 2004, aged 74; survived by his wife, Simone, and children Mona, Robert, Roger, Andre, Jean-Marc, Lise and Gerald.

Layden, Joseph M., Mulgrave, NS; Dalhousie University, 1958. Died June 19, 2004, aged 76.

Lowson, Colin, Montréal; University of London (UK), 1954; psychiatry. Died May 22, 2004, aged 73.

MacMillan, Charles C., Rothesay, NB; McGill University, 1954; ophthalmology. Died July 27, 2004, aged 74; survived by his wife, Sheila.

Magowan, W. Kenneth, Pitt Meadows, BC; Queen's University of Belfast (UK), 1979; general practice. Died June 19, 2004, aged 49.

Mainprize, Graham W., Saskatoon; University of Toronto, 1953; family medicine; CCFP, FCFP; former district coroner, Central Butte, Sask. Died Aug. 16, 2004, aged 82.

Mallek, Josephine, Vancouver; McGill University, 1936; internal medicine; medical director, Louis Brier Home and Hospital. Died July 24, 2004, aged 92.

Margison, Malcolm E., Woodstock, NB; Dalhousie University, 1959; anesthesia. Died July 9, 2004, aged 73; survived by his wife, Joan.

Martel, Emmanuel, Sherbrooke, Que.; Université de Sherbrooke; medical student. Died July 20, 2004, aged 22.

Martin, Jeffrey R., Calgary; University of Calgary; medical student, class of 2006. Died Aug. 15, 2004, aged 26.

Mayman, Abraham, Hampstead, Que.; McGill University, 1947; internal medicine; CM; staff, Sir Mortimer B. Davis Jewish General Hospital. Died July 28, 2004, aged 85; survived by his wife, Esther Skarf, and 7 children.

Pearlman, David, Winnipeg; University of Alberta, 1953; family medicine. Died July 10, 2004, aged 77; survived by his wife, Evelyn.

Rayes, Adballa A.; Mont-Royal, Que.; Cairo University (Egypt), 1949; cardiology; BCh, DIM; staff and director of cardiology, Reddy Memorial Hospital. Died July 28, 2004, aged 79.

Sultan, Abdel-Mohsen, Toronto; Alexandria University (Egypt), 1952; family medicine. Died Aug. 1, 2004, aged 77; survived by his wife, Nadia, and 3 children. He continually reminded his wife how lucky he was to have lived a life that went "far beyond his expectations."

Taylor, William B., St. Thomas, Ont.; McGill University, 1939; diagnostic and therapeutic radiology; MD CM; staff, Elgin General Hospital. Died July 13, 2004, aged 93; survived by his wife, Margaret, and son Eric. "He was a keen photographer, naturalist and a patient, competent bridge partner."

Tompkins, James B., Dominion, NS; Dalhousie University, 1951; family medicine. Died July 19, 2004, aged 83; survived by his 7 children. A colleague noted: "His devotion remains a role model for practitioners. His patients are privileged by his services and his colleagues are honoured to be associated with him."

Tremblay, Caroline, Baie-Saint-Paul, Que.; Université de Montréal, 1994; psychiatry. Died July 27, 2004, aged 34; survived by her husband, Dr. Martin Dussault.

QUERY

Anson Liaw

Think of the following cast of characters as superantiheroes.

Dr. Plustar is neurotic about paperwork: he can't get any of it done. His desk is a swamp of tardiness. Complaints have been lodged with the College regarding late workers' compensation claims, late referral letters, late insurance forms. Dr. P's kryptonite is paper: it paralyzes him. This weakness affects the rest of us in the practice because we take pity on him. He leaves sheaves of paper behind wherever he goes, which we obligingly restore to him.

I resent picking up after Dr. P.

Dr. Longstem cannot arrive on time. This is not lateness of the fashionable variety. Dr. L has on several occasions been more than an hour late for handover in Emergency: *très gauche*. (Luckily, Dr. Angry has never been kept waiting.) I've never known Dr. L to be prompt for M & M rounds or medical staff meetings, either. His nefarious superpower lies in forcing his colleagues to adjust to his lateness. I'm frustrated when he arrives late but not late *enough*, in the middle of whatever task I'd started in anticipation of his tardiness.

I resent waiting for Dr. L.

Dr. Angry is fearsome. He's not scary-looking or physically imposing (actually, he's a little guy) but Dr. A can switch from an easy-going, laissez-faire manner to vein-popping indignation the very instant he feels slighted. Dr. A has been angry with everyone in the practice; his anger cycles among us. His superpower comes not in his anger, which admittedly is super-sized, but in making everyone walk on eggshells.

I resent pussyfooting around Dr. Anger.

Dr. Comeuppance is engaged in an Armageddon with the adjacent clinic. He accuses that outfit of malpractice daily, and his favourite patients are those who defect from that practice to ours. I can only imagine what he says to these patients behind the examining room door. Whenever I see him he's got a new tale of medical misadventure to report. Dr. C's superpower lies not in his aptitude for medical sabotage but in getting me to concur that the clinic across the street is staffed by "charlatans and buffoons."

I resent being made to agree with Dr. C.

Dr. Never is a notorious shirker. When on night call he avoids seeing patients, advising them to come to the clinic the next morning, when someone else is on duty. His vacations are always padded with a few days at the beginning and end, which we are meant to interpret as sick time. Dr. N's superpower lies not in his irresponsibility but in his ability to escape being assigned duties that the group knows he won't do anyway.

I resent doing Dr. N's work.

And who am I? To say I'm Dr. Resent would not suffice, for I am also Dr. Complicit. I don't have to be Dr. P's janitor or Dr. L's daytimer, but instead I allow their behaviours to continue and my resentment to build.

Maybe that's how Dr. Angry got started.

— Dr. Ursus

DOI:10.1503/cmaj.1040814