

## Correspondence

## Why Did the FDA Approve These Advertisements?

**David Oaks**

I would like to thank *PLoS Medicine* for publishing Lacasse and Leo's important and methodical Essay that debunks the "chemical imbalance" advertisements for psychiatric drugs [1]. Why would the United States Food and Drug Administration (FDA) approve such ads? Our human rights group, MindFreedom International, has been asking that question for a long time. On behalf of MindFreedom, US Senator Ron Wyden contacted the FDA for an explanation about why they approve such advertising. In their response—which took over one year to receive—the FDA could cite no scientific literature or studies. It turns out there's a good reason that the FDA can't find any scientific evidence for the claims of a "chemical imbalance" in these ads: the scientific evidence in support of the serotonin hypothesis is very weak.

Readers who would like more information about the psychiatric industry's advertising suggesting a "chemical imbalance" in depression may be interested in the following: (1) MindFreedom's debate with Pfizer, manufacturer of Zoloft, available at <http://www.mindfreedom.org/mindfreedom/pfizerlies.shtml>, and (2) a historic debate with the American Psychiatric Association resulting from MindFreedom's 2003 hunger strike, available at <http://www.mindfreedom.org/mindfreedom/hungerstrike.shtml> (Researcher Jonathan Leo was on the MindFreedom International Scientific Panel for the hunger strike). ■

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1. Lacasse JR, Leo J (2005) Serotonin and depression: A disconnect between the advertisements and the scientific literature. *PLoS Med* 2: e392. DOI: 10.1371/journal.pmed.0020392

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**Competing Interests:** DO directs MindFreedom International, a nonprofit human rights organization. We are pro-choice on psychiatric drugs, and many of our members choose to take prescribed psychiatric drugs. However, we have engaged in protests of what we perceive as the psychiatric drug industry's unfair dominance of the mental health system.

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## Evident Exception in Clinical Practice Not Sufficient to Break Traditional Hypothesis

**Milan Sarek**

I read with interest the Essay written by Jeffrey R. Lacasse and Jonathan Leo [1]. They have found that pharmaceutical companies marketing selective serotonin reuptake inhibitors (SSRIs) in the United States commonly declare that SSRIs

correct chemical imbalance in depression caused by a lack of serotonin. The authors argue that serotonin deficiency in depression is scientifically unsupportable; therefore, statements about the lack of serotonin should not be used.

I agree with the authors. Nevertheless, I would like to add information about another drug that supports their arguments. I believe this drug should be mentioned in every article describing the serotonin system and depression. The drug is not authorized in English-speaking countries (see Micromedex Health Series at <http://www.micromedex.com>), and this may possibly explain why the information about its controversial mechanism is not largely shared in scientific literature.

The name of this drug is tianeptine. It has been used for over one decade in several European and some other countries (e.g., Brazil, India, Russian Federation, Thailand, Turkey, etc.) to relieve depression. Tianeptine increases serotonin reuptake; therefore, it has the opposite effect on the serotonin system compared with that of SSRIs (see Micromedex Health Series at <http://www.micromedex.com>) [2,3]. The antidepressant efficacy of tianeptine versus tricyclics and SSRIs has been demonstrated in several studies [2,3]. Because of this opposite action on the serotonin system, it has a different adverse event profile; e.g., the elevated frequency of sexual dysfunction commonly seen after SSRIs is not so frequently observed with tianeptine [4]. The mechanism of tianeptine's action is difficult to understand, but comparing this drug with other antidepressants provides us with an intellectual challenge [5].

Tianeptine has been in clinical use for over 12 years in the Czech Republic, but statements about serotonin deficiency in depression are still presented to the public by the media and in the patient information leaflets accompanying the majority of registered SSRIs. One of the reasons for this may be that it is difficult for the single producer of tianeptine to argue against the "traditional" hypothesis that supports the numerous leading pharmaceutical companies that market SSRIs.

For these reasons, I propose that the most direct way to conquer the unsupportable, but widely proclaimed, concept of serotonin deficiency in depression is to act through regulatory authorities who are responsible for the information given to the public and who also have the power to change the information that is provided about registered drugs. ■

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## Consumer Advertising Can Be Misleading

### Karl Rickels

The Essay by Lacasse and Leo [1] demonstrates clearly how consumer advertising—in all fields of medicine, not only psychiatry—can at the least be misleading, making patients choose treatments that may not be the best choice in each particular circumstance. I agree with the authors that the “serotonin” hypothesis does not fully explain the mechanism of the serotonin reuptake inhibitors (SSRIs) in the treatment of anxiety disorders and depression.

In my clinical treatment of patients, consumer advertising is not only not helpful but often causes significant management problems. In addition, consumer advertising only focuses on expensive, patented medications and not on equally good generic alternatives. A good example is the consumer advertising of “the purple pill,” Nexium, while generic Prilosec, equally effective in almost all patients, is not advertised.

Let’s prohibit all consumer advertising of patented medications. It will save physicians much headache, and patients or their insurers a great deal of money. ■

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## Should Industry Speak the Loudest in Informing the Public on Medical Matters?

### Gordon McCarter

Lacasse and Leo make an important contribution in the debate over prescription drug advertising [1]. Their demonstration of the ubiquity of the scientifically unsupported claim that serotonin reuptake inhibitors (SSRIs) “correct a chemical imbalance” points out the need for better

regulation of direct-to-consumer (DTC) advertising by the United States Food and Drug Administration (FDA). This question then leads to a larger issue: how does the public get unbiased information to rationally choose between different treatment options that may be available for particular diseases.

First, it should be emphasized that the “monoamine hypothesis” of depression has not been proven wrong; it is simply very incomplete. Inhibiting the serotonin and/or norepinephrine transporter(s) clearly relieves the symptoms of major depression for many patients, and the safety profiles of the current SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) are quite favorable. Nevertheless, the exclusively pharmaceutical and commercial approach to the treatment of depression that the typical consumer is exposed to in the media does a grave disservice to those who might benefit from the many other treatment options available.

The realization that depression is a true physical disease has allowed millions of sufferers to seek treatment, and has removed much of the guilt and shame (or proud forbearance) that sometimes resulted from a predominately psychodynamic conception of the causes of depression. Earlier, when very little else was known about the etiology of the disease, it might have been helpful to describe the action of the available drugs to patients as “correcting an imbalance” in brain neurotransmitters. Now, with so much more known or strongly suggested about the biology of depression, it is irresponsible for anyone in the medical community to describe it as simply a “chemical imbalance.” The implications of the heritability of a predisposition, the role of early life trauma, the involvement of stress hormones, the observations of neuronal atrophy, and the possible link to hippocampal neurogenesis all have implications for treatment that lead in many directions other than simply a pharmaceutical approach. These include nutrition, exercise, and certain forms of psychotherapy, especially cognitive-behavioral therapy.

But how would a depressed person know about all these treatment options? If lucky, the person might be induced, perhaps by DTC advertising, to visit a doctor, who would then describe current thinking about depression and try to determine the best treatment for the patient’s situation. But doctors are extremely overworked these days, and they, too, are targeted by the advertising of pharmaceutical companies. Indeed, “medical education” is a huge industry through which these firms, at one remove, attempt to influence medical practice by the sponsoring of meetings, symposia, and journal supplements and by the well-remunerated enlistment of academic “opinion leaders” to present and to be credited as authors for what are usually ghost-written pieces. The result is a knowledge environment that is overwhelmingly dominated by the perspective of commercial interests.

The solution to this problem, of course, is education, both of physicians and of patients. A nice way to achieve this, and to refrain from infringing on anyone’s free speech, would be to require that any expenditure on advertising by pharmaceutical or medical device manufacturers be matched by contributions to an unbiased education fund administered by the FDA, the National Institutes of Health (NIH), or both. This fund could be used to produce public service announcements of clear and balanced information regarding

the particular therapeutic area that the company's product addresses. However it is funded, the federal government is the only entity with the resources and reach to be an effective counterweight to the commercial medical perspective. There are few roles that may be as important for a national government than the protection of its citizens' health through effective regulation of the presentation of medical information. ■

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1. Lacasse JR, Leo J (2005) Serotonin and depression: A disconnect between the advertisements and the scientific literature. *PLoS Med* 2: e392. DOI: 10.1371/journal.pmed.0020392

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#### Authors' Reply

We are pleased to see that our Essay [1] has sparked this discussion regarding consumer advertising of psychiatric medications.

There seems to be no disagreement with our main theses—antidepressant advertisements do not accurately represent the evidence base from psychopharmacology, experimental psychiatry, and neuroscience; are not strictly based on the United States Food and Drug Administration (FDA)-approved prescribing label; and may mislead consumers.

We believe many have bought into the serotonergic hypothesis of depression/generalized anxiety/social anxiety/obsessive-compulsive disorder/panic disorder/post-traumatic stress/bulimia/premenstrual dysphoric disorder largely because the serotonin reuptake inhibitor (SSRI) medications are licensed for these conditions. We reemphasize that pathophysiology cannot be established through clinical efficacy [2], yet this critical point seems to have been largely overlooked, particularly by regulators.

At the date of this letter, the advertising we presented in our Essay is still widespread, and quite visible on consumer advertising Web sites of SSRI manufacturers. ■

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## Other Studies Show Aspirin Use Is High

### Jonathan Brown

The importance of prophylactic aspirin use in both developed and developing countries can hardly be overemphasized. I am troubled, however, by Stafford and colleagues' failure to cite and discuss United States studies that show much higher rates of antithrombotic use than they report [1]. Using a cross-sectional postal survey of 2,500 Kaiser Permanente members with atherosclerotic cardiovascular disease, Brown et al. [2] found that 84% were currently taking prophylactic aspirin (72%) or a prescription agent (12%, usually warfarin) in 1999. In an earlier study of another nonprofit-integrated US medical care system, HealthPartners, O'Connor et al. [3] similarly found that 71% of members with clinically diagnosed coronary heart disease were taking aspirin. These results are almost triple the approximately 25% that Stafford et al. now report for the 1999–2000 time period (the low point in their time series), and about double the 34% that Stafford [4] previously reported from the National Ambulatory Medical Care Study for patients with coronary heart disease.

Two factors probably account for these differences. First, Stafford et al.'s federal surveys of ambulatory care encounters miss a significant proportion of aspirin use. Studies in a variety of populations that used direct patient surveys and other methods, some of which are cited in Brown et al. [1], have found higher rates of aspirin use in a variety of settings than Stafford et al. have reported over the years. Second, nonprofit-integrated medical care programs emphasize and promote aspirin aggressively and effectively. Their members probably have higher rates of aspirin use than individuals in other US care-delivery settings.

The experience of the nonprofit-integrated systems is also important because it calls into question Stafford et al.'s suggestion, emphasized in PLoS's accompanying synopsis, that direct-to-consumer advertising of statins explains the 1997–2000 dip in aspirin use in their data. Kaiser Permanente and HealthPartners members were equally exposed to direct advertising, but maintained high aspirin use during this period—despite probably also using statins (and angiotensin converting enzyme [ACE] inhibitors) at higher rates than individuals in other US care-delivery settings.

The US nonprofit HMO experience nevertheless reinforces the authors' main conclusion that “aggressive and targeted interventions are needed to enhance provider and patient adherence to consensus guidelines for CVD risk reduction” [1]. Aggressive and targeted interventions are exactly what these settings use. Major structural factors such as lack of universal health insurance, fee-for-service rather than population-based orientation, and failure to use comprehensive electronic medical record systems will continue to hamper the US, however. Direct-to-consumer advertising, although symptomatic, pales in importance against these other problems. ■

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## Authors' Reply

Brown correctly points out that the rates of prophylactic aspirin use from our study [1] were much lower than the rates reported in some other United States studies, particularly those of Brown et al. [2] and O'Connor et al [3]. The latter studies represent practices in two large, integrated health maintenance organizations, which may represent special examples of best practices. Based on two nationally representative ambulatory-care surveys, our results are comparable to those from the Third National Health and Nutrition Examination Survey (NHANES III) [4]. As detailed in our discussion of data limitations, National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data are reported by physicians on a per-patient visit basis, which may generate different findings than a population-based survey. Complementing earlier studies, our findings suggest that underutilization of aspirin as a cost-effective cardiovascular prevention strategy remains widespread in the US.

It is critical to discern factors associated with variation in aspirin use. This can lead to targeting some subpopulations for improvement or, alternatively, for attempts to promulgate features of best practice to other settings. For example, our analysis suggested that after adjusting for level of cardiovascular risk, women had significantly lower use of aspirin than men. As Brown points out, nonprofit-integrated medical care exemplifies one system in which prophylactic use of aspirin can be aggressively and effectively implemented. These settings have mechanisms in place that encourage sustained aspirin therapy, including guidelines, messages to clinicians, nursing-care management, alerts and routines embedded in electronic medical records, and direct mailings to patients [2]. Greater adoption of these mechanisms outside of integrated systems may have a favorable impact on national patterns of aspirin use. The issue of making our nation's health-care system more responsive to available evidence is a complex undertaking. We agree with Brown that direct-to-consumer drug advertising is a secondary factor in current patterns of aspirin use. Nonetheless, among other factors, direct-to-consumer drug advertising should be

included as a potential barrier that may interfere with the translation of clinical evidence into practice. ■

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## Does Genetic Testing Really Improve the Prediction of Future Type 2 Diabetes?

**A. Cecile J. W. Janssens, Marta Gwinn, Subramony Subramonia-Iyer, Muin J. Khoury**

From their study on the genetic prediction of future type 2 diabetes (T2D), Lyssenko and colleagues conclude that “genetic testing might become a future approach to identify individuals at risk of developing T2D” [1]. One of their most striking findings is an impressive 21.2-fold increased risk for T2D in obese carriers of the *PPARG* PP and *CAPN10* SNP43/44 GG/TT genotypes with elevated fasting plasma glucose (FPG).

A closer look at their results reveals that the hazard ratio of 21.2 was obtained by comparing the T2D risks of persons who have all three risk factors (“risk genotypes,” obesity, and elevated FPG) with those who have none of these factors. This hazard ratio, thus, measures the combined increase in risk due to *PPARG* PP and *CAPN10* SNP43/44 GG/TT genotypes, obesity, elevated FPG, and their interactions. Among obese persons with elevated FPG, the incidence of T2D was 44.7% in carriers of risk genotypes and 10.7% in persons with other genotypes, yielding a risk ratio of 4.2 (95% confidence interval [CI], 2.3–7.8; follow-up time, age, and sex were not taken into account)—a result that is statistically significant but considerably smaller. Furthermore, genotyping did not significantly alter the risk of T2D in any other subgroups defined by body mass index (BMI) or FPG. Apart from this, the case for predictive genetic testing depends not merely on the magnitude of the risk ratio, but rather on the extent to which the test results are useful for improving prediction

of disease [2]. In this study, does testing for *PPARG* PP and *CAPN10* SNP43/44 genotypes improve the prediction of T2D based on BMI and FPG alone? The usefulness of genetic testing for predicting disease can be evaluated by comparing the discriminative accuracy of predictions based on models that do and do not include the genetic test results [3]. The discriminative accuracy of a test is indicated by its sensitivity and specificity (dichotomous test results), or by the area under the receiver-operating characteristic (ROC) curve (variable test results) [4]. Sensitivity is the probability of a positive test result among persons who will develop the disease, and specificity is the probability of a negative test result among persons who will not develop the disease. In a perfect test, both sensitivity and specificity equal one. For tests with variable (not dichotomous) results, a cut-off probability must be chosen. Sensitivity and specificity of the test will vary with the choice of cut-off probability. When sensitivity and specificity are calculated for each possible cut-off value and plotted as an ROC curve, the area under the curve (AUC) measures the discriminative ability of the test. AUC can vary from 0.5 (no discrimination) to one (perfect discrimination) [4].

Using the data presented by Lyssenko et al. [1], we estimated the discriminative accuracy of predictions of T2D risks that did and did not take genotype into account. We used logistic regression to obtain the risks of T2D for all individuals in the study, considering three different prediction models. In the first model, risk of T2D was predicted by BMI (BMI less than 30 kg/m<sup>2</sup>; BMI greater than or equal to 30 kg/m<sup>2</sup>) and FPG (FPG less than 5.6 mmol/l; FPG greater than or equal to 5.6 mmol/l). The second model included BMI, FPG, and carrier status of the combined *PPARG* PP and *CAPN10* SNP43/44 GG/TT genotypes, and the third model also included all interaction effects among the three predictors. ROC curves and estimated values for the AUC were obtained using SPSS 11.0.1. For predictions of T2D risk based on BMI and FPG alone, the AUC was 0.68 (95% CI, 0.63–0.73), indicating a moderately discriminative accuracy. In comparison, AUCs of approximately 0.77 have been estimated for both serum cholesterol testing for predicting coronary heart disease and neuropsychological testing for predicting Alzheimer disease in asymptomatic persons [5,6]. When genotype was added to the predictive model including BMI and FPG, AUC remained the same (0.68; 95% CI, 0.63–0.73, for main effect only), even when all interaction effects were considered (0.69; 95% CI, 0.64–0.74). The AUCs of the three prediction models are presented in Figure 1. Thus, the data of Lyssenko et al. suggest that genetic testing for *PPARG* PP and *CAPN10* SNP43/44 genotypes will not improve the prediction of T2D in the presence of information on the nongenetic factors, BMI and FPG. The differences in our conclusions are explained by the fact that Lyssenko et al. focused on the highest-risk category rather than on differences in risk among all participants. Individuals who had 21.2-fold increased risk were already in the highest-risk category based on BMI and FPG alone. Genotyping only further subdivided each risk category, without substantially altering the ranking of the categories. And finally, the 21.2-fold risk applied to the second-smallest subgroup, which included only 38 of the 2,243 participants. Testing for *PPARG* PP and *CAPN10* SNP43/44 genotypes did not change the T2D risk for the vast majority of the population. ■

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## Authors' Reply

In their correspondence to our paper, “Genetic Prediction of Type 2 Diabetes” [1], Janssens et al. question whether genetic testing really will improve prediction of future type 2 diabetes (T2D) [2].

Their criticism is well taken and important for the discussion on the causes of T2D. It is assumed, although not yet proven, that T2D results from the complex interaction between multiple genetic variants and environmental risk factors. In an earlier paper [3], we listed three of those risk factors: family history of T2D, body mass index (BMI) greater than or equal to 30 kg/m<sup>2</sup>, and non-normal fasting plasma glucose (FPG) greater than 5.5 mmol/l. Two of these risk factors (BMI and FPG) were replicated in a study of Israeli military men [4]. If we assume that T2D results from the interaction between these risk factors and genetic variants, it is not unreasonable to test whether genetic risk factors improve the predictive value of the environmental risk factors.

Therefore, the main objective of our analysis was to find a joint genetic and environmental model that accurately describes the effects on the time distribution of the age at onset, and to use that model to quantify the genetic and environmental effects. For that purpose, we have performed forward stepwise multivariate Cox regression analysis, adding one covariate at a time. The resulting multivariate model has

then been tested against a “null” model with a likelihood-ratio test to assess the overall fit of the model. To address the question asked in the introduction, we choose to study the effects of having all the significant risk factors elevated against the effects of having none by using the estimates in the resulting model. This approach is open for discussion; one alternative approach would be the approach presented by Janssens et al.

They make a group division and use logistic regression to assess genetic effects on the development of T2D. There are two drawbacks with this approach. The first is that by dividing the population into subgroups one lowers the power to find significant effects and also obtains large variances in the estimated effects, thus getting a large degree of uncertainty in both significance and size of the estimated effects. Secondly, logistic regression disregards the fact that individuals have been followed prospectively. In contrast, we perform calculations of estimated effects in the obtained multivariate model, thereby using all the available data in the variance calculations. This allows us to assess the size of an increment of a risk factor for prediction of the disease, e.g., the estimated hazard ratio (HR) for a continuous covariate is the ratio of the hazards for an increase of one in the covariate.

Using our multivariate model, the genetic factors confer a T2D risk of the same magnitude (HR, 3.69) as, e.g., FPG (HR, 3.25) and BMI (HR, 1.77).

Janssens et al. claim that a receiver-operating characteristic (ROC) analysis on our data does not support the claim that there is significant gene effect for discriminative purposes. However, Janssens et al. perform an ROC and an area under the curve (AUC) analysis based on a logistic regression, thus treating each individual as affected versus nonaffected and not taking into consideration age effects, the drawbacks of which are discussed above.

An ROC analysis may not be the best way to describe modest effects of genetic variants contributing to risk of a polygenic disorder such as T2D. This is further hampered by the use of longitudinal data with several time points. Although the ROC analysis recently [5] has been applied to survival analysis data, the complexity of the situation in T2D limits its value. Using this approach, we obtain an AUC of 0.76 for the full model and an AUC of 0.75 for the model excluding genetic effects.

However, an ROC analysis could work for genetic prediction of a monogenic disorder such as maturity-onset diabetes of the young (MODY). MODY 3 is a dominant form of early-onset diabetes with strong penetrance, and is caused by mutations in the hepatocyte nuclear factor 1, *HNF-1 $\alpha$*  gene [6]. In an analysis of 33 carriers of MODY mutations followed for a mean of 4.7 years, the AUC for diagnosis of MODY was 0.86.

We should keep in mind that we have only tested a few potential common genetic variants contributing to T2D. It was recently suggested that only approximately 20 genes may be needed to explain 50% of the disease burden in the population [7]. However, for individual genetic prediction, we need to establish how much of the relative risk ( $\lambda$ s) is accounted for by genetic variants. For this purpose, we need to know all variants which contribute to risk of T2D. Hopefully, genome-wide single nucleotide polymorphism (SNP) scans in the future can provide us with that information. ■

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## Community-Based Learning in a Time of Conflict

**Bishnu Giri, P. Ravi Shankar**

We read with interest the Editorial “Improving Health by Investing in Medical Education” [1]. The emphasis on problem-based, community-oriented, integrated teaching was of special interest. In Nepal, though community-based learning (CBL) has been carried out for many years, the majority of teaching still occurs in acute hospital settings. The ongoing conflict in Nepal has had an impact on all sectors, including medical education. CBL has been quite severely affected.

The Institute of Medicine (IOM), Kathmandu, the first medical college in Nepal, organizes community diagnosis programs (comprehensive assessments of the health status of a community in relation to its social, physical, and biological environment) [2].

The Manipal College of Medical Sciences (MCOMS), Pokhara, Nepal, admits mainly students from Nepal, India, and Sri Lanka for the undergraduate medical (MBBS) course. The revised curriculum of Kathmandu University [3], to which the college is affiliated, emphasises CBL. Community diagnosis, school health studies, family studies, participation in rural health camps, and health education are the various activities carried out. The Department of Pharmacology conducts exercises to acquaint students with the processes of the Community Drug Program (a system of

community financing of drugs) and with the investigation of medicine use in peripheral health centres using drug-use indicators.

Around six years ago, when the insurgency was just taking root, students used to visit remote areas in Kaski (the district which includes the city of Pokhara) and neighbouring districts as a part of their community diagnosis studies. They stayed there for a few days, interacting closely with local communities. Community field trips were, however, gradually curtailed with the rise of the insurgency, and were finally limited to the Pokhara Valley. The college authorities were apprehensive about the possible harm to students and faculty members. Other colleges have also curtailed their CBL because of the spread of the insurgency. A friend from IOM wrote recently saying, "The prevailing situation is affecting the site selection for community studies. The studies used to be conducted at sites outside the Kathmandu Valley, but these days the sites are preferentially chosen inside the valley" (S. Gurung, personal communication).

In private medical colleges, students mainly come from economically well-off families and have little idea of poverty and deprivation. Some of my friends were surprised to see a family living in a small hut on a hillside in a village just outside Pokhara. Young women often give birth without trained medical assistance in rural areas. Women carry heavy loads of firewood and fodder for their cattle along steep mountain trails well into late pregnancy. Empathy and sympathy for the less fortunate may be qualities lacking in doctors who are not exposed to rural life. Their impression of the community's health status may be lopsided. In their future practice, students may not consider the patient's economic status while prescribing treatment.

The deleterious effects of conflict on health status of a community are an established fact. Urban students having little experience in rural Nepal may find it difficult to adjust if posted to a rural health centre after graduation. The present curtailment of CBL in rural areas may lead to production of less competent manpower and ineffective policymaking in the not too distant future. We sincerely hope that, with the hope of peace being reestablished, CBL in Nepal will be strengthened and expanded. ■

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